Safety Assessment of Glyceryl Acrylates as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: February 11, 2022
Panel Meeting Date: March 7-8, 2022

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

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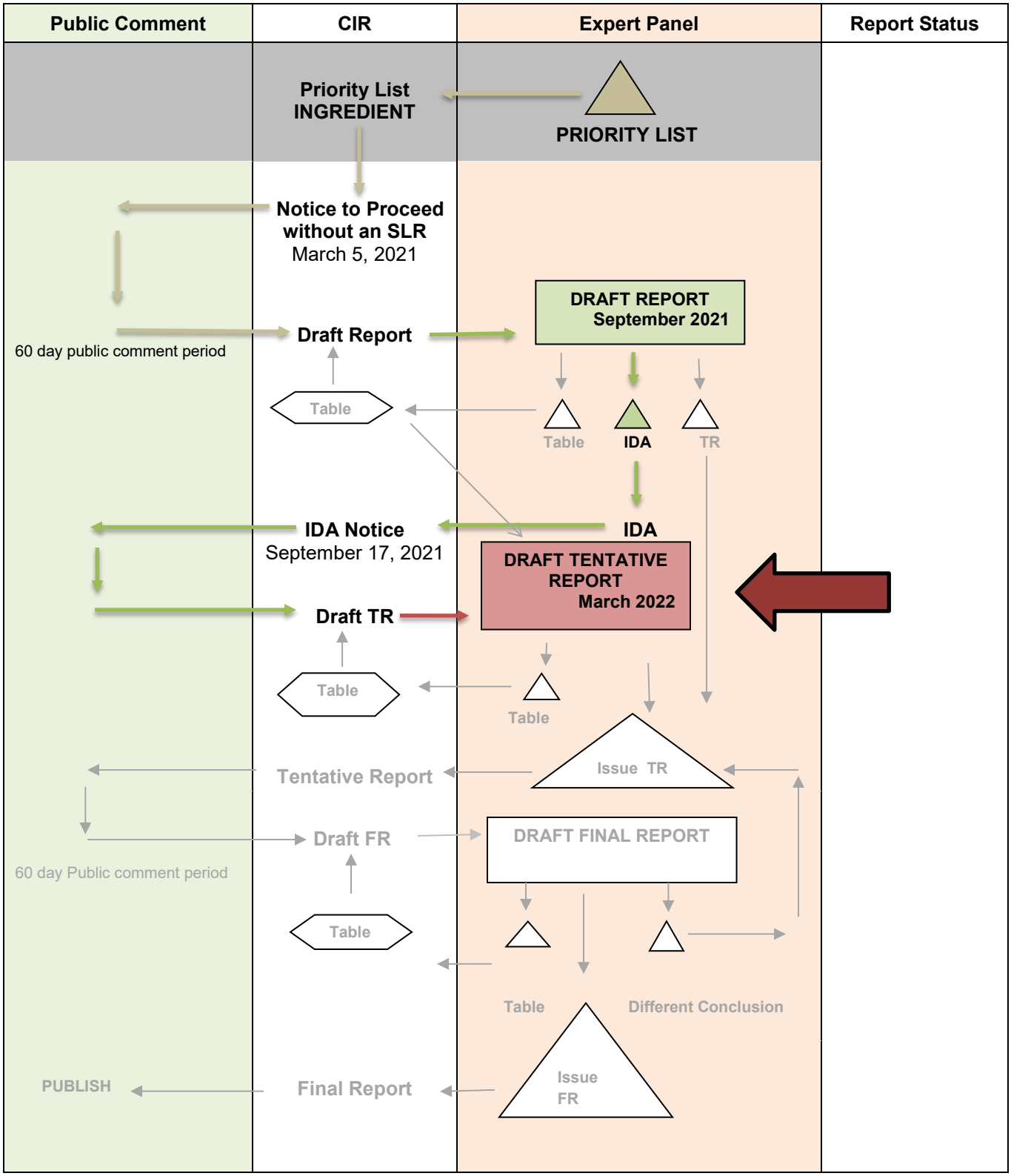
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Glyceryl Acrylates

MEETING March 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Regina Tucker
Scientific Analyst/Writer
Date: February 11, 2022
Subject: Safety Assessment of Glyceryl Acrylates as Used in Cosmetics

Enclosed is the Draft Tentative Report of the Safety Assessment of Glyceryl Acrylates as Used in Cosmetics. (It is identified in this report package as *report_GlycerylAcrylates_032022*.) Upon initial review, at the September 2021 meeting, this report included 3 ingredients. However, at that meeting, the Panel determined that it was appropriate to consider a 4th ingredient, Glyceryl Polyacrylate; consequently, this ingredient has been added to the safety assessment.

After reviewing the Draft Report at the September 2021 meeting, the Panel issued an Insufficient Data Announcement (IDA), with the following data needs:

For all, except Glyceryl Polymethacrylate:

- Method of manufacture data

For all 4 ingredients:

- Molecular weights and impurities, including residual monomers
    - Depending on the data received (especially residual monomer content), 28-d dermal toxicity, skin penetration data, and other toxicity endpoints may be needed
- Genotoxicity data
- Skin irritation and sensitization data at maximum use concentration

The following data were received, and have been incorporated into the report (as indicated by yellow highlighting):

- concentration of use data for Glyceryl Polyacrylate (*data1_GlycerylAcrylates_032022*)
- toxicology summary on Glyceryl Acrylate/Acrylic Acid Copolymer (impurities, acute oral toxicity, skin, ocular, and mucosal membrane irritation; *data2_GlycerylAcrylates_032022*)
- summary data on Glyceryl Polyacrylate (molecular weight and impurities, genotoxicity, and skin irritation and sensitization; *data3_GlycerylAcrylates_032022*)
- irritation and sensitization data (*data4_GlycerylAcrylates_032022*)
    - Anonymous. 2006. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (product contains 7.7% Glyceryl Polymethacrylate).
    - Anonymous. 2006. Clinical evaluation report: Human patch test (product contains 7.7% Glyceryl Polymethacrylate).
    - Anonymous. 2015. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (product contains 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer).
    - Anonymous. 2014. Clinical evaluation report: Human patch test (product contains 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer).
    - Anonymous. 2014. Repeated insult patch test (product contains 0.5% Glyceryl Polyacrylate).

Updated VCRP (2022) data have been received, and are also included (*VCRP_GlycerylAcrylates_032022*). No significant changes in frequency of use were noted.

A safety assessment of Glyceryl Polyacrylate was previously published by the Panel (2004), and in 2018, the Panel issued a final amended report on 126 acrylates copolymers. Although there are no data specific to Glyceryl Polyacrylate or glyceryl acrylates in these reports, they are being provided for the Panel as possible supporting information. (*originalreport-GlyPolyacrylate_GlycerylAcrylates_032022*; *supportingreport-AcrylatesCopol_GlycerylAcrylates_032022*, respectively).

The following are also included as a part of this report package:

report flowchart	*flow_GlycerylAcrylates_032022*
report history	*history_GlycerylAcrylates_032022*
data profile	*dataprofile_GlycerylAcrylates_032022*
search strategy	*search_GlycerylAcrylates_032022*:
transcripts	*transcripts_GlycerylAcrylates_032022*

The Panel should carefully consider and discuss the data (or lack thereof), and issue a Tentative Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion. The draft Discussion should also be reviewed, and additional discussion items identified.

CIR History: Glyceryl Acrylates

SLR NTP: March 5, 2021
A Scientific Literature Review (SLR) Notice to Proceed (NTP) was issued

Concentration of use data and the limited safety test data that were identified in the published literature were incorporated into the draft report. No other data were received.

Draft Report: September 13-14, 2021

The Panel issues an Insufficient Data Announcement, with the following data needs:
For all except Glyceryl Polymethacrylate:

- Method of manufacture data

For all 4 ingredients:

- Molecular weights and impurities, including residual monomers
    - Depending on the data received (especially residual monomer content), 28-d dermal toxicity, skin penetration data, and other toxicity endpoints may be needed
- Genotoxicity data
- Skin irritation and sensitization data at maximum use concentration

Draft Tentative Report: March 7-8, 2022

The following unpublished data were received, and have been incorporated into the report:

- concentration of use data for Glyceryl Polyacrylate
- toxicology summary on Glyceryl Acrylate/Acrylic Acid Copolymer ((impurities, acute oral toxicity, skin, ocular, and mucosal membrane irritation)
- summary data on Glyceryl Polyacrylate (molecular weight and impurities, genotoxicity, and skin irritation and sensitization
- Maximization assay for a product containing 7.7% Glyceryl Polymethacrylate.
- Human patch test for a product containing 7.7% Glyceryl Polymethacrylate.
- Maximization assay for a product containing 0.586% Glyceryl Poly Acrylate/Acrylic Acid Copolymer.
- Human patch test for a product containing 0.586% Glyceryl Polyacrylate/Acrylic Acid Copolymer.
- Insult patch test for a product containing 0.5% Glyceryl Polyacrylate.

Glyceryl Acrylates Profile – March 2022 – Writer, Regina Tucker (and previously, Wilbur Johnson)

				Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization			Photo-tox	Ocular Irritation		Mucous Membrane Irritation		Clinical Studies	
	VCRP	**Method of Mfg**	**Impurities**	**Dermal Penetration**	**ADME**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**In Vitro**	**In Vivo**	**Dermal**	**Oral**	**In Vitro**	**Animal**	**Human**	**In Vitro**	**Animal**	**Human**		**In Vitro**	**Animal**	**Animal**	**Human**	**Retrospective/ Multicenter**	**Case Reports**
Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer	**0**																												
Glyceryl Acrylate/Acrylic Acid Copolymer	**295**		X				X							X					X	X			X			X			
Glyceryl Polyacrylate	**119**		X											X									X						
Glyceryl Polymethacrylate	**142**	X																		X			X						

* "X" indicates that data were available in a category for the ingredient

GLYCERYL ACRYLATES

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Glyceryl Acrylate/Acrylic Acid Copolymer		Yes		0		No	0	0	0	0	0	0	0	0	0	0	0	Yes
Glyceryl Polymethacrylate	146126-21-8 28474-30-8	Yes		8		No	0	0	0	0	0	0	0	0	0	0	0	Yes
Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer		Yes		0		No	0	0	0	0	0	0	0	0	0	0	0	Yes
Glyceryl Polyacrylate**	104365-75-5	Yes		1		No		0	0	0	0	0	0	0	0	0	0	Yes

** Glyceryl Polyacrylate search: 1999 forward; ingredient added to group at September 2021 Panel meeting

Search Strategy

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

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

LINKS

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

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

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1

IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

SEPTEMBER 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 13, 2021

DR. BELSITO: Glyceryl Acrylates. So this is the first time that we're reviewing the three ingredients in the report, and it's reported to be used in 286 cosmetic products, mostly leave-ons. Glyceryl Acrylates have the greatest reported use frequency. We got concentrations of use and so we need to look and see where we are with this grouping and data. So, my first question is to you, Dan, are you okay with the grouping?

DR. SNYDER: Yeah.

DR. BELSITO: Particularly Caprylyl Glycol.

DR. SNYDER: Which report are you on, Don, sorry, which report?

DR. LIEBLER: Glyceryl Acrylates, Paul. Glyceryl Acrylates. Let us know when you got it.

DR. SNYDER: I got it.

DR. LIEBLER: Okay.

DR. SNYDER: Thanks.

DR. LIEBLER: So, with respect to the question of the grouping, yes, I'm okay with the grouping. And, furthermore, there was a suggestion in the Council memo that we add Glycerol Polyacrylate, and I'm okay with that, at least in terms of the chemistry. I think it's probably due for a re-review, but if there's any programmatic issue, Monice can fill us in. Monice, anything to consider there?

MS. FIUME: So it is actually scheduled for re-review next year as part of the Glycerol monoesters, I believe, report. I forget.

MR. JOHNSON: Yeah, that's right.

MS. FIUME: Yes, but, Wilbur, you looked back at the original document, and you stated there are no data on that ingredient in that original document, is that correct?

MR. JOHNSON: You're right, no safety test data.

MS. FIUME: Yes. So, adding that ingredient, if it fits better here than there, is great, would be fine. But just be aware that there are no data to pull from the old report on Glycerol Polyacrylate itself.

DR. SNYDER: If the absence of data is the basis to include in this report, that's fair, because there's no data on this whole group.

DR. LIEBLER: So, the question I have is about the other report that the Glyceryl Acrylates are currently in, you said that was Glycerol esters?

MR. JOHNSON: Glycerol Monoesters.

DR. LIEBLER: Monoesters. Are those polymers?

MS. FIUME: Let me grab the report.

MR. JOHNSON: No.

DR. LIEBLER: It doesn't sound like they're polymers, and if they're not, if that was like an orphan polymer thrown in with a bunch of non-polymers, it probably belongs in this report instead.

MR. JOHNSON: Mm-hmm.

MS. FIUME: It's a compilation of Glycerol monoesters.

DR. LIEBLER: Yeah, Glyceryl Polyacrylate is a polymer, so --

DR. ANSELL: Yeah, I think the point here is not the amount of data, but whether this is the right family.

DR. LIEBLER: Yeah.

DR. ANSELL: And we believe it is.

DR. BELSITO: No, I was being facetious, Jay, sorry.

DR. LIEBLER: It sure sounds like it is.

DR. BELSITO: Dan, you want to add Glyceryl Polyacrylate to this report?

DR. LIEBLER: That's correct. That's the Council's suggestion. Jay, if I've got that right, the feeling that it belongs more in this report than in the Glycerol monoesters.

DR. ANSELL: That's right.

DR. LIEBLER: Okay. I agree with that.

DR. BELSITO: Okay.

DR. LIEBLER: So, to get back to my assessment of this, so, the groupings are fine, the ingredients are fine with the additional Glyceryl Polyacrylate. And, then, this is insufficient for method of manufacture and impurities. And, most importantly, we need molecular weight information. These are polymers, so they should be high molecular weight. If they are, you know, greater than like 5,000, there will be no dermal absorption and the systemic endpoints really won't be needed.

We would need residual monomer and then, the other data needs that we would have to consider. Don, you can take the lead on that. But, anyway, I think insufficient method of manufacture and impurities, and residual monomer.

DR. BELSITO: And you said molecular weight?

DR. LIEBLER: Yeah. We don't need chapter and verse on method of manufacture. A sentence or two would probably be adequate. It's molecular weight range characterization. You know, even broad numbers would be adequate. We just need to verify that these are high molecular weight molecules.

DR. BELSITO: Okay, so manufacturing, impurities, molecular weight, and residual monomer.

DR. LIEBLER: Yep. I mean, these are, if you look at the uses, humectant, viscosity increasing agent, this is hallmarks of polymers, film formers, and so forth. So I think that we'll -- it won't be too hard for industry to provide the information we need to focus this report appropriately.

DR. BELSITO: Okay. And so, then, I'm assuming if we get that and there isn't any significant residual monomer and they're high molecular weight, we really don't need the toxicogenic studies because in the discussion we can assume that they won't be absorbed, is that correct?

DR. LIEBLER: That's correct. So that circumvents the whole 28-day dermal and all that stuff. And then it's sensitization, irritation.

DR. BELSITO: Okay. And, then I had a question on PDF page 12, the effect on burn wound healing? How long were they treated and were only the wounds assessed or were there any other tox endpoints that were looked at? Because that would give us some additional toxicity data. I'm assuming none of that was, in fact, reported, I didn't have time to look at the individual reference.

MR. JOHNSON: No, Dr. Belsito, just, you know, as stated here, you know, beginning on Day 0 until healing was complete.

DR. BELSITO: Okay.

DR. SNYDER: We don't even know the concentration of the Glycerol Polymethacrylate in the cream.

DR. BELSITO: Right.

MR. JOHNSON: Yeah.

DR. SNYDER: This is not very informative.

DR. BELSITO: Okay. So, then, again, with the lack of developmental and repro, if we have the residual monomer and the molecular weights, we don't have to worry about that. So, in the discussion, we would have the respiratory boilerplate. So I had insufficient. We needed, as Dan mentioned, manufacturing, impurities, molecular weight, residual monomer. We need mutagenicity. We need irritation and sensitization at 1.9 percent for the polymethacrylate, which is the most frequently used in the highest concentration of use. And that's what I have for insufficiencies. Does anyone have others?

DR. SNYDER: Well, we just have to qualify that insufficiency, because if there's molecular weights that would suggest that it is absorbed, then we need the 28-day dermal.

DR. BELSITO: Okay. So, then depending on molecular weight in residual monomer?

DR. SNYDER: Correct.

DR. LIEBLER: That's right.

DR. BELSITO: Let me just add that. Anything else on this?

MR. JOHNSON: Dr. Belsito, you said irritation and sensitization data at what concentration?

DR. BELSITO: One point nine for the Polymethacrylate.

MR. JOHNSON: For the Polymethacrylate. Okay.

DR. LIEBLER: And, if we bring in Glyceryl Polyacrylate and it's got uses, if it's higher then, you know, we need to key off of that one.

DR. BELSITO: Right.

MS. FIUME: Typically, the request will go out at maximum concentrations of use.

DR. BELSITO: Okay.

MS. FIUME: Is that wording okay, or --

DR. BELSITO: That's perfect.

MS. FIUME: Okay.

DR. LIEBLER: Yeah.

DR. BELSITO: That would cover the Glycerol if it's used at a higher --

DR. SNYDER: Wouldn't that also be qualified with the monomer content? If we have one that has a high monomer content?

DR. BELSITO: Yeah, but I mean, you would pick that up if, well, I guess -- so, depending upon molecular weight and residual monomer, we may need 28-day dermal toxicity and possibly other endpoints?

DR. SNYDER: Sensitization data or irritation data, yeah.

DR. LIEBLER: Yeah. The monomer usually is not any issue at all. I mean, we need to document it if we can.

If the method of manufacture indicates that the polymer is produced and then describes any sort of use wash or clean up steps, then that's going to mitigate our need for hard data on residual monomer because the acrylates are very volatile.

DR. BELSITO: Right.

DR. LIEBLER: So any residual monomer, you know, is going to evaporate and is going to be removed by wash steps in the cleanup of these. So, depending on what else we get, we can kind of audible on how we handle the monomer, but I don't anticipate it's going to be a problem for us such that we would need data on the monomer per se.

DR. BELSITO: Okay. Any other comments?

MR. JOHNSON: Yeah, Dr. Belsito, you said depending on the molecular weight and residual monomer data, 28-day dermal toxicity data may be needed, any additional data needs based upon that?

DR. BELSITO: Possibly sensitization and irritation, if there's significant monomer.

MR. JOHNSON: Okay. Thank you.

DR. LIEBLER: And, I don't know, I just want to make a comment here, and Jay might be able to tell me. If we're really short on data with these and we need it, this might be an example where there might be other acylate polymers that have similar alphol hydroxyl functional substituents. I don't know if, you know, we probably don't have any in vivo endpoint -- I mean, any, you know, we don't have -- we'll probably not going to have repeat dose and DART and so forth, but I guess, when we look at the data we have, we can consider whether we need any kind of read across.

DR. ANSELL: Yeah, I guess if the question is, are there other members which could contribute data? I mean, we can look at that.

DR. LIEBLER: Okay.

DR. ANSELL: You know, this is the first review. Other than the Polyacrylate, I didn't really have any comments about ingredient additions, but relevant data from other materials would be a good question.

DR. LIEBLER: Okay.

DR. BELSITO: Anything else? Okay.

Cohen Team – September 13, 2021

DR. COHEN: Okay. We'll move on to glyceryl acrylates. This is a draft report. This is the first time we're reviewing this. This assessment is for three derived chemicals. They're used as skin conditioning agents, humectants, and viscosity increasing agents. We have max use reported of 1.9 percent in a leave-on product. We have frequency of use reported. It looks like we

don't have method of manufacturing and impurities. No acute, short-term tox data, no DART, no genotox, and we need irritancy and sensitization at max use. And, Lisa, can we read across this list?

DR. PETERSON: I don't know. Probably some. Let's just go -- there is a method of manufacturing in the report for the glyceryl polymethacrylate.

DR. COHEN: Oh yes. Well --

DR. PETERSON: I think there's a box that needs to be checked, but I do think that -- so the caprylyl glycol/glycerin/polyacrylic acid copolymer, there's no uses. So, again, one could say why should it be in here? There's no data. But my concern about impurities is the presence of unreacted monomers.

DR. COHEN: Yeah.

DR. PETERSON: And so I would want impurities on all. Clearly, probably the method of manufacturing could be read across, but I think we should ask for the one for the 286, the glyceryl acrylate/acrylic acid copolymer. But I thought, yeah, method of manufacturing and impurities. And I thought we could maybe drop the third one.

DR. COHEN: Drop?

DR. PETERSON: Because there's no uses. This gets to the conversation we had earlier. There are no uses. There's no data.

DR. BERGFELD: We don't have to drop it right away. (Inaudible).

DR. SLAGA: (Inaudible) report, though.

DR. PETERSON: Yes. You could ask for this.

DR. HELDRETH: So you mean for caprylyl glycol/glycerin/polyacrylic acid copolymer?

DR. COHEN: Yeah.

DR. HELDRETH: Yes, we have nothing in VCRP, but we did get survey data back suggesting there's at least one use because we got 0.2 percent concentration use in a leave-on.

DR. PETERSON: Okay. I missed that. Then, yes, we need method of manufacturing and impurities. Again, the reason for the impurities is the unreacted starting material would have some irritation or since tissue toxicity is related with it.

DR. SHANK: Can we use the Panel's 2018 report on acrylate copolymers, about 126 of them found to be safe? Can we use that to satisfy some of the toxicology needs for the current compounds? Maybe Lisa and Dan can discuss that tomorrow. If you can, then we don't need all of these toxicology studies. If we cannot, then there are quite a few needs.

DR. COHEN: So that was an acrylate copolymer report in 2018?

DR. SHANK: 2018, yes. There were 126 copolymers reviewed and found to be safe.

DR. COHEN: So that's a bit of a read-across question, no?

DR. SHANK: Yeah.

DR. PETERSON: You mean the glyceryl is not going to -- one might think you could read across unless I'm not seeing -- to me the big issue with these compounds is the presence of the starting material present in the final product, that polymers are going to be huge.

DR. COHEN: So that's the basis for your impurities ask?

DR. PETERSON: Yes.

DR. COHEN: You want to know if there's monomer in there, and then that changes the whole discussion quite a bit.

DR. PETERSON: Well, it's going to impact a lot of things, but yes. But it's worth having a conversation with Dan.

DR. COHEN: Ron, would you go as far as suggesting that the copolymer report of 2018 would obviate the need for sensitization and irritancy data on these?

DR. SHANK: If the chemist agreed that that report can be used for read across.

DR. PETERSON: So is it possible -- I guess I can search for that report and --

DR. SHANK: Okay. If you go on to the CIR site under ingredients, it is listed there as acrylate copolymers.

DR. COHEN: So one question then, could this be an addendum or an update to the existing report? Why is it its own report at this point?

DR. SHANK: That's a good question. That's basically what I was asking. Why weren't these included in 2018? And maybe the question is there are significant differences in the copolymers -- of the monomers, which could be various impurities, like

Dr. Peterson has asked for. But I don't know enough about how these things are put together and cleaned up before they're sold as a polymer.

DR. COHEN: Wilbur or Bart, do we have any insight why this came as a separate report and not 127 through 129 on the other copolymer report? I just don't know.

MR. JOHNSON: I would have to yield to Bart's expertise on that, Dr. Cohen.

DR. COHEN: Bart, are you on?

DR. HELDRETH: I'm here. Off the top of my head, I don't see why it couldn't have been, but maybe this glyceryl functional group was considered to make it different enough to leave them out of this report. But I'm not sure that that --

DR. PETERSON: Yeah. So I'm looking at the report, the other report. And they are mostly all hydrocarbons. They don't have the free alcohol, although there is one that has a carboxylic acid.

DR. COHEN: Oh, glycol.

DR. PETERSON: But there aren't structures for everything, and there's a lot of names. It's going to take time. I mean, there's 126 of them.

DR. HELDRETH: Right.

DR. PETERSON: So there's a lot of structures there to go through. But my guess is that -- well, there's a penta -- a three -- there are some polyols there -- diol; there's some ethylene glycol.

DR. COHEN: So perhaps we can come out with an IDA with the asks that we discussed, which are method of manufacturing for two of the three, impurities for all three, tox DART, genotox for all of them, irritancy and sensitization, and open for a discussion on whether there's a reason to just update the 2018 report and not have this as a separate report. So we can announce the IDA but consider another pathway.

DR. SHANK: Yeah. I like that.

DR. SLAGA: Sounds good.

DR. COHEN: All right, and then the two teams can -- the chemists can hash it out a little bit.

MR. JOHNSON: Excuse me, Dr. Cohen, will you list those data needs again, please?

DR. COHEN: Sure. So we need method of manufacturing for two of the three. We have it for glyceryl polymethacrylate. We need impurities on all three. We need acute and short-term tox, DART, and maybe genotox. And we need irritancy and sensitization at max use.

DR. SHANK: Probably skin penetration if it's available because if these don't -- they're big -- so if they don't penetrate the skin, the epidermis, then you don't need the systemic tox.

DR. COHEN: So that would be direct skin penetration data, not just molecular weight devoid of impurities we worry about?

DR. SHANK: Yes. We have log Kow -- sorry, I was reading something else -- data. Anything that could be used to judge the ability of these to cross the skin.

DR. COHEN: Got it.

MR. JOHNSON: Dr. Cohen, you said genotoxicity data maybe?

DR. COHEN: Well, Tom, would you want the genotox?

DR. SLAGA: Yes. Especially if there's some impurities like the monomer.

DR. COHEN: Okay. Take out "maybe."

MR. JOHNSON: Okay. Thank you.

Full Panel – September 14, 2021

DR. BELSITO: This is the first time we're looking at three ingredients in this report. The SLR was issued on March 5th. We received VCRP data; it's reported to be used in 286 cosmetic products, mainly leave-ons. Three Glyceryl Acrylates are reviewed. Of the three, Glyceryl Acrylate has the greatest reported use frequency. And, in terms of use concentration, Glyceryl Polymethacrylate is the max at 1.9 in leave-on products.

So, looking at the data, our group found that the information was insufficient. We need manufacturing for all -- we need manufacturing except for Polymethacrylate. We need impurities for all three, and depending upon these, other endpoints like reproductive and developmental toxicity may be needed. We need mutagenicity data. We need irritation and sensitization at maximum concentration of use, which is 1.9 for the Polymethacrylate. And depending on molecular weight and residual monomer, we may need 28-day dermal and oscillate sensitization and irritation if that monomer is present in significant amounts.

DR. COHEN: So, I can second that, Don; we really align very well on that. So, without reiterating everything you just said, we have an alternative pathway we thought you might consider, which is, there was an Acrylate Copolymer report of 2018, which assessed the safety of 126 acrylate copolymers some of which were polyols in that report. Would we consider adding an addendum of that report, or we have the other pathway which was exactly how you articulated it.

DR. BERGFELD: Do you have a comment on that, Don?

DR. BELSITO: So it was a 2008 report, David?

DR. COHEN: 18.

DR. BELSITO: So that's not going to be up for re-review until 2033. So, why would we want to open up that whole thing to add these three ingredients?

DR. SHANK: It's not to open it up but to use it as a read across.

DR. LIEBLER: So the data could be --

DR. BELSITO: So Dan and Lisa are going to have to comment on the potential for read across there, I can't.

DR. LIEBLER: Yeah, so, Ron, it's a good idea in that the data for these other copolymers, that would be structurally analogous, could be very useful read across if there are data insufficiencies for this group.

The issue initially here is that even though it's strongly implied that these are polymers, we don't have any information that would confirm their high molecular weight and other sort of basic characterization that we would need anyhow even if we were using read across to fill data gaps. So, we still need that basic information on these.

And then the Council also suggested putting in Glyceryl Polyacrylate, which, as I understand it, was sort of an orphan in a previous report of lower molecular weight glyceryl esters. And it seems like it would belong in this report, so I thought that that would make sense to bring that one in as well.

DR. SHANK: Okay.

DR. PETERSON: I agree with that.

DR. BERGFELD: So it looks like it'll be a stand-alone document? Is that correct?

DR. SNYDER: Yeah, but the suggestion to possibly bring in data for read across is a good one.

DR. BERGFELD: And, David, you agree and your team agrees?

DR. COHEN: Yeah, we agree with Dan's suggestion and Don's motion.

DR. BERGFELD: Okay. So it's quite a long list of needs, and the scientific writer is, who?

MR. JOHNSON: It's Wilbur.

DR. BERGFELD: Oh, it's Wilbur?

MR. JOHNSON: Yes.

DR. BERGFELD: Wilbur, are you clear?

MR. JOHNSON: No, because I don't think I see in Teams the need for skin penetration data was mentioned, and if that occur then developmental and reproductive toxicity data may be needed. So I'm just wondering whether or not that should be stated in that way in this particular need.

DR. LIEBLER: Wilbur, what we really need first is chemical properties definitions. If these are more than 5,000 molecular weight, as I expect they are, the polymers, then we don't need skin penetration; it's not going to penetrate. And then it basically will boil down to irritation and sensitization.

DR. BERGFELD: Okay, any addition to that?

MR. JOHNSON: So just chemical properties particularly molecular weight data are needed.

DR. LIEBLER: Correct.

MR. JOHNSON: And irritation and sensitization data at the maximum use concentration.

DR. LIEBLER: Yeah, if we can get residual monomer that would be very helpful as well.

DR. BERGFELD: So you're asking for impurities.

DR. LIEBLER: Correct.

DR. BELSITO: Yes. So, Wilbur, what we need is manufacturing for the Acrylate/Acrylic Acid Copolymer and the Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer. So, we need manufacturing for those two. We need impurities for all three, particularly residual monomer. And then depending upon the molecular weight and levels of residual monomer, we may need a 28-day dermal or other skin-penetration data on them.

And then, in addition, we're looking for sensitization and irritation for significant monomer, if that exist. Otherwise, if they're high molecular weight compounds, they're not going to penetrate the skin, really the only thing we'd be interested in would be potentially irritation. But we can ask for sensitization.

MR. JOHNSON: Dr. Belsito, (audio skip) skin irritation and irritation for significant monomer?

DR. BELSITO: No, well, there are two separate parts to it, Wilbur. We're asking -- although we may not really need it at this point it's a first look -- we're asking for sensitization and irritation at the max concentration of use, which is 1.9 percent for the Polymethacrylate.

MR. JOHNSON: Uh-huh.

DR. BELSITO: And then if there's significant residual monomer, we may want to -- and say the Polymethacrylate doesn't have significant residual monomer, but the Acrylate/Acrylic Acid Copolymer does, then we would want information on sensitization and irritation for that specific residual monomer.

What we really need right now are the impurities, molecular weight, and residual monomers, sensitization, irritation for the Polymethacrylate at highest concentration of use. And then depending upon this information, other toxicity endpoints may be needed.

MR. JOHNSON: Okay. Just one more point of clarification. The skin sensitization and irritation data are on the Polymethacrylate only, or for all three ingredients?

DR. BELSITO: No, right now at the finished product it's for the Polymethacrylate at 1.9 percent.

MR. JOHNSON: Okay, thank you.

DR. LIEBLER: And, Wilbur, I can add that if you can't get irritation and sensitization on any of these, we can still consider the previous report that Ron Shank mentioned where we have a structurally analogous polymer that we can consider. And that we would need to take a look at that, at the structures and data for those. But that's a possibility to address a data gap for the skin endpoints.

MR. JOHNSON: Okay, thank you.

DR. BELSITO: Monice?

DR. BERGFELD: Wilbur should do that right away?

MS. FIUME: I just have a question. Since Glyceryl Polyacrylate has been added, for the purposes of the conversation of the data needs, is that ingredient included with all of the data needs, does that amend the list at all for the IDA if we're adding that ingredient to the report?

DR. LIEBLER: We don't know what the data are for it, so if it has all those data -- I don't know if it has all those data needs or if it comes with data that supported it you can look at that and decide which ones are still needed.

MS. FIUME: Okay. Yeah, I do know the previously report --

MR. JOHNSON: Dr. Liebler, they're --

MS. FIUME: Go ahead, Wilbur.

MR. JOHNSON: I was just going to say that in the -- Glyceryl Polyacrylate is included in the report on glyceryl monoesters. And, that report does not include any safety test data on Glyceryl Polyacrylate.

DR. LIEBLER: Okay. So it's part of the data needs then.

MS. FIUME: Thank you.

MR. JOHNSON: Okay, thank you.

DR. BERGFELD: Monice, do you have something else?

MS. FIUME: Nope, that was it.

DR. BERGFELD: So, we're going out for an insufficient data announcement, and I think we've clarified what the needs are and what we're requesting. Does anyone else have a comment about that before we call the vote? Okay, going to call the vote then, those opposing? Abstaining? Unanimously accepted IDA report on this ingredient.

Safety Assessment of Glyceryl Acrylates as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: February 11, 2022
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: Lisa, A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., former Senior Scientific Analyst/Writer, and Regina Tucker, Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

aq.	aqueous
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
FDA	Food and Drug Administration
FHSLA	Federation of Health Science Library Associations
HRIPT	human repeated insult patch test
NR	not reported
Panel	Expert Panel for Cosmetic Ingredient Safety
PII	primary irritation index
SIOPT	single-insult occlusive patch test
SLS	sodium lauryl sulfate
VCRP	Voluntary Cosmetic Registration Program
wINCI	web-based *International Cosmetic Ingredient Dictionary and Handbook*
US	United States

DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 4 glyceryl acrylates as used in cosmetic formulations. Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer and Glyceryl Acrylate/Acrylic Acid Copolymer are both reported to function in cosmetics as skin-conditioning agents, and Glyceryl Polyacrylate and Glyceryl Polymethacrylate as film formers. The Panel considered the available data and concluded [TBD]).

INTRODUCTION

The safety of the following 4 glyceryl acrylates as used in cosmetics is reviewed in this safety assessment:

Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer
Glyceryl Acrylate/Acrylic Acid Copolymer
Glyceryl Polyacrylate
Glyceryl Polymethacrylate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer and Glyceryl Acrylate/Acrylic Acid Copolymer are both reported function in cosmetics as a skin-conditioning agents; Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer is also reported to function as a humectant, and Glyceryl Acrylate/Acrylic Acid Copolymer as a viscosity increasing agent (Table 1).[1] Glyceryl Polyacrylate and Glyceryl Polymethacrylate are both reported to function in cosmetics as a film former.

The safety of Glyceryl Polyacrylate as used in cosmetics was previously reviewed by the Expert Panel for Cosmetic Ingredient Safety (Panel). In 2004, the Panel published a report, concluding that Glyceryl Polyacrylate is safe as a cosmetic ingredient in the present practices of use and concentration [described in that report].[2] Additionally, in 2018, the Panel issued a final amended report on 126 acrylates copolymers (not glyceryl) with the following conclusion, "Acrylates copolymers are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating."[3]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://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 Structure

Two ingredients defined as copolymers, i.e., Caprylyl Glycol/Glycerin/ Polyacrylic Acid Copolymer and Glyceryl Acrylate/Acrylic Acid Copolymer, and two esters of glycerin, i.e., Glyceryl Polyacrylate and Glyceryl Polymethacrylate, are reviewed in this safety assessment.[1] These ingredients are each vinyl-type polymers, resulting from the esterification of acrylic acid or methacrylic acid with glycerin. The figure for Glyceryl Polymethacrylate, an ester of glycerin and polymethacrylic acid, is depicted in Figure 1.

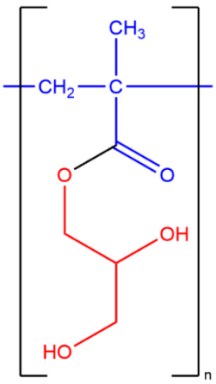


Figure 1. Glyceryl Polymethacrylate

The definitions, idealized structures, and available CAS Nos. of the glyceryl acrylates included in this safety assessment are presented in Table 1.

Chemical Properties

According to one supplier, Glyceryl Polyacrylate has a molecular weight > 500,000 Da.[4] Properties data on a Glyceryl Acrylate/Acrylic Acid Copolymer trade name mixture, but not on the ingredient alone, were found and are presented in Table 2. This mixture (which contains 1.71 – 2.09% Glyceryl Acrylate/Acrylic Acid Copolymer, 36.5 – 44.6% glycerin, 50- 62% water, and 0.85 – 1.1% propylene glycol) is water-soluble and has a relative density of 1.15 g/ml.[5]

Method of Manufacture

Glyceryl Polymethacrylate

According to one paper, the mixing of 4-aminocarbonylazo-2-pyrimidinone with mildly acidic solutions of 1-glyceryl methacrylate resulted in polymerization to Glyceryl Polymethacrylate.[6]

Method of manufacture data on glyceryl acrylates for use in cosmetics were not found in the published literature, and unpublished data were not provided.

Impurities

Glyceryl Acrylate/Acrylic Acid Copolymer

Potential impurities of Glyceryl Acrylate/Acrylic Acid Copolymer include acrylic acid (< 5 ppm), methyl vinyl ether (< 0.5 ppm), and maleic acid (< 5 ppm).[7]

Glyceryl Polyacrylate

Glyceryl Polyacrylate may contain < 5 ppm residual acrylic acid.[4]

USE

Cosmetic

The safety of glyceryl acrylates is evaluated based on data received from the US 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. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2022 FDA VCRP data, Glyceryl Acrylate/Acrylic Acid Copolymer has the greatest frequency of use; it is reported to be used in 295 cosmetic products, 288 of which are leave-on products (Table 3).[8] The results of concentration of use surveys conducted by the Council, and provided to CIR in 202,1 indicate that Glyceryl Polymethacrylate has the highest concentration of use; it is used at maximum use concentrations up to1.9% in leave-on products (body and hand products).[9,10] The frequency of use of Glyceryl Polyacrylate has increased since it was originally reviewed by the Panel; in 1998, 1 use was reported,[2] and in 2022, 119 uses are reported[8] (Table 4). The maximum reported concentration of use of Glyceryl Polyacrylate has decreased slightly since the original review; in 1999, this ingredient was reported to be used at a maximum of 2% in face and neck creams, lotions, powders, and sprays,[2] and in 2001, it was reported to have a maximum use concentration of 0.99% in face and neck products (not sprays).[10]

Cosmetic products containing glyceryl acrylates may incidentally come in contact with the eyes (e.g., Glyceryl Acrylate/Acrylic Acid Copolymer at concentrations up to 0.62% in eye lotions), and 3 of these 4 ingredients are also used in products are reported to be used in formulations that come in contact with mucous membranes (concentrations not stated). Additionally, the potential for incidental ingestion exists with these ingredients; Glyceryl Acrylate/Acrylic Acid Copolymer is reported to be used in 12 lipstick formulations (concentration not stated). Use in baby products is also reported (e.g., Glyceryl Polyacrylate is used at up to 0.09% in baby lotions, oils, and creams.)

Some of these ingredients are used in cosmetic products that could possibly be inhaled. For example, Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer is reported to be used at a maximum concentration of 0.2% in perfumes, and Glyceryl Polymethacrylate (concentration not reported) is reported to be used in face powders. 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.[11,12] 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.[13,14] 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.[15-17]

The glyceryl acrylates reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[18]

Non-Cosmetic

Glyceryl Polymethacrylate – collagen composite hydrogels have been developed for implantation in surgical lesions of the rat brain. Such materials provide porous matrices that can serve as support systems for growth of scar tissue and axonal growth.[19,20] It has been noted that this technology has considerable potential for basic as well as for clinical research in central nervous system regeneration. Other reported uses of Glyceryl Polymethacrylate include autoclavable lubricant and moisturizer for medical and surgical use.[21]

TOXICOKINETIC STUDIES

Toxicokinetic data on glyceryl acrylates were not found in the published literature, and unpublished data were not provided.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Glyceryl Acrylate/Acrylic Acid Copolymer

The acute oral toxicity of Glyceryl Acrylate/Acrylic Acid Copolymer was evaluated in rats (number of animals not provided).[7] Fasted animals were dosed by gavage with up to 5 g/kg, and observed fore 14 d; no mortality was reported. The oral LD_{50} of Glyceryl Acrylate/Acrylic Acid Copolymer was > 5 g/kg in rats.

Short-Term, Subchronic, and Chronic Toxicity Studies

Repeated dose toxicity studies on glyceryl acrylates were not found in the published literature, and unpublished data were not provided.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity data on glyceryl acrylates were not found in the published literature, and unpublished data were not provided.

GENOTOXICITY STUDIES

In Vitro

Glyceryl Acrylate/Acrylic Acid Copolymer

The mutagenic potential of Glyceryl Acrylate/Acrylic Acid Copolymer was evaluated in an Ames test using *Salmonella typhimurium* TA97a, T98, TA100, and TA102, and TA1535.[7] A concentration of 5000 µg/plate was tested with and without metabolic activation. Vehicle and positive controls were used; however, the control substances were not identified. Glyceryl Acrylate/Acrylic Acid Copolymer was not mutagenic.

Glyceryl Polyacrylate

An Ames test was conducted on 1.9% Glyceryl Polyacrylate.[4] The test substance was not mutagenic. No details were provided.

CARCINOGENICITY STUDIES

Carcinogenicity data on glyceryl acrylates were not found in the published literature, and unpublished data were not provided.

OTHER RELEVANT STUDIES

Effect on Burn-Wound Healing

Glyceryl Polymethacrylate

Eight domestic pigs were subjected to burn wounds in the paravertebral area. Some wounds were exposed to an experimental cream, and other wounds served as air-exposed controls.[22] The cream consisted of Glyceryl Polymethacrylate in an oil-in-water emulsion with the following components: fibronectin (40 ppm), proline, arginine, and glycine. Beginning on day 0 (day of wounding), the wounds were treated once daily with the cream (~ 0.2 g/wound site) to completely cover the wound until healing was complete. The wounds treated with the cream developed a soft eschar, when compared to air-exposed control wounds. Erythema was not observed after application of the cream.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal irritation and sensitization studies are described in Table 5, and summarized below.

In rabbits, application of an occlusive patch of Glyceryl Acrylate/Acrylic Acid Copolymer (applied neat) for 24 h was not irritating.[7] In clinical single insult occlusive patch tests (SIOPT), a product containing 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer (23 subjects)[23] and a product containing 7.7% Glyceryl Polymethacrylate (19 subjects)[24] were non-irritating; the primary irritation index (PII) in each study was 0 and 0.05, respectively.

Glyceryl Acrylate/Acrylic Acid Copolymer (tested neat; 55 subjects; occlusive patch),[7] a product containing 0.5% Glyceryl Polyacrylate (100 subjects; semi-occlusive patch),[25] and Glyceryl Polyacrylate (1.9%; 51 subjects; patch type not specified)[4] were not irritants or sensitizers in human repeated insult patch tests (HRIPT). Sensitization also was not observed in maximization assays with a product containing 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer (25 subjects)[26] and a product containing 7.7% Glyceryl Polymethacrylate (17 subjects).[27]

OCULAR IRRITATION STUDIES

Animal

Glyceryl Acrylate/Acrylic Acid Copolymer

The ocular irritation potential of Glyceryl Acrylate/Acrylic Acid Copolymer was evaluated following instillation of 0.1 ml of the test substance into the conjunctival sac of one eye of each of 6 albino rabbits; the eyes were not rinsed.[7] The contralateral eye served as a control. Each eye was evaluated after 24, 48, and 72 h, and no signs of irritation were observed. Glyceryl Acrylate/Acrylic Acid Copolymer was not irritating to the eyes of rabbits.

MUCOUS MEMBRANE IRRITATION STUDIES

Animal

Glyceryl Acrylate/Acrylic Acid Copolymer

The vaginal mucosal irritation potential of Glyceryl Acrylate/Acrylic Acid Copolymer was evaluated using groups of 6 albino rabbits.[7] The test material (1.0 ml) was applied to the vaginal orifice of the animals, and the animals were observed 5x/d for 7 d for gross signs of edema, erythema, and excretion. For the negative controls, the tip of an empty 1.0 ml syringe was inserted. Glyceryl Acrylate/Acrylic Acid Copolymer was not irritating to the vaginal mucosa of rabbits; the mucosal irritation index was 0.

SUMMARY

The safety of 4 glyceryl acrylates as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer and Glyceryl Acrylate/Acrylic Acid Copolymer are both reported to function in cosmetics as skin-conditioning agents, and Glyceryl Polyacrylate and Glyceryl Polymethacrylate as film formers.

The mixing of 4-aminocarbonylazo-2-pyrimidinone with mildly acidic solutions of 1-glyceryl methacrylate was reported to result in polymerization to Glyceryl Polymethacrylate. According to data submitted by industry, both Glyceryl Acrylate/ Acrylic Acid Copolymer and Glyceryl Polyacrylate may contain < 5 ppm residual acrylic acid. Glyceryl Acrylate/Acrylic Acid Copolymer may also contain methyl vinyl either (< 0.5 ppm) and maleic acid (< 5 ppm).

According to 2022 FDA VCRP data, Glyceryl Acrylate/Acrylic Acid Copolymer has the greatest frequency of use; it is reported to be used in 295 cosmetic products (288 leave-on products and 7 rinse-off products). The results of a concentration of use surveys provided by the Council in 2021 indicate Glyceryl Polymethacrylate has the highest concentration of use; it is used at maximum use concentrations up to1.9% in leave-on products.

The acute oral toxicity of Glyceryl Acrylate/Acrylic Acid Copolymer was evaluated in rats; the test article was administered by gavage. The oral LD_{50} was > 5 g/kg.

The mutagenic potential of Glyceryl Acrylate/Acrylic Acid Copolymer and 1.9% Glyceryl Polyacrylate were evaluated in the Ames test. Neither substance was mutagenic.

Eight domestic pigs were subjected to burn wounds in the paravertebral area. The wounds were exposed to an experimental cream that consisted of Glyceryl Polymethacrylate in an oil-in-water emulsion. Daily treatment with the cream (~ 0.2 g/wound site) was continued until wound healing was complete. Application of the cream resulted in a soft eschar, but erythema was not observed.

In rabbits, application of an occlusive patch of Glyceryl Acrylate/Acrylic Acid Copolymer (applied neat) for 24 h was not irritating. In clinical SIOPTs, a product containing 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer (23 subjects) and a

product containing 7.7% Glyceryl Polymethacrylate (19 subjects) were non-irritating; the PII in each study was 0 and 0.05, respectively.

In an HRIPT, Glyceryl Acrylate/Acrylic Acid Copolymer (tested neat; 55 subjects; occlusive patch), a product containing 0.5% Glyceryl Polyacrylate (tested neat; 100 subjects; semi-occlusive patch), and Glyceryl Polyacrylate (1.9%; 51 subjects; patch type not specified) were not irritants or sensitizers. Sensitization also was not observed in maximization assays with a product containing 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer (25 subjects) and a product containing 7.7% Glyceryl Polymethacrylate (17 subjects).

Glyceryl Acrylate/Acrylic Acid Copolymer was not irritating to rabbit eyes. It also was non-irritating when applied to the vaginal mucosa of rabbits.

DRAFT DISCUSSION

[Note: This Discussion is in draft form, and changes will be made following the Panel meeting.]

This assessment reviews the safety of 4 glyceryl acrylates as used in cosmetic formulations. The Panel reviewed the available data and concluded [TBD].

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer is reported to be used at up to 0.2% in perfumes, and Glyceryl Polymethacrylate (concentrations unavailable) is reported to be used in face powders). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

To be determined.

TABLES

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

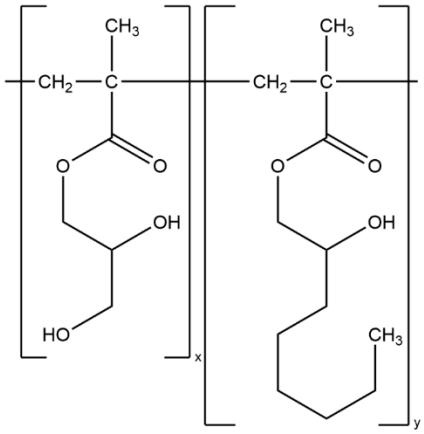
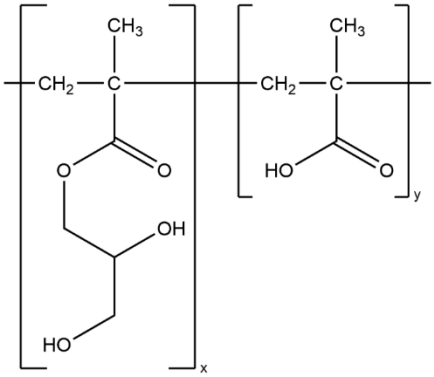
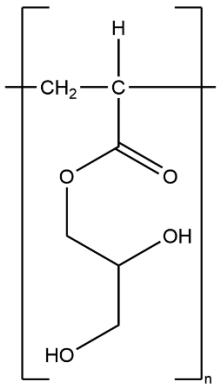
Ingredient/CAS No.	Definition & Structures	Function(s)
Caprylyl Glycol/Glycerin/ Polyacrylic Acid Copolymer	Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer is a copolymer of caprylyl glycol, glycerin, and polyacrylic acid monomers  *Drawn as a simple block-type copolymer for demonstration; other monomer connectivity patterns possible.*	humectant; skin-conditioning agent - emollient
Glyceryl Acrylate/Acrylic Acid Copolymer	Glyceryl Acrylate/Acrylic Acid Copolymer is a copolymer of glyceryl acrylate and acrylic acid  *Drawn as a simple block-type copolymer for demonstration; other monomer connectivity patterns possible.*	skin-conditioning agent - humectant; viscosity increasing agent - aqueous
Glyceryl Polyacrylate 104365-75-5	Glyceryl Polyacrylate is the ester of glycerin and polyacrylic acid 	film former

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

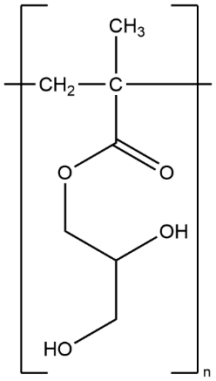
Ingredient/CAS No.	Definition & Structures	Function(s)
Glyceryl Polymethacrylate 146126-21-8 28474-30-8	Glyceryl Polymethacrylate is the ester of glycerin and polymethacrylic acid 	film former

Table 2. Chemical properties

Property	Value/Results	Reference
Glyceryl Acrylate/Acrylic Acid Copolymer trade name mixture (also containing glycerin, water, and propylene glycol)		
Form	Clear, colorless viscous gel	
Solubility	Water-soluble	
Relative density (g/ml)	1.15	
Viscosity (cps)	250,000 – 350,000	
Melting point (ºC)	< 0	
Boiling point (ºC)	> 100	

Table 3. Frequency (2022)[8] and concentration (2020)[9,10] of use according to duration and type of exposure.

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Caprylyl Glycol/Glycerin/ Polyacrylic Acid Copolymer		Glyceryl Acrylate/Acrylic Acid Copolymer		Glyceryl Polymethacrylate	
Totals*/Conc. Range	**NR**	**0.2**	**295**	**0.00001-0.62**	**142**	**0.048 – 1.9**
Duration of Use						
Leave-On	*NR*	*0.2*	*288*	*0.00001-0.62*	*138*	*0.048 – 1.9*
Rinse off	*NR*	*NR*	*7*	*0.012-0.42*	*4*	*NR*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	24	0.035-0.62	9	NR
Incidental Ingestion	NR	NR	12	NR	NR	NR
Incidental Inhalation- Sprays	NR	0.2	88[a];131[b]	0.012-0.62[a]	54[a];49b	NR
Incidental Inhalation- Powders	NR	NR	131[b]; 1[c]	0.02-0.1[c]	1;40[b]	0.08-1.9[c]
Dermal Contact	NR	0.2	278	0.00001-0.62	142	0.08-1.9
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	4	NR	NR	NR
Mucous Membrane	NR	NR	13	NR	1	NR
Baby Products	NR	NR	1	NR	NR	NR

NR = Not Reported

* 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 these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories

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

Table 4. Current and historical frequency and concentration of use of Glyceryl Polyacrylate

	# of Uses		Max Conc of Use (%)	
	2022[8]	**1998[2]**	**2021[10]**	**1999[2]**
Totals*/Conc. Range	**119**	**1**	**0.008 – 0.99**	**0.2 – 2**
Duration of Use				
Leave-On	*110*	*1*	*0.0099 – 0.99*	*0.2 – 2*
Rinse-Off	*9*	*NR*	*0.008 – 0.4*	*0.4*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	15	NR	0.25 – 0.5	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	47[a]; 19[b]	1[b]	0.01[a]	0.2[a]; 2[b]
Incidental Inhalation-Powder	19[b]	1[b]	0.09[c]	2[b]
Dermal Contact	118	1	0.008 – 0.99	2
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	0.01	0.2 – 0.4
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR
Baby Products	NR	NR	0.0099 – 0.09	NR

NR = Not Reported

* 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 these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories

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

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL					
Irritation					
Glyceryl Acrylate/Acrylic Acid Copolymer	0.5 ml or 0.5 g; applied neat	6 rabbits	Primary skin irritation testing conducted according to FHSLA, 16 CFR 1500.41. The trunk of each animal was clipped free of hair, and 2.5 cm^2 patches were placed on intact and abraded skin. The trunk of each animal was wrapped with rubberized elastic cloth, and neck collars were placed on the animals. All test sites were evaluated 24 and 72 h after application.	PII = 0.0 not a primary irritant	7
HUMAN					
Irritation					
product containing 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer	tested neat	23 subjects	SIOPT (24 h); a reference control was used (no additional details provided)	PII = 0 no irritation reported for any of the subjects	23
product containing 7.7% Glyceryl Polymethacrylate	tested neat	19 subjects	SIOPT (24 h); a reference control was used (no additional details provided)	PII = 0.05 no irritation in 18 subjects; score of 1 observed for 1 subject	24
Sensitization					
product containing 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer	0.05 ml; tested neat	25 subjects	maximization assay. During induction, an occlusive patch with 0.25% aq. SLS was applied for 24 h; upon removal, an occlusive patch with test article was applied to the same site for 48 h (72 h on weekends). This sequence was repeated for a total of 5 induction exposures. After a 10-d non-treatment period, a previously-untreated site was pretreated with 1% SLS for1 h under an occlusive patch; upon removal, a challenge patch containing the test material was applied to the site for 48 h. The challenge site was scored upon patch removal, and 24 h after removal. Protocol deviations included no SLS pretreatment prior to the last induction patch, due to a scheduling issue.	not a sensitizer; no adverse reactions were observed during the study	26
Glyceryl Acrylate/Acrylic Acid Copolymer	0.2 g; tested neat	55 subjects	HRIPT. During induction, nine 24-h occlusive patches were applied (3x/wk for 3 wk). After a 2-wk non-treatment period, challenge patches were applied for 24 h to a previously untreated site on the back of each subject, and the challenge sites were evaluated 24 and 72 h after patching.	not an irritant or a sensitizer; no significant dermal reactions were observed.	7
product containing 0.5% Glyceryl Polyacrylate	0.2 ml; tested neat	100 subjects	HRIPT. Same HRIPT protocol as described above, with the exception that the patches (2 cm^2) were semi-occlusive, and challenge sites were evaluated 48 and 72h after patching	not a sensitizer During induction: 1 subject discontinued due to experiencing definite erythema and edema after the 5th induction patch; definite erythema, no edema was reported for .9% of the subjects; minimal or doubtful response was recorded for 9.6% of the subjects	25
Glyceryl Polyacrylate	1.9%	51 subjects	HRIPT (details were not provided)		4
product containing 7.7% Glyceryl Polymethacrylate	0.05 ml; tested neat	27 subjects	maximization assay. Same maximization assay protocol as described above, with the exception that 5% SLS was used for pre-treatment at challenge, and no protocol deviations occurred	not a sensitizer; no adverse reactions were observed during induction	27

Abbreviations: aq. – aqueous; CFR – Code of Federal Regulations: FHSLA - Federation of Health Science Library Associations; HRIPT – human repeated insult patch test; PII – primary irritation index; SIOPT – single-insult occlusive patch test; SLS – sodium lauryl sulfate.

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Final Report of the Amended Safety Assessment of Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate[1]

The safety of 43 glyceryl monoesters listed as cosmetic ingredients was reviewed in a safety assessment completed in 2000. Additional safety test data pertaining to Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate were received and served as the basis for this amended report. Glyceryl monoesters are used mostly as skin-conditioning agents—emollients and/or surfactant—emulsifying agents in cosmetics. The following 20 glyceryl monoesters are currently reported to be used in cosmetics: Glyceryl Laurate, Glyceryl Alginate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Cocoate, Glyceryl Erucate, Glyceryl Hydroxystearate, Glyceryl Isostearate, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Myristate, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Stearate/Acetate, and Glyceryl Undecylenate. Concentration of use data received from the cosmetics industry in 1999 indicate that Glyceryl Monoesters are used at concentrations up to 12% in cosmetic products. Glyceryl Monoesters are not pure monoesters, but are mostly mixtures with mono-, di-, and tri-esters. The purity of commercial and conventional Monoglyceride (Glyceryl Monoester) is a minimum of 90%. Glyceryl Monoesters (monoglycerides) are metabolized to

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free fatty acids and glycerol, both of which are available for the resynthesis of triglycerides. Glyceryl Laurate enhanced the penetration of drugs through cadaverous skin and hairless rat skin in vitro and has been described as having a wide spectrum of antimicrobial activity. A low-grade irritant response was observed following inhalation of an aerosol containing 10% Glyceryl Laurate by test animals. Glyceryl monoesters have little acute or short-term toxicity in animals, and no toxicity was noted following chronic administration of a mixture consisting mostly of glyceryl di- and mono- esters. Glyceryl Laurate did have strong hemolytic activity in an in vitro assay using sheep erythrocytes. Glyceryl Laurate, Glyceryl Isostearate, or Glyceryl Citrate/Lactate/Linoleate/Oleate were not classified as ocular irritants in rabbits. Undiluted glyceryl monoesters may produce minor skin irritation, especially in abraded skin, but in general these ingredients are not irritating at concentrations used in cosmetics. Glyceryl monoesters are not sensitizers, except that Glyceryl Rosinate and Hydrogenated Glyceryl Rosinate may contain residual rosin, which can cause allergic reactions. These ingredients are not photosensitizers. Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic in the Ames test system. Glyceryl Laurate exhibited antitumor activity and Glyceryl Stearate was negative in a tumor promotion assay. At concentrations higher than used in cosmetics, Glyceryl Laurate did cause moderate erythema in human repeat-insult patch test (RIPT) studies, but the other glyceryl monoesters tested failed to produce any significant positive reactions. Glyceryl Rosinate was irritating to animal skin at 50%, but did not produce sensitization in clinical tests at concentrations up to 10% and covered with semioccluded patches. There is reported use of Glyceryl Rosinate at 12% in mascara, which is somewhat higher than the concentration in the clinical testing. It was reasoned that the available data do support the safety of this use because there would be minimal contact with the skin and no occlusion. The safety of Arachidonic Acid was not documented and substantiated for cosmetic product use in an earlier safety assessment and those same safety questions apply to Glyceryl Arachidonate. Based on these data, the Cosmetic Ingredient Review (CIR) Expert Panel found that these glyceryl monoesters are safe as cosmetic ingredients in the present practices of use and concentration: except that the available data are insufficient to support the safety of Glyceryl Arachidonate. Additional data needed to support the safety of Glyceryl Arachidonate include (1) dermal absorption data; and, based on the results of the absorption studies, there may be a need for (2) immunomodulatory data; (3) carcinogenicity and photocarcinogenicity data; and (4) human irritation, sensitization, and photosensitization data.

INTRODUCTION

Glyceryl monoesters are a group of ingredients comprising esters of glycerin and assorted fatty acids or fatty acid derivatives. The 43 glyceryl monoesters listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Pepe et al. 2002), which have uses in a wide variety of cosmetic products, mostly as conditioning agents, are included in this safety assessment. A final safety assessment of glyceryl monoesters was updated with additional safety test data for Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate and an amended conclusion was reached.

Only 16 of the 43 ingredients were reported to the U.S. Food and Drug Administration (FDA) by industry as being used in cosmetics, but data received directly from industry indicate that an additional 4 ingredients are being used in cosmetics. If ingredients that are currently not used were to be used in the future, the Cosmetic Ingredient Review (CIR) Expert Panel expects that the types of products and the concentrations used would be similar to those in current use.

Safety test data are available for only a limited number of ingredients. The CIR Expert Panel also considered safety assessments of related ingredients to be relevant. These include the earlier safety assessments of Glyceryl Stearate and Glyceryl Stearate SE (Elder 1982), Glyceryl Oleate (Elder 1986), and Arachidonic Acid (Andersen 1993).

CHEMISTRY

Chemical and Physical Properties

The glyceryl monoesters of fatty acids are primarily white to yellow oils or oily waxes with faint fatty odors. These substances are not pure monoesters, but are mixtures with mono-, di-, and tri-ester contents of approximately 4:4:2 (Unichema International 1997b). Danisco Ingredients (1999c, 1999d) guarantees that the purity of their commercial and conventional Monoglyceride is a minimum of 90%.

The octanol/water partition coefficient (K_{ow}) is normally a measured value defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. The partition coefficient is normally represented by its $\log_{10}$ value.

The octanol/water partition coefficient may be calculated. One method for calculating $\log(K_{ow})$ involves the use of fragment constants (Leo, Hansch, and Elkins 1971; Lyman, Reehl, and Rosenblatt 1982). The development of a method for calculation of $\log(K_{ow})$ for glycerol monoesters is based on the known values of glycerol monoacetate and glycerol monobutyrate. Knowing these values, the fragment-constant of the glycerol-ester part can be calculated. From this value, the $\log(K_{ow})$ of any glycerol monoester can be calculated using the chain-length and the number of double bonds (DB) of the acid part.

Physical properties of glyceryl monoesters are listed in Table 1.

These ingredients may be supplied as trade mixtures. The physical properties of one such trade mixture (50% Gylceryl Rosinate with 50% octyldecyl myristate) are shown in Table 2.

Further descriptions of the ingredients in this safety assessment follow.

Glyceryl Laurate (CAS nos. 142-18-7 and 27215-38-9) is the monoester of glycerin and lauric acid that conforms generally to the formula (Pepe, Wenninger, and McEwen 2002):

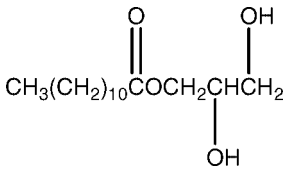


TABLE 1
Physical properties of Glyceryl Monoesters

Property	Description	Reference
	Glyceryl Laurate	
Form	Cream-colored paste	Lewis 1993
	White crystalline	Hüls America, Inc., no date
	White to cream-colored powder	Henkel KgaA 1996
	Off-white pellets	Danisco Ingredients 1996
Solubility	Dispersable in water; soluble in methanol, ethanol, toluene, naphtha, mineral oil, cottonseed oil, and ethyl acetate	Lewis 1993
	Practically insoluble in water; hardly soluble to readily soluble in acetone, diethyl ether, and heptane	Hüls America, Inc., no date
Odor	Faint	Lewis 1993
	Faint, fatty odor	Hüls America, Inc., no date
Molecular weight	274.4	Kabara 1984
Melting point	23–27°C	Scientific & Technical Information Network (STN) International 1997
	56–60°C	Hüls America, Inc., no date Henkel KgaA 1996
Dropping point	56°C	Hüls America, Inc., no date Henkel KgaA 1996
Density	0.98	Lewis 1993
pH	8.0–8.6 (25°C for 5% aqueous dispersion)	Lewis 1993
	4–5 (10% in methanol/water 1:1)	Hüls America, Inc., no date
Hydroxyl value	395	Danisco Ingredients 1996
Iodine value	5–8	Lewis 1993
	2% max. (based on I_2)	Hüls America, Inc., no date Henkel KgaA 1996
	<1	Danisco Ingredients 1996
Iodine color	3 mg/100 ml max. (based on I_2)	Hüls America, Inc., no date
Saponification value	200–206	STN International 1997
	195–205 mg KOH/g	Hüls America, Inc., no date Henkel KgaA 1996
	205	Danisco Ingredients 1996
Acid value	3 mg KOH/g max.	Hüls America, Inc., no date
	3% max.	Henkel KgaA 1996
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Behenate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 288 nm and 290 nm	Danisco Ingredients 1999e
	Glyceryl Caprate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 287 nm and 291 nm	Danisco Ingredients 1999e
	Glyceryl Caprylate	
Form	White crystalline	Hüls America, Inc., no date
Solubility	Practically insoluble in water; hardly soluble to readily soluble in various water/ethanol mixtures; readily soluble in acetone, diethyl ether, and heptane	Hüls America, Inc., no date
Iodine value	1 g/100 g max. (based on I_2)	Hüls America, Inc., no date
Iodine color	3 mg/100 ml max. (based on I_2)	Hüls America, Inc., no date
Saponification value	245–265 mg KOH/g	Hüls America, Inc., no date
Acid value	3 mg KOH/g max.	Hüls America, Inc., no date

(Continued on next page)

TABLE 1
Physical properties of Glyceryl Monoesters *(Continued)*

Property	Description	Reference
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Caprylate/Caprate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Citrate/Lactate/Linoleate/Oleate	
Form	Viscous, yellowish liquid	Hüls America, Inc., no date
Odor	Odor likened to soya bean oil; neutral taste	Hüls America, Inc., no date
pH	6–7 (10% in water)	Hüls America, Inc., no date
Saponification value	230–250 mg KOH/g	Hüls America, Inc., no date
Acid value	15 mg KOH/g max.	Hüls America, Inc., no date
	Glyceryl Cocoate	
Form	White to slightly yellowish liquid	Hüls America, Inc., no date
Solubility	Practically insoluble in water; hardly soluble to soluble in variouys water/ethanol mixtures; readily soluble in acetone, soluble in diethyl ether, and hardly soluble in heptane	Hüls America, Inc., no date
Odor	Odor likened to coconut oil	Hüls America, Inc., no date
Melting point	31–37°C	Hüls America, Inc., no date
Iodine value	3 g/100 g max. (based on I_2)	Hüls America, Inc., no date
Iodine color	5 mg/100 ml max. (based on I_2)	Hüls America, Inc., no date
Saponification value	200–300 mg KOH/g	Hüls America, Inc., no date
Acid value	2 mg KOH/g max.	Hüls America, Inc., no date
	Glyceryl Collagenate	
Appearance	Clear to hazy amber liquid	Brooks Industries 1998
Odor	Proteinaceous odor	Brooks Industries 1998
Solubility	At 5%, soluble in water, glycerine, 40% aqueous alcohol, sodium lauryl sulfate, and cocamidopropyl betaine	Brooks Industries 1998
Specific gravity at 20°C	1.2	Brooks Industries 1998
Boiling point	215°C	Brooks Industries 1998
% volatile by volume	80%	Brooks Industries 1998
	Glyceryl Erucate	
Calculated Octanol/water partition coefficient ($\log(K_{ow})$)	8.61	Danisco Ingredients 1999a
UV absorption	λ_{max} at 238 nm; λ_{min} at 287 nm and 291 nm	Danisco Ingredients 1999e
	Glyceryl Isostearate	
Form	Crystals; color <6 on Gardner scale	Gattefossé 1998
Odor	Faint	
Specific gravity at 20°C	0.930 to 0.970	Gattefossé 1998
Refractive index at 20°C	1.455 to 1.475	Gattefossé 1998
Viscosity at 20°C	0.7 to 1.2 Pa	Gattefossé 1998
Hydroxyl value	180–280 mg KOH/g	Gattefossé 1998
Iodine value	<15 g/100 g (based on I_2)	Gattefossé 1998
Saponification value	150–170 mg	Gattefossé 1998
Acid value	<4 mg KOH/g	Gattefossé 1998
	Glyceryl Linoleate	
Form	Crystals obtained from benzene as solvent	Lide and Frederikse 1993
	Soft plastic	Danisco Ingredients 1996
Solubility	Soluble in ether, benzene, and chloroform	Lide and Frederikse 1993

(Continued on next page)

TABLE 1
Physical properties of Glyceryl Monoesters *(Continued)*

Property	Description	Reference
Refractive index	1.4758 at 20°C	Lide and Frederikse 1993
Molecular weight	354.53	Lide and Frederikse 1993
Melting point	14.5°C	Lide and Frederikse 1993
	45°C (completely melted)	Danisco Ingredients 1996
Hydroxyl value	310	Danisco Ingredients 1996
Iodine value	105	Danisco Ingredients 1996
Saponification value	160	Danisco Ingredients 1996
UV absorption	λ_{max} at 238 nm; λ_{min} at 270 nm	Danisco Ingredients 1999e
	Glyceryl Myristate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 293 nm	Danisco Ingredients 1999e
	Glyceryl Oleate/Elaidate	
UV absorption	λ_{max} at 239 nm; λ_{min} at 270 nm	Danisco Ingredients 1999e
	Glyceryl Palmitate	
Specific rotation	−4.37 (in pyrimidine)	Lide and Frederikse 1993
Calculated Octanol/water partition coefficient ($\log(K_{ow})$)	6.38	Danisco Ingredients 1999a
Molecular weight	330.51	Lide and Frederikse 1993
Melting point	71–72°C	Lide and Frederikse 1993
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Palmitate/Lactate	
Form	Off-white pellets	Danisco Ingredients 1996
Dropping point	50°C	Danisco Ingredients 1996
Hydroxyl value	160	Danisco Ingredients 1996
Iodine value	<2	Danisco Ingredients 1996
Saponification value	245–265	Danisco Ingredients 1996
Acid value	5 max.	Danisco Ingredients 1996
UV absorption	λ_{max} at 239 nm; λ_{min} at 287 nm	Danisco Ingredients 1999e
	Glyceryl Palmitate/Stearate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Palmitoleate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 270 nm and 280 nm	Danisco Ingredients 1999e
	Glyceryl Sesquioleate	
UV absorption	λ_{max} at 239 nm	Danisco Ingredients 1999e
	Glyceryl Stearate/Citrate	
Form	White ivory-colored powder	Hüls America, Inc., no date
Solubility	Well soluble in acetone; insoluble in alcohols and ethers; sparingly soluble in ethanol; and turbid soluble in medium shain triglycerides and fatty oils	Hüls America, Inc., no date
Odor	Neutral, fatty odor	Hüls America, Inc., no date
Melting point	59–63°C	Hüls America, Inc., no date
pH	10–30 (10% in water 1:1)	Hüls America, Inc., no date
Saponification value	230–260 mg KOH/g	Hüls America, Inc., no date
Acid value	15–25 mg KOH/g max.	Hüls America, Inc., no date

TABLE 2
Physical properties of Purified Ester Gum-2-OctylDodecyl Myristate (Purified Ester Gum/M.O.D.), a trade mixture containing 50% Glyceryl Rosinate and 50% Octyldecyl Myristate

Property	Description	Reference
Appearance	Viscous transparent light-brown liquid with almost no odor	Shin-Ei Chemical Company Ltd. 1998
Description	Viscous liquid made up of purified ester gum dissolved in 2-octyl dodecyl myristate in a 50:50 ratio. Ester gum is a rosin ester whose main component is ester of abietic acid and glycerol	Cosmo Trends, no date
Specific Gravity (d_{25}^{25})	0.9625 to 0.9725	U.S. Cosmetics Corporation 1998
Refractive Index (n_D^{20})	1.4930 to 1.4980	U.S. Cosmetics Corporation 1998
Solubility	Soluble in olive oil, castor oil, petrolatum, and liquid paraffin. Insoluble in glycerin, water, and propylene glycol	Shin-Ei Chemical Company Ltd. 1998
Melting point	No data available	Shin-Ei Chemical Company Ltd. 1998
Flash point	272°C	U.S. Cosmetics Corporation 1998
Acid value	<12	U.S. Cosmetics Corporation 1998
Heavy metals (ppm)	<20	U.S. Cosmetics Corporation 1998
Arsenic (ppm)	<2	U.S. Cosmetics Corporation 1998
Moisture (%)	<0.1 g	U.S. Cosmetics Corporation 1998
Solid content (%)	50 ± 2	U.S. Cosmetics Corporation 1998
Percent volatile	Almost none	Shin-Ei Chemical Company Ltd. 1998
Volatile organic compounds	None identified	Shin-Ei Chemical Company Ltd. 1998
Oxidation	Little tendency to oxidize	Shin-Ei Chemical Company Ltd. 1998
Stability	Stable with almost no reactivity	Shin-Ei Chemical Company Ltd. 1998
Hazardous decomposition products	Almost none	Shin-Ei Chemical Company Ltd. 1998

According to Danisco Ingredients (1999c), two isomeric forms (α and β) exist; the structure above is the α form. Glyceryl Laurate also has been described as a distilled monoglyceride that is made from edible vegetable fatty acids (mainly lauric acid) (Danisco Ingredients 1999c) as well as a molecular distillated lauric acid monoglyceride (Henkel KgaA 1994). Other names for this chemical include Dodecanoic Acid, 2,3-Dihydroxypropyl Ester; Dodecanoic Acid, Monoester with 1,2,3-Propanetriol; Glyceryl Monolaurate; and Lauricidin (Pepe, Wenninger, and McEwen 2002); Laurin, 1-Mono; alpha-Monolaurin; 1-Glyceryl Laurate; 1-Monododecanoylglycerol; 1-Monolaurin; Dodecanoic Acid alpha-Monoglyceride; Glycerin 1-Monolaurate; Glycerol alpha-Monolaurate; Glycerol 1-Laurate; Glycerol 1-Monolaurate; Glyceryl Monododecanoate; Glyceryl Monolaurate; Lauric Acid alpha-Monoglyceride; and Lauric Acid 1-Monoglyceride (Scientific & Technical Information Network [STN] International 1997).

Commercial Glyceryl Laurate consists of 90% monoester, free glycerol (maximum 4%), and free fatty acid (maximum 1%). Its fatty acid profile is as follows: C_{10} (maximum 10%), C_{12} (maximum 90%), and C_{14} (maximum 8%) (Kabara 1984).

Henkel KgaA (1996) confirmed the 90% monoester content of Glyceryl Laurate and indicated that free glycerin is present at concentrations up to 2%.

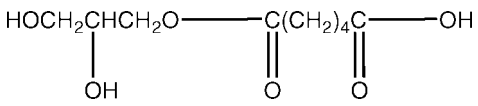
Hüls America, Inc. (no date) states that Glyceryl Laurate contains free glycerol (1%), monoglycerides (95%), diglycerides (2%), and water (maximum 1%).

Danisco Ingredients (1996) states that the composition of Glyceryl Laurate is as follows: monoester content (minimum 90%), free glycerol (maximum 1%), and free fatty acids (maximum 1.5%).

Glyceryl Laurate SE is a self-emulsifying grade of Glyceryl Laurate that contains some sodium and/or potassium laurate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Laurate/Oleate is the monoester of glycerin and a blend of lauric and oleic acids (Pepe, Wenninger, and McEwen 2002).

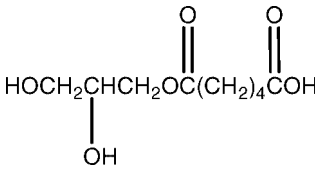
Glyceryl Adipate (CAS no. 26699-71-8) is the ester of glycerin and adipic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Hexanedioic Acid, Monoester with 1,2,3-Propanetriol is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

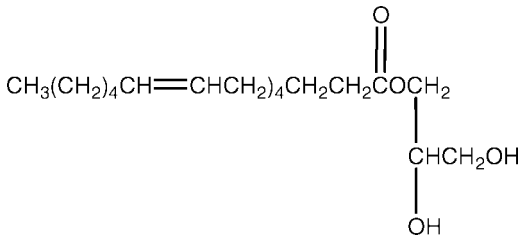
Glyceryl Alginate is the ester of glycerin and alginic acid. Alginic Acid, Glyceryl Ester is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

Glyceryl Arachidate (CAS nos. 30208-87-8 and 50906-68-8) is the ester of glycerin and arachidic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



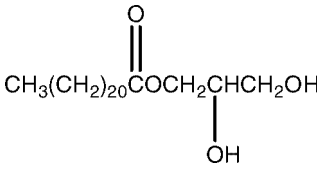
Other names for this chemical include 2,3-Dihydroxypropyl Eicosanoate; Eicosanoic Acid, 2,3-Dihydroxypropyl Ester; Eicosanoic Acid, Monoester with 1,2,3-Propanetriol; and Glyceryl Monoarachidate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Arachidonate (CAS no. 35474-99-8) is the monoester of glycerin and arachidonic acid that conforms to the following formula (Wenninger et al. 2000):



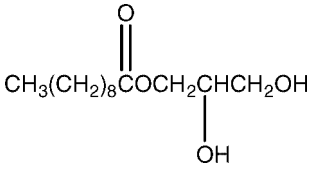
Other names for this chemical include: Arachidonic Acid, Monoester with 1,2,3-Propanetriol; 2,3-Dihydroxypropyl 5,8,11,14-Eicosatetraenoate; 5,8,11,14-Eicosatetraenoic Acid, 2,3-Dihydroxypropyl Ester-; and Glyceryl Monoarachidonate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Behenate (CAS nos. 6916-74-1 and 30233-64-8) is the monoester of glycerin and behenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



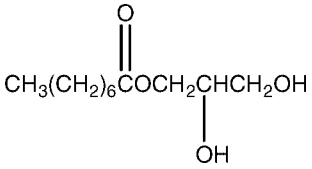
Other names for this chemical include 2,3-Dihydroxypropyl Docosanoate; Docosanoic Acid, 2,3-Dihydroxypropyl Ester; Docosanoic Acid, Monoester with 1,2,3-Propanetriol; and Glyceryl Monobehenate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Caprate (CAS no. 26402-22-2) is the monoester of glycerin and capric acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Decanoic Acid, Monoester with 1,2,3-Propanetriol and Glyceryl Monocaprate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Caprylate (CAS no. 26402-26-6) is the monoester of glycerin and caprylic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):

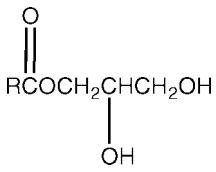


It has a molecular weight of 218.29 (Budavari 1989). Other names for this chemical include Glyceryl Monocaprylate and Octanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002), and Monooctanoin (Budavari, 1989). The typical composition of Glyceryl Caprylate is described as follows: free glycerol (1%), monoglycerides (90%), diglycerides (7%), triglycerides (1%), and water (maximum 1%) (Hüls America, Inc., no date).

Glyceryl Caprylate/Caprate is a mixture of monoglycerides of caprylic and capric acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Citrate/Lactate/Linoleate/Oleate is the ester of glycerin and a blend of citric, lactic, linoleic and oleic acids (Pepe, Wenninger, and McEwen 2002). More specifically, it is a partially neutralized ester of mono- and diglycerides of unsaturated edible fatty acids with citric acid and lactic acid (Hüls America, Inc., no date).

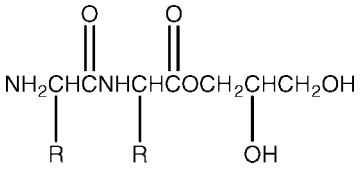
Glyceryl Cocoate (CAS no. 61789-05-7) is the monoester of glycerin and coconut fatty acids that conforms to the following formula, where R represents the fatty acids derived from coconut oil (Pepe, Wenninger, and McEwen 2002):



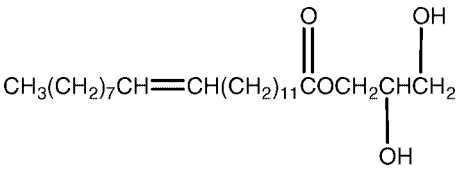
More specifically, it is composed of partial glycerides (mono/di/triglycerides) of the saturated fatty acids of coconut oil. The chain length is C_{10} to C_{18}; the main component is C_{12}, as in coconut oil (Hüls America, Inc., no date). Other names for this chemical include: Glycerides, Coconut Oil Mono-; Glycerol Mono Coconut Oil; Glyceryl Coconate; and Glyceryl Monococoate (Pepe, Wenninger, and McEwen 2002). The typical composition of Glyceryl Cocoate is described as follows: free glycerol (1%), monoglycerides (45%), diglycerides (35%), triglycerides (15%), and water (maximum 1%) (Hüls America, Inc., no date).

Glyceryl Collagenate is the ester of glycerin and collagen (q.v.) (Pepe, Wenninger, and McEwen 2002). It consists

of ~25% solids and its chemical structure, where R is an amino group typical of collagen, is included below (Brooks Industries 1998):



Glyceryl Erucate (CAS no. 28063-42-5) is the monoester of glycerin and erucic acid that conforms generally to the following formula (Pepe, Wenninger, and McEwen 2002):

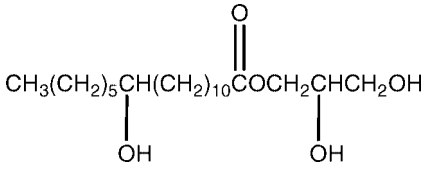


Other names for this chemical include Glyceryl Monoerucate and Erucic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Hydrogenated Rosinate is the monoester of glycerin and hydrogenated mixed long chain acids derived from rosin (Pepe, Wenninger, and McEwen 2002). It also exists as a mixture of 50% Glyceryl Hydrogenated Rosinate and 50% Octyldodecyl Myristate (McEwen 2000).

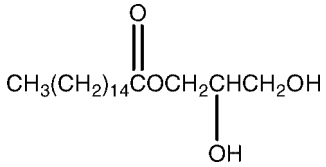
Glyceryl Hydrogenated Soyate is the monoester of glycerin (q.v.) and hydrogenated mixed long chain acids derived from soy (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), this ingredient is a distilled monoglyceride made from edible, fully hydrogenated vegetable oil.

Glyceryl Hydroxystearate (CAS no. 1323-42-8) is the monoester of glycerin and hydroxystearic acid (q.v.) that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



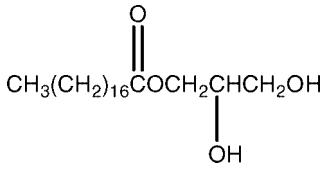
Other names for this chemical are as follows: Glyceryl Hydroxystearate (1); Glyceryl Hydroxystearate (2); Glyceryl Monohydroxystearate; Hydroxystearic Acid, Monoester with Glycerol; and Stearic Acid, Hydroxy-, Monoester with Glycerol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isopalmitate is the monoester of glycerin and a branched chain 16-carbon aliphatic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Isopalmitic Acid, 2,3-Dihydroxypropyl Ester and Isopalmitic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isostearate (CAS nos. 66085-00-5 and 61332-02-3) is the monoester of glycerin and isostearic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Glyceryl Isostearate (1), Glyceryl Monoisostearate, and Isooctadecanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Gattefossé s.a. (1998) described the composition of Glyceryl Isostearate as containing 1-monoglycerides (>30%), free glycerol (<7%), and water (<0.50%).

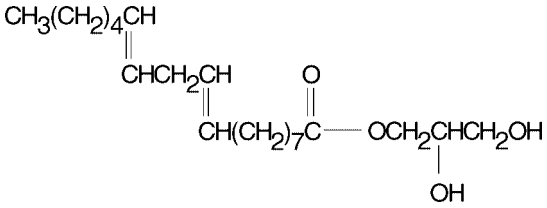
Glyceryl Isostearate/Myristate is the monoester of glycerin and a blend of isostearic and myristic acids. Glyceryl Monisostearate Monomyristate is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isostearates is a mixture of the mono-, di-, and triesters of glycerin and isostearic acid. This chemical is also known as Glyceryl Isostearate (2) (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isotridecanote/Stearate/Adipate is the ester of glycerin (q.v.) and a blend of isotridecanoic acid, stearic acid, and adipic acid (Pepe, Wenninger, and McEwen 2002).

Glyceryl Lanolate is the monoester of glycerin and lanolin acid (q.v.). Other names for this chemical include Glyceryl Monolanolate and Lanolin Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Linoleate (CAS no. 2277-28-3) is the monoester of glycerin and linoleic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002).

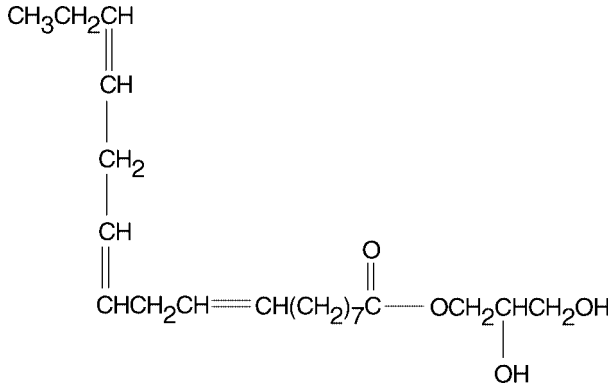


Other names for this chemical include 2,3-Dihydroxypropyl 9,12-Octadecadienoate; Glyceryl Monolinoleate; Linoleic Acid,

Monoester with 1,2,3-Propanetriol; Monolinolein; 9,12-Octadecadienoic Acid, 2,3-Dihydroxypropyl Ester; and 9,12-Octadecadienoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Danisco Ingredients (1996) stated that the composition of Glyceryl Linoleate is as follows: monoester content (minimum 90%); free glycerol (maximum 1%); free fatty acid (maximum 1.5%); butyl hydroxy anisole (BHA), as antioxidant (maximum 200 ppm); and citric acid, as antioxidant (maximum 200 ppm) (*Note*: Citric acid is dissolved in propylene glycol.)

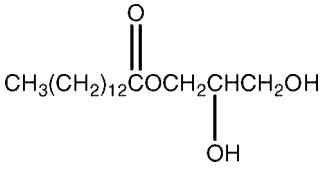
Glyceryl Linolenate (CAS no. 18465-99-1) is the monoester of glycerin and linolenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



According to Danisco Ingredients (1999c), Glyceryl Linolenate is a distilled monoglyceride that is made from edible, refined sunflower oil. Other names for Glyceryl Linolenate include 2,3-Dihydroxypropyl 9,12,15-Octadecatrienoate; Glyceryl monolinolenate; Linolenic Acid, Monoester with 1,2,3-Propanetriol; and 9,12,15-Octadecatrienoic Acid, 2,3-Dihydroxypropyl Ester (Pepe, Wenninger, and McEwen 2002).

Glyceryl Montanate (CAS no. 68476-38-0) is the monoester of glycerin and montan acid wax. Other names for this chemical include 2,3-Dihydroxypropyl Octacosanoic Acid; Glycerides, Montan-Wax; Montan-Wax Fatty Acids, Glyceryl Esters; and Octacosanoic Acid, 2,3-Dihydroxypropyl Ester (Pepe, Wenninger, and McEwen 2002).

Glyceryl Myristate (CAS nos. 589-68-4 and 27214-38-6) is the monoester of glycerin and myristic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):

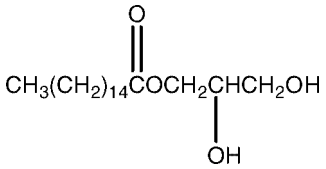


According to Danisco Ingredients (1999c), it is a distilled monoglyceride that is made from vegetable fatty acids (mainly myristic acid). Other names for this chemical include: Glyceryl Monomyristate; Monomyristin; and Tetradecanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Oleate SE is a self-emulsifying grade of Glyceryl Oleate (q.v.) that contains some sodium and/or potassium oleate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Oleate/Elaidate is a mixture of monoglycerides of oleic and elaidic acids (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), it is a distilled monoglyceride made from edible, partially hydrogenated soya bean oil.

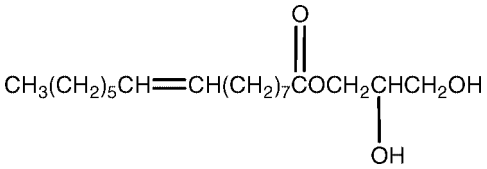
Glyceryl Palmitate (CAS no. 26657-96-5) is the monoester of glycerin and palmitic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include: Glyceryl Monopalmitate; Hexadecanoic Acid, 2,3-Dihydroxypropyl Ester; and Hexadecanoic Acid, Monoester with 1,2,3-Propanetriol; Hexadecanoic acid α-monoglyceride; Palmiric Acid Monoglyceride; Palmitin, mono-; and Palmitin, 1-mono- (Pepe, Wenninger, and McEwen 2002).

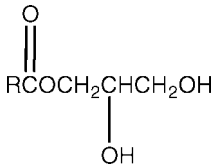
Glyceryl Palmitate/Stearate (CAS no. 68002-71-1) is the monoester of glycerin and a blend of palmitic and stearic acids (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), it is a distilled monoglyceride made from edible, fully hydrogenated lard or tallow.

Glyceryl Palmitoleate is the monoester of glycerin and palmitoleic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



According to Danisco Ingredients (1999c), it is a distilled monoglyceride that is made from edible, refined palm oil. Other names for this chemical include Glyceryl Monopalmitoleate; Palmitoleic Acid, 2,3-Dihydroxypropyl Ester; and Palmitoleic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Pentadecanoate is the monoester of glycerin and pentadecanoic acid that conforms to the following formula, where RCO- represents the pentadecanoyl radical (Pepe, Wenninger, and McEwen 2002):



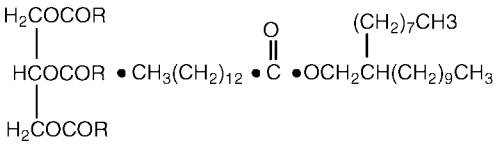
Another name for this chemical is 2,3-dihydroxypropane-pentadecanoate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Polyacrylate is the ester of glycerin (q.v.) and polyacrylic acid (q.v.) (Pepe, Wenninger, and McEwen 2002).

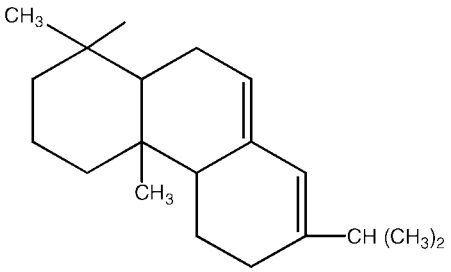
Glyceryl Rosinate (CAS no. 8050-31-5) is the monoester of glycerin and mixed long chain acids derived from rosin (q.v.). Glycerin monorosinate and resin acids and rosin acids, esters with glycerin are two other names for this chemical (Pepe, Wenninger, and McEwen 2002).

In an FDA review of safety (FDA 1988), rosin is the residue remaining when the volatile oil is distilled from turpentine or a product of the distillation, solvent extraction, or both, of the stumps or fallen trees of various species of *Pinus*. Abietic acid and dehydroabietic acid are the main components that have been identified. Rosin nomenclature is based on the source from which it is obtained. Thus, rosin obtained from offical (gum) turpentine is known as gum rosin. Wood rosin is rosin distilled or extracted out of the wood of stumps of fallen trees. These rosins differ in color, % resene, and in the softening point.

Glyceryl Rosinate is supplied as a trade mixture that is known as Purified Ester Gum-2-OctylDodecyl Myristate (Purified Ester Gum/M.O.D.) (US Cosmetics Corporation, no date). Purified Ester Gum-2-OctylDodecyl Myristate consists of 50% Glyceryl Rosinate and 50% octyldodecyl myristate (Shin-Ei Chemical Company Ltd. 1998), and properties of this trade mixture are presented in Table 2. The structural formula for Purified Ester Gum-2-Octyldodecyl Myristate is indicated below (US Cosmetics Corporation, no date):



Where R =



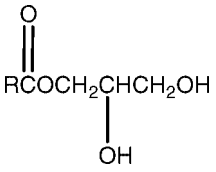
Glyceryl Sesquioleate is a mixture of mono- and di-esters of glycerin and oleic acid (Pepe, Wenninger, and McEwen 2002).

Glyceryl/Sorbitol Oleate/Hydroxystearate is the mixed esterification product of glycerin and sorbitol with hydroxystearic and oleic acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Stearate/Acetate is the monoester of glycerin and a blend of stearic and acetic acids. Glyceryl monostearate monoacetate is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

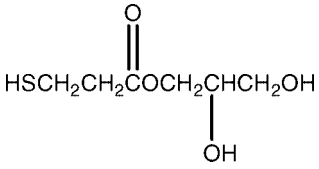
Glyceryl Stearate/Maleate is the monoester of glycerin and a blend of stearic and maleic acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Tallowate is the monoester of glycerin and tallow fatty acids that conforms to the following formula, where RCO- represents the fatty acids derived from tallow (Pepe, Wenninger, and McEwen 2002):

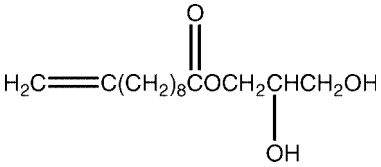


Another name for this chemical is glyceryl monotallowate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Thiopropionate is the organic compound that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Glyceryl Undecylenate is the ester of glycerin and undecylenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical are glyceryl monoundecylenate and undecylenic acid, monoester with 1,2,3-propanetriol (Pepe, Wenninger, and McEwen 2002).

Octanol/Water Partition Coefficients

Measured octanol/water partition coefficients were not available. Calculated values received from one supplier are given in Table 3.

Analytical Methods

Glyceryl Laurate has been analyzed by thin-layer chromatography, gas-liquid chromatography (Kabara 1984), reverse-phase high performance liquid chromatography (HPLC) (Maruyama and Yonese 1986; Takano and Kondoh 1987), capillary supercritical fluid chromatography (Giron, Link, and Bouissel 1992), and ultraviolet (UV) spectral analysis—results are summarized in Table 1 (Danisco Ingredients 1999e).

TABLE 3
Calculated octanol/water partition coefficients of Glyceryl Monoesters (Danisco Ingredients 1999a)

Ingredient	log (*Ko*/w)
Glyceryl Laurate	4.22
Glyceryl Oleate	7.00
Glyceryl Behenate	9.62
Glyceryl Caprate	3.14
Glyceryl Caprylate	2.06
Glyceryl Erucate	8.61
Glyceryl Linoleate	5.44
Glyceryl Linolenate	4.60
Glyceryl Myristate	5.30
Glyceryl Elaidate	6.45
Glyceryl Palmitate	6.38
Glyceryl Stearate	7.69
Glyceryl Palmitoleate	5.37
Glyceryl Hydroxystearate	5.59

Methods of Production

According to Kabara (1984), industrial monoglycerides can be prepared by the direct esterification of glycerol with a fatty acid, yielding mixtures of mono-, di-, and tri- glycerides, depending on the molar ratio of the reactants. In the case of Glyceryl Laurate, the lauric acid that is used for esterification is generally derived from the oil of various species of palm, such as coconut and babassu. The glycerolysis of fats and oils, a transesterification reaction, is a common commercial method for the preparation of monoglycerides.

Glyceryl Collagenate is produced via the esterification of hydrolyzed collagen with United States Pharmacopeia (USP) glycerine 99% (Brooks Industries 1998).

Glyceryl Rosinate is contained in a trade mixture of purified ester gum-2-octyldodecyl myristate (containing 50% Glyceryl Rosinate and 50% octyldecyl myritstate), which is prepared by mixing (with heat) purified ester gum and 2-octyldodecyl myristate in a 1:1 ratio. The mixture is then subjected to purification processes such as decoloration, dehydration, deodorization and filtration (US Cosmetics Corporation, no date).

Composition/Impurities

Data on the chemical characterization of Glyceryl Monoesters are shown in Table 4.

Danisco Ingredients (1999d), indicated that a content of 3.5% to 4% total (mono)glycerol diester's are common in the manufacturing of distilled monoglyceride's. In the manufacturing of any less than 90% monoglyceride (commonly referred to as mono-diglycerides, albeit the INCI name does not differentiate), the content of (mono)glycerol diester's is higher. Because there is some diglycerol then there is also a "family" of diglycerol esters (mono- and di-esters). Consequently one can read from the tabulation of "impurities" for instance for a main product like DIMODAN PM [Glyceryl Palmitate/Stearate], that out of approximately 4% (mono)glycerol diester's, then approximately 29% of this is 1,2 (mono)glycerol diester. This would correspond to an approximate concentration of 1,2 (mono)glycerol diester of 1.2%.

Glyceryl Laurate contains ash (maximum 0.1%) (Hüls America, Inc., no date) and heavy metals, as Pb (<10 mg/kg) (Danisco Ingredients 1996).

TABLE 4
Impurities data on Glyceryl Monoesters (Danisco Ingredients 1999c, 1999d)

Ingredients	% glycerol	% diglycerol	% free fatty acid	% diglycerol monoester	Ratio of 1,2-(mono)glycerol diester to total (mono)glycerol diester
Glyceryl Laurate	0.07	0.24	0.16	—	24.8
Glyceryl Behenate	0.03	0.09	0.15	—	29.1
Glyceryl Caprate	1.03	0.43	0.06	—	21.0
Glyceryl Caprylate/Caprate	5.37	—	—	—	34.3
Glyceryl Linolenate	0.03	0.15	0.11	—	35.8
Glyceryl Myristate	0.30	0.57	0.14	—	27.8
Glyceryl Oleate/Elaidate	0.03	0.12	0.35	—	33.4
Glyceryl Palmitate	0.03	0.06	0.79	—	10.6
Glyceryl Palmitate/Lactate	0.04	—	0.82	—	30.6
Glyceryl Palmitate/Stearate	0.27	0.10	0.98	0.28	29.2
Glyceryl Palmitoleate	0.04	0.14	0.41	—	27.3
Glyceryl Sesquioleate	0.24	—	0.42	—	30.5
Glyceryl Hydrogenated Soyate	0.60	0.28	0.11	—	26.0

Glyceryl Caprylate and Glyceryl Cocoate contain ash at a maximum concentration of 0.1% (Hüls America, Inc., no date).

Glyceryl Collagenate contains a low level of sodium chloride, byproduct of the production process (Brooks Industries 1998). It also contains nonvolatile matter (25% to 31%) and moisture (67% to 73%).

Glyceryl Hydrogenated Soyate specifications, given by Danisco Ingredients (1999c), include: monoester content (minimum 90%), iodine value (maximum 2%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point (≈72°C), and form (beads). Specifications for heavy metal impurities include: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), Cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg).

Glyceryl Isostearate impurities are as follows: alkaline impurities (<80 ppm NaOH), sulfated ash content (<0.2%), and heavy metals (<10 ppm Pb) (Gattefossé s.a. 1998).

Glyceryl Linoleate contains heavy metals (as Pb) at <10 mg/kg (Danisco Ingredients 1996).

Glyceryl Linolenate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), iodine value (approximately 10%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), temperature at which completely melted (≈45°C), and form (paste). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). Glyceryl Linolenate also contains the antioxidants, BHA (maximum 200 ppm) and citric acid dissolved in propylene glycol (maximum 200 ppm).

Glyceryl Myristate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), free glycerol (maximum 1%), and free fatty acids (maximum 1.5%). The typical value for heavy metals (as Pb) in Glyceryl Myristate is <10 mg/kg.

Glyceryl Oleate/Elaidate specifications, given by Danisco Ingredients (1999c), include arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). It also contains the antioxidants, citric acid ester (maximum 300 ppm), α-tocopherol (maximum 200 ppm), and ascorbyl palmitate (maximum 200 ppm).

Glyceryl Palmitate/Stearate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), iodine value (maximum 2%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point (≈70°C), and form (beads). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg).

Glyceryl Palmitoleate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), iodine value (≈40), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point (≈60°C), and form (plastic). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). Glyceryl Palmitoleate also contains the antioxidants, BHA (maximum 200 ppm) and citric acid dissolved in propylene glycol (maximum 200 ppm).

Stability/Reactivity

Glyceryl Laurate is classified as a combustible material (Lewis 1993). It is compatible with most emulsifiers, but is inactivated in the presence of sodium lauryl sarcosine and ethoxylated and propoxylated nonionics (e.g., Tween 80, a.k.a. Polysorbate 80) (Kabara 1984).

Glyceryl Cocoate is stable against oxidation and forms an emulsion with water when heated (Hüls America, Inc., no date).

Glyceryl Isostearate reacts with strong acids and oxidizing agents. Additionally, incomplete combustion of Glyceryl Isostearate leads to the release of monoxyd carbon and dioxyd carbon (Gattefossé s.a. 1999).

USE

Cosmetic Use

Glyceryl Monoesters are used mostly as skin conditioning agents—emollients and/or surfactant-emulsifying agents, but several other uses are reported (Pepe, Wenninger, and McEwen 2002). The current function in cosmetics for each ingredient in this safety assessment is summarized in Table 5.

Table 6 presents information on the types of products in which these ingredients are used (FDA 1998; CTFA 1999), the frequency with which they are used as reported by industry to FDA (FDA 1998), and the current concentration at which the ingredients are used as reported by industry (CTFA 1999). Although only 16 of the 43 ingredients in this safety assessment were reported to FDA as being used in cosmetics, the current concentration of use data received from the cosmetics industry indicates that four additional glyceryl monoesters are in use. Also, concentrations of use are reported in product groups for which no uses were reported in 1998.

Cosmetic products containing glyceryl monoesters are applied to most areas of the body, and could come in contact with the ocular and nasal mucosae. These products could be used on a daily basis, and could be applied frequently over a period of several years.

None of the 43 ingredients reviewed in this safety assessment is included among the substances listed as prohibited from use in cosmetic products marketed in the European Union (European Economic Community 2001).

Japan describes the following 11 categories of cosmetic preparations: 1. skin cleansing; 2. hair care; 3. treatment;

TABLE 5
Functions of Glyceryl Monoesters in Cosmetics (Pepe, Wenninger, and McEwen 2002)

Ingredients	Functions
Glyceryl Laurate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Laurate SE	As above
Glyceryl Laurate/Oleate	As above
Glyceryl Adipate	As above
Glyceryl Alginate	Skin-conditioning agent—emollient; viscosity-increasing agent—aqueous
Glyceryl Arachidate	Skin-conditioning agent—emollient; surfactant-emulsifying agent; viscosity-increasing agent—nonaqueous
Glyceryl Arachidonate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Behenate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Caprate	As above
Glyceryl Caprylate	As above
Glyceryl Caprylate/Caprate	As above
Glyceryl Citrate/Lactate/Linoleate/Oleate	As above
Glyceryl Cocoate	As above
Glyceryl Collagenate	Hair-conditioning agent; skin-conditioning agent—emollient; skin-conditioning agent—miscellaneous
Glyceryl Erucate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Hydrogenated Rosinate	As above
Glyceryl Hydrogenated Soyate	As above
Glyceryl Hydroxystearate	As above
Glyceryl Isopalmitate	As above
Glyceryl Isostearate	As above
Glyceryl Isostearate/Myristate	As above
Glyceryl Isostearates	As above
Glyceryl Isotridecanoate/Stearate/Adipate	As above
Glyceryl Lanolate	Hair-conditioning agent; Skin-conditioning agent—emollient; surfactant—emulsifying agent
Glyceryl Linoleate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Linolenate	As above
Glyceryl Montanate	As above
Glyceryl Myristate	As above
Glyceryl Oleate SE	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Oleate/Elaidate	As above
Glyceryl Palmitate	As above
Glyceryl Palmitate/Stearate	As above
Glyceryl Palmitoleate	As above
Glyceryl Pentadecanoate	As above
Glyceryl Polyacrylate	Film former
Glyceryl Rosinate	As above
Glyceryl Sesquioleate	As above
Glyceryl/Sorbitol Oleate/Hydroxystearate	As above
Glyceryl Stearate/Acetate	As above
Glyceryl Stearate/Maleate	As above
Glyceryl Thiopropionate	Hair-waving/straightening agent; reducing agent
Glyceryl Undecylenate	Skin-conditioning agent—emollient; surfactant—emulsifying agent

4. makeup; 5. fragrance; 6. suntan/ sunscreen; 7. nail makeup; 8. eyeliner; 9. lip product; 10. oral product; and 11. bath product. Table 7 lists the ingredients in this safety assessment according to the *International Cosmetic Ingredient Dictionary and Handbook* name (INCI name), the categories for which there is precedent (or not) for use in Japan, and any limitations on use (Rempe and Santucci 1997).

TABLE 6
Product formulation data on Glyceryl Monoesters

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Glyceryl Laurate		
Eye shadow (551)	2	—
Eye makeup remover (99)	1	0.1
Other fragrance preparations (173)	1	—
Permanent waves (211)	9	—
Shampoos (noncoloring) (851)	—	0.3–2
Tonics, dressings, and other hair-grooming aids (577)	—	0.4
Wave sets (53)	—	0.4
Other hair preparations (noncoloring) (276)	—	0.4
Bath soaps and detergents (405)	4	—
Deodorants (underarm) (247)	4	—
Douches (5)	—	0.3
Other personal cleanliness products (307)	3	—
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	4
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	5	—
Other skin care preparations (715)	—	4
1998 total uses for Glyceryl Laurate	29	
Glyceryl Alginate		
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	1	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	0.5
1998 totals for Glyceryl Alginate	1	
Glyceryl Arachidonate		
Suntan gels, creams, and liquids (136)	2	—
1998 totals for Glyceryl Arachidonate	2	
Glyceryl Behenate		
Mascara (187)	—	2
Suntan gels, creams, and liquids (131)	—	5
1998 totals for Glyceryl Behenate	—	
Glyceryl Caprylate/Caprate		
Hair sprays (aerosol fixatives) (267)	1	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
1998 totals for Glyceryl Caprylate/Caprate	1	
Glyceryl Cocoate		
Bubble bath (209)	—	1
Lipstick (942)	—	0.3–2
Bath soaps and detergents (405)	—	4
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	1	1–5
1998 totals for Glyceryl Cocoate	1	
Glyceryl Erucate		
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	0.5
1998 totals for Glyceryl Erucate	—	

TABLE 6
Product formulation data on Glyceryl Monoesters *(Continued)*

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Glyceryl Hydroxystearate		
Other eye makeup preparations (151)	—	2
Lipstick (942)	1	—
Deodorants (247)	—	2
Other personal cleanliness products (307)	1	—
Shaving Cream (133)	1	—
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	4	—
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	5	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	2
Foot powders and sprays (35)	1	—
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	8	0.8
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	4	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	3	—
Suntan gels, creams, and liquids (131)	1	—
1998 totals for Glyceryl Hydroxystearate	32	
Glyceryl Isostearate		
Bath oils, tablets, and salts (140)	—	1
Eye shadow (551)	23	0.5–2
Eye lotion (23)	—	0.8
Face powders (301)	1	—
Foundations (319)	24	4–6
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	3
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	1	2
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	3
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	—	0.3
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Isostearate	32	
Glyceryl Lanolate		
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	—
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	1	—
1998 totals for Glyceryl Lanolate	3	
Glyceryl Linoleate		
Eye shadow (551)	1	—
Other fragrance preparations (173)	1	—
Face powders (301)	1	—

(Continued on next page)

TABLE 6
Product formulation data on Glyceryl Monoesters *(Continued)*

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Foundations (319)	2	0.7
Lipstick (942)	3	0.7
Other personal cleanliness products (307)	—	0.7
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	3	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	2	1
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	—
Paste masks (mud packs) (269)	1	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Linoleate	17	
Glyceryl Linolenate		
Eye shadow (551)	1	—
Foundations (319)	—	0.7
Lipstick (942)	3	0.7
Other personal cleanliness products (307)	—	0.7
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	1	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	2	1
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Linolenate	10	
Glyceryl Myristate		
Other fragrance preparations (173)	1	—
Makeup bases (136)	1	—
Deodorants (underarm) (247)	1	—
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	3	1–6
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	6
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	4	—
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	3	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	6
Suntan gels, creams, and liquids (131)	1	—
Other suntan preparations (37)	1	—
1998 totals for Glyceryl Myristate	19	
Glyceryl Oleate/Elaidate		
Foundations (319)	—	2
Makeup bases (136)	—	0.3

TABLE 6
Product formulation data on Glyceryl Monoesters *(Continued)*

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	2
Moisturizing creams, lotions, powders, and sprays (881)	—	2
1998 totals for Glyceryl Oleate/Elaidate	—	
Glyceryl Polyacrylate		
Hair conditioners (630)	—	0.4
Tonics, dressings, and other hair-grooming aids (577)	—	0.2
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	1	2
1998 totals for Glyceryl Polyacrylate	1	
Glyceryl Rosinate		
Eyebrow pencil (99)	—	10
Eye shadow (551)	—	2
Mascara (187)	2	0.08–12
Other hair coloring preparations (59)	—	3
Blushers (all types) (243)	—	2
Foundations (319)	1	0.06-4
Lipstick (942)	—	0.4–6
Depilatories (28)	1	—
1998 totals for Glyceryl Rosinate	4	
Glyceryl Stearate/Acetate		
Tonics, dressings, and other hair-grooming aids (577)	—	7
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	2
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
Moisturizing creams, lotions, powders, and sprays (881)	—	3
Suntan gels, creams, and liquids (131)	—	3
Indoor tanning preparations (68)	—	2
1998 totals for Glyceryl Stearate/Acetate	—	
Glyceryl Undecylenate		
Moisturizing creams, lotions, powders, and sprays (881)	2	—
1998 totals for Glyceryl Undecylenate	2	

Noncosmetic Use

Glyceryl Laurate has noncosmetic uses as an emulsifying and dispersing agent for food products, oils, waxes, and solvents; an antifoaming agent; and a dry-cleaning soap base (Lewis 1993). It has also been detected in pharmaceutical excipients (Giron, Link, and Bouissel 1992).

Glyceryl Caprylate has been used to dissolve gallstones by direct biliary infusion (Budavari 1989).

Glyceryl Isostearate is used in textiles (Unichema International 1997b).

Glyceryl Behenate has been approved for use as a direct food additive (21 CFR 184.1328). Additionally, Glyceryl Monoesters have been approved for use as components of adhesives, coatings, paper and paperboard, and other materials that come in contact with food (i.e., indirect food additive uses) (21 CFR 175.105; 175.300; 176.170; 176.180; 176.200; 176.210; 177.1210; 177.2800; 178.3120; 178.3800; and 178.3870).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate both contain rosin. Rosin is regulated for use as a diluent in color additive ink mixtures for marking gum, confectionery, fruits, vegetables, and tablet forms of food supplements. Rosin (as colophony, a.k.a. Portuguese gum rosin) is listed for use as a flavoring agent in alcoholic beverages. Derivatized and some of the modified rosins are regulated as softeners for chewing gum

TABLE 7
Glyceryl Monoesters used in Japan (Rempe and Santucci 1997)

INCI name	Japanese name	Category with precedent for use*	Category with no precedent for use*
Glyceryl Laurate	Glyceryl Monoaurate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Behenate	Glyceryl Behenate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Cocoate	Glyceryl Cocoate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Erucate	Glyceryl Monoerucate	All	—
Glyceryl Hydroxystearate	Glyceryl Hydroxystearate (1)	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
	Glyceryl Hydroxystearate (2)	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
	Glyceryl Monohydroxystearate	All	—
Glyceryl Isostearate	Glyceryl Isostearate (1)	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Isostearate/Myristate	Glyceryl Monoisostearate Monomyristate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Lanolate	Glyceryl Monolanolate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Linoleate	Glyceryl Linoleate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Myristate	Glyceryl Monomyristate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Sesquioleate	Glyceryl Sesquioleate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Stearate/Acetate	Glyceryl Monostearate Monoacetate	1, 2, 3, 4, 5, 6, 7, 11	8, 9, 10
Glyceryl Stearate/Maleate	Glyceryl Stearate Maleate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11

*See text for explanation of categories.

base. Wood rosin and certain derivatized modified forms of rosin are listed for use as coatings on fresh citrus fruits. Indirect uses of derivatized rosin as components of paper and paperboard in contact with dry food are permitted (FDA 1988).

BIOLOGICAL PROPERTIES

Absorption and Metabolism

The metabolic fate of monoglycerides (glyceryl monoesters) is summarized below. Because monoglycerides are products of triglyceride and diglyceride metabolism, these compounds are also mentioned.

Triglyceride digestion begins in the intestinal tract. Initially, the triglyceride is hydrolyzed to α,β-diglyceride, which is then hydrolyzed to β-monoglyceride. These hydrolytic reactions occur at an oil-water interface. Approximately 28% of the β-monoglyceride is isomerized to α-monoglyceride, and approximately 75% of the α-monoglyceride is further hydrolyzed to free glycerol. Free glycerol enters the intestinal wall independent of the lipids, and it has no further use in terms of lipid absorption. The free fatty acids and glycerol are available for the resynthesis of triglycerides. β-Monoglycerides are not hydrolyzed because of their transfer to a water-soluble phase and, also, because of enzyme specificity. However, they can be acylated directly to triglyceride (Mattson and Volpenhein 1964).

Skin Penetration Enhancement

Glyceryl Laurate

The effect of Glyceryl Laurate or Dilaurate on the penetration of naloxone-HCl across cadaver skin was evaluated using Franz diffusion cells. Naloxone is a potent opioid antagonist used for the reversal of narcosis. Naloxone concentrations in the reservoir were determined by HPLC using UV detection. Glyceryl Laurate was evaluated at a concentration of 10% in propylene glycol. The average flux through human cadaver skin (10 experiments) for naloxone alone was 1.6 ± 0.4 $\mu g/cm^2 \cdot h$. In the presence of Glyceryl Dilaurate (10% in propylene glycol), average Naloxone flux increased to 18.7 ± 1.8 $\mu g/cm^2 \cdot h$ (3 experiments), and increased even greater in the presence of Glyceryl Laurate (23.4 ± 3.6 $\mu g/cm^2 \cdot h$; 3 experiments). In the presence of urea (10% in propylene glycol), the average Naloxone flux was 0.4 ± 0.1 $\mu g/cm^2 \cdot h$ (3 experiments) (Aungst, Rogers, and Shefter 1986).

In another study, the effect of Glyceryl Laurate on penetration of the water-soluble drug, papaverine HCl through hairless rat skin (from abdominal area) was demonstrated using diffusion cells. The mean flux of papaverine HCl was 23.7 ± 5.2 $\mu g/cm^2/h$ (three to five experiments) in the presence of 10% Glyceryl Laurate. This value was compared with the mean value for papaverine HCl flux in the presence of the water control (1.1 ± 0.2 $\mu g/cm^2/h$) (Okumura et al. 1990).

Platelet Aggregation

Glyceryl Arachidonate

Phosphatidylcholine liposomes containing 1-Arachidonyl-Monoglyceride caused aggregation of human platelets in vitro (Gerrard and Graff 1980).

Enzyme Activity

Glyceryl Laurate

The effect of Glyceryl Laurate and various fatty acids and derivatives on 5α-reductase activity in vitro was evaluated

because of the established link between cancer of the prostate gland and high dietary fat intake. Prostate gland tissue specimens (human) were used. 5α-Reductase catalyzes the reduction of testosterone to dihydrotestosterone, which controls cellular division in the prostate gland. It has been suggested that the modulation/inhibition of this enzyme could prevent carcinogenesis in the prostate gland. Results indicated that the inhibitory effect of lauric acid on 5α-reductase activity was decreased by esterification to Glyceryl Laurate and was totally lost by esterification to Glyceryl Dilaurate and Trilaurin (Niederpruem et al. 1995).

Signal Transduction

This section is included because glyceryl diesters may be present in glyceryl monoester ingredients. Although most glyceryl diesters that are found would be expected to be 1,3-glyceryl diesters, some may be 1,2-diesters, which can have signal transduction effects.

Lee and Severson (1994), in a review signal transduction in smooth muscle, state that the generation of intracellular second messengers is a common mechanism of signal transduction for external stimuli such as hormones, neurotransmitters, growth factors, and drugs (agonists) that interact with plasma membrane receptors. They go on to say that the established role of phospholipid turnover in signal transduction mechanisms is based on the observations that agonist-induced hydrolysis of a minor phospholipid in the plasma membrane, phosphatidylinositol 4,5-bisphosphate (PIP_2), in a reaction catalyzed by a phosphoinositide-specific phospholipase C (PI-PLC) enzyme generated the following two intracellular second messengers: (1) inositol 1,4,5-triphosphate (IP_3), responsible for the mobilization of Ca^{2+} from intracellular stores, and (2) diacylglycerol, responsible for the activation of protein kinase C (PKC). Lévy et al. (1994) reported that PKC consists of a family of 10 isozymes that phosphorylate serine and threonine residues. Classical PKC isozymes (α, β_I, β_{II}, γ) are dependent on Ca^{2+} and phospholipids and are activated by diacylglycerol. These isozymes transduce mitotic signals induced by growth factors.

Sánchez-Piñera et al. (1999) studied the lipid activation of PKC α by comparing the activation capacity of different 1,2-diacylglycerols and 1,3-diacylglycerols incorporated into mixed micelles or vesicles. PKC α, as well as other isoenzymes in this family, are activated by Ca^{2+}, phosphatidylserine, and diacylglycerols. Diacylglycerols are considered to be hydrophobic anchors that may recruit PKC to the membrane, leading to an increase in the enzyme's membrane affinity and to the activation of PKC.

Unsaturated 1,2-diacylglycerols were more potent activators of protein kinase C α than saturated 1,2-diacylglycerols when 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoserine (POPS)/Triton X-100 mixed micelles and pure POPS vesicles were used. These differences were not observed when 1-palmitoyl -2-oleoyl-sn-glycero-3-phosphocholine (POPC)/POPS (4:1 molar ratio) vesicles were used. Additionally, 1,2-diacylglycerols had a considerably greater activating capacity than 1,3-diacylglycerols in POPS Triton X-100 mixed micelles and in POPC/POPS vesicles. However, the difference between 1,2- and 1,3-diacylglycerols was smaller when pure POPS vesicles were used. That is, both were able to activate PKC α practically to the same extent. Nevertheless, saturated diacylglycerols induced significant activation of PKC α in Triton X-100 micelles and in pure POPS vesicles in this study (Sánchez-Piñera et al. 1999).

Unlike the preceding study, a very low capacity for 1,3-diacylglycerol–induced activation was demonstrated in an earlier study (Nomura et al. 1986). In the Nomura et al. (1986) study, however, sonicated phosphatidylserine vesicles were used, whereas unsonicated preparations of multilamellar vesicles were used in the Sánchez-Piñera et al. (1999) study.

Cell Growth and Proliferation

This section is included because glyceryl diesters may be present in glyceryl monoester ingredients. Although most glyceryl diesters that are found would be expected to be 1,3-glyceryl diesters, some may be 1,2-diesters, which can have cell growth and proliferation effects.

Huckle and Earp (1994) report that activation of the type 1 angiotensin II receptor rapidly increases intracellular levels of inositol phosphates, notably inositol 1,4,5-triphosphate (IP_3), and 1,2-diacylglycerol (DAG) in adrenal cortical cells, hepatocytes, and vascular smooth muscle. The type 1 angiotensin II receptor is responsible for all known physiologic actions of angiotensin II. Angiotensin II, an octapeptide, is well known as an acute regulator of vasomotor tone and fluid homeostasis. It exhibits many characteristics of the 'classical' peptide growth factors such as epidermal growth factor/transforming growth factor alpha (EGF/TGFα), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF)-1. Characteristics of these growth factors include the regulation of growth in a self-contained autocrine/paracrine fashion, and the ability to stimulate tyrosine phosphorylation, to activate MAPKs (mitogen-activated protein kinases), and to increase expression of nuclear proto-oncogenes. Angiotensin II has trophic or mitogenic (increases rate of cell division) effects on a variety of target tissues, including adrenal cells and vascular smooth muscle cells.

In vascular smooth muscle, hydrolysis via the lipase pathway is the predominant metabolic fate of diacylglycerol. The activation of PKC in vascular smooth muscle modulates agonist-stimulated phospholipid turnover, produces an increase in contractile force, and regulates cell growth and proliferation (Lee and Severson 1994).

Blobe, Obeid, and Hannun (1994) reviewed various studies indicating that the sustained activation or inhibition of PKC (diacylglycerol-activated isoenzyme) activity in vivo may play a critical role in the regulation of long term cellular events such as proliferation, differentiation, and tumorigenesis. Many of the signals transduced by PKC are mitogenic signals that have been sent by growth factors (e.g., platelet-derived growth factor [PGDF] and epidermal growth factor [EGF]). For

example, PGDF binds to its high-affinity receptor (PDGFR) and activates this receptor's intrinsic tyrosine kinase activity to mediate the initiation of DNA synthesis and other cellular effects. It is important to note that PKC has been linked directly to the pathogenesis of human skin, colon, and breast cancers. In the epithelium, long-term changes in PKC activity, either through the action of phorbol esters or by specific changes in PKC isoenzyme levels, either leads to growth of melanocytes, the differentiation of keratinocytes, or to transformation. In colon cancer, PKC acts as a tumor suppressor. Thus, decreasing the levels of PKC activity can result in transformation. In breast cancer, an increase in PKC activity appears to correlate with enhanced oncogenicity.

Evidence of increased PKC activity in hyperplastic pituitary cells has also been reported. Furthermore, the increase in diacylglycerol content paralleled the increase in PKC activity (Lévy et al. 1994).

Antimicrobial Activity

Glyceryl Laurate

Lauricidin (registered trademark for Glyceryl Laurate) has been described as having a wide spectrum of antimicrobial activity against diverse microbial species (viruses, fungi, molds, yeasts, and bacteria included). However, it is generally inactive against gram-negative bacteria. When Lauricidin was tested in cell culture using 16 human RNA- and DNA-enveloped viruses, all viruses were reduced in infectivity by 99.9% at relatively low concentrations (1.0%) of Lauricidin. Antifungal activity (inhibition of mycelial growth) of Glyceryl Laurate has been demonstrated in 12 strains at a concentration of 0.5%, and in three additional strains at a concentration of 0.05% (Kabara 1984).

Glyceryl Laurate inhibited the production of staphylococcal toxic shock toxin-1, the toxin responsible for toxic shock syndrome, at assay concentrations of 20, 100, and 300 μg/ml (Schlievert et al. 1992) and 17 mg/L (Holland, Taylor, and Farrell 1994). Projan et al. (1994) reported that Glyceryl Laurate inhibited the synthesis of most staphylococcal toxins at the level of transcription. It blocked the induction but not the constitutive synthesis of β-lactamase, suggesting that transmembrane signal transduction was the target of Glyceryl Laurate action.

Other studies on the bactericidal activity of Glyceryl Laurate include inhibition of bacterial spores and vegetative cells (Chaibi, Ababouch, and Busta 1996a, 1996b); inhibition of *Listeria monocytogenes* (Oh and Marshall 1996); and susceptibility of *Heliobactor pylori* (Petschow, Batema, and Ford 1996).

ANIMAL TOXICOLOGY

General

The safety of mono- and diglycerides in food has been reviewed by the Food Protection Committee of the National Academy of Sciences National Research Council Food and Nutrition Board (National Academy of Sciences 1960). The Food Protection Committee concluded that there appears to be no reason to question the safety of mono-, di-, or triglycerides of lauric acid (i.e., Glyceryl Laurate, Glyceryl Dilaurate, or Glyceryl Trilaurate [Trilaurin]) as food additives. This conclusion was based on the following: (1) Lauric acid glycerides are used in important foods, such as human and cow's milk, at concentrations of 3% to 6% and large quantities are present in coconut oil. The use of these foods has not been accompanied by recognized toxic effects. (2) Lauric acid glycerides undergo the usual metabolic changes of the higher fatty acids. (3) When lauric acid glycerides are fed in diets containing a variety of glycerides, there is not evidence of a specific toxic or harmful effect.

Acute Inhalation Toxicity

Glyceryl Laurate

A low-grade irritant response was noted following inhalation of an aerosol containing 10% Glyceryl Laurate. The strain of animals tested and details concerning the test protocol and study results were not included (Unichema International 1997b).

Acute Oral Toxicity

Glyceryl Laurate

The acute oral toxicity of Glyceryl Laurate was evaluated using 31 male rats (strain not stated; weights = 150 to 220 g). The test substance was administered by stomach tube after 18 h of fasting. An LD_{50} of 53.4 ml/kg was reported (Eagle and Poling 1955).

Glyceryl Laurate (in olive oil) was administered orally to young Wistar rats (weights not stated). Doses of 10,000 and 20,000 mg/kg were administered to five male and five female rats, respectively. The LD_{50} was >20,000 mg/kg. (Henkel KgaA 1994).

Glyceryl Isostearate

A single oral dose (2 g/kg body weight) of Glyceryl Isostearate did not result in any harmful effects in rats. Details concerning the test protocol were not provided (Unichema International 1997a).

Glyceryl Rosinate

The acute oral toxicity of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using fasted Wistar albino rats (five males, five females; weight range 220 to 292 g). A single oral dose of the test substance (5 g/kg) was administered to each animal. Dosing was followed by a 14-day observation period, and gross necropsy (results not included) was performed on all animals. None of the animals died, and it was concluded that the test substance was not toxic (LD_{50} > 5 g/kg) (Consumer Product Testing Company 1990a).

Glyceryl Citrate/Lactate/Linoleate/Oleate

Hüls AG (1996a) provided unpublished data on the acute oral toxicity of Glyceryl Citrate/Lactate/Linoleate/Oleate using five male and five female Wistar rats. The undiluted test substance (highly viscous) was liquefied by heating in a water bath and then administered to each animal using a rigid gastric pharyngeal probe. Each rat received a single oral dose of 2000 mg/kg (dose volume = 2.004 ml/kg body weight). The animals were observed over a period of 14 days after dosing. None of the animals died. Body weight gain was described as normal, and no signs of toxicity were noted. Grossly detectable organ changes were not noted at necropsy. The LD_{50} was >2000 mg/kg in male and female rats.

Acute Dermal Toxicity

Glyceryl Citrate/Lactate/Linoleate/Oleate

The acute dermal toxicity of Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated using five male and five female Wistar rats. The undiluted test substance (highly viscous) was liquefied by heating in a water bath and then applied dermally (dose = 2000 mg/kg; dose volume = 2.004 ml/kg) to each animal using a gauze patch. Each patch was secured with a semiocclusive dressing for 24 h. None of the animals died, and gross lesions were not observed. Particularly, no gross changes were observed in the subcutaneous tissue in the area of application. The acute dermal LD_{50} was >2000 mg/kg in male and female rats (Hüls AG 1996b).

Short-Term Inhalation Toxicity

Glyceryl Laurate

The short-term inhalation toxicity of Glyceryl Laurate was evaluated using rats. The animals were given a total of 14 1-hour exposures during a 3-week period. Although details concerning the test protocol and study results were not included, a no-effect level of 280 mg/m^3 was reported (Unichema International 1997b).

Short-Term Oral Toxicity

Glyceryl Laurate

The short-term oral toxicity of Glyceryl Laurate was evaluated using 10 weanling rats. The test substance was administered orally at a concentration of 25% in the diet for a period of 10 weeks. No gross or microscopic lesions were found that were attributable to administration of the test diet (Procter & Gamble Company 1950).

Chronic Oral Toxicity

Glyceryl Laurate

Fitzhugh, Schouboe, and Nelson (1960) fed two groups of 24 albino rats of the Osborne-Mendel strain a mixture consisting of Trilaurin (8%), Glyceryl Dilaurate (45%), and Glyceryl Laurate (40% to 45%) at a concentration of 25% in the diet for 2 years. The individual glyceryl esters were fed at effective dietary concentrations of ~2% (Trilaurin), ~11% (Glyceryl Dilaurate), and ~10% to 11% (Glyceryl Laurate). Of the two control groups, one was fed 25% hydrogenated cottonseed oil in the diet (concurrent control), and, the other, basal diet only.

After 26 or 52 weeks of dosing, no significant differences in weight gain between the test and concurrent control groups were noted. No significant differences in the total number of deaths were noted when the test group was compared with both control groups. At necropsy, no gross lesions were observed in test animals. At microscopic examination, a slight increase in hepatic cell fatty change was observed in test animals, compared to the control group fed the basal diet. However, this finding in test animals was no greater than that observed in the control group fed hydrogenated cottonseed oil. The same difference occurred to a lesser and questionably significant degree when the incidence of intrahepatic bile duct proliferation in test animals was compared to that noted in controls (Fitzhugh, Schouboe, and Nelson 1960).

Ocular Irritation

Glyceryl Laurate

The ocular irritation potential of undiluted Glyceryl Laurate was evaluated in the Draize test using three albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of one eye of each animal. Untreated eyes served as controls. Ocular reactions were scored every 24 h up to day 7 post instillation. Mean scores (average of 24-, 48-, and 72-h readings) for corneal reactions and erythema of the conjunctiva were 0.17 (maximum score, corneal lesions = 80) and 1.33 (maximum score, conjunctival lesions = 20), respectively. Reactions were not observed in the iris (Henkel KgaA 1994).

Kabara (1984) evaluated the ocular irritation potential of a 20% Glyceryl Laurate emulsion using six albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of the right eye of each animal. Untreated left eyes served as controls. Ocular reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale: 0 to 110.

According to the test protocol, reactions would be classified as positive if the test substance induced any of the following: ulceration of the cornea (other than a slight dulling of the normal luster), inflammation of the iris (other than a slight circumcorneal injection of the blood vessels), or if the substance produced in the conjunctivae an obvious swelling with partial eversion of the lids or a diffuse crimson-red with individual vessels not easily discernible. Study results were positive only if four or more animals had positive reactions.

An average irritation score (six animals) of 0 was reported for both corneal opacity and inflammation of the iris. The average irritation score for conjunctival irritation was 3.7. Because only one rabbit had a positive reaction, the 20% Glyceryl Laurate emulsion was classified as a "negative ocular irritant" (Kabara 1984).

Glyceryl Isostearate

Although details concerning the test protocol were not provided, Unichema International (1997a) concluded that Glyceryl Isostearate was not an ocular irritant in rabbits. Reactions classified as minior ocular irritation had cleared by 48 h post instillation, reactions were not observed in the cornea or iris.

In a study by the Institut Français de Recherches et Essais Biologiques (1977), the ocular irritation potential of Glyceryl Isostearate was evaluated using six male New Zealand white rabbits. The test substance (undiluted, 0.1 ml) was instilled into the left conjunctival sac of each animal. Untreated right eyes served as controls. After instillation, the eyelids were held together for several seconds to avoid loss of the test substance. The animals were restrained for a period of 18 h. Ocular reactions were scored at 1, 2, 3, 4, and 7 days post instillation (maximum score = 20). Glyceryl Isostearate was classified as a nonirritant.

The Centre de Recherche et d'Elevage des Oncins (1975) evaluated a mixture consisting of Glyceryl Isostearate in an ocular irritation test. Other components of the mixture included glyceryl stearate, propylene glycol isostearate, propylene glycol stearate, ceteth-25, and oleth-25, but the concentration of each component was not provided. The mixture, 20% in sterile water, was instilled (0.1 ml) into the conjunctival sac of the left eye of each of six New Zealand rabbits. Contralateral eyes served as controls. Reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale. Mean Draize ocular irriation scores were 3.0 (at 24 h), 2.67 (at 48 h), and 1.67 (at 72 h). Total Draize scores (Scale: 0 to 110) were 18, 16, and 10 at 24 h, 48 h, and 72 h, respectively. The mixture was classified as a nonirritant based on the mean ocular irritation scores that were recorded.

Glyceryl Rosinate

The ocular irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using six New Zealand white rabbits. The test substance was instilled (0.1 ml) into the conjunctival sac of one eye of each animal. Untreated eyes served as controls. Eyes were not rinsed for up to 24 h post instillation. Ocular reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale (maximum total score = 110). Reactions were also scored at days 4 and 7 if irritation reactions persisted. Average Draize scores of 1.3 and 0.3 were reported at 24 and 48 h post instillation, respectively. At 72 h, an average score of 0 was reported. The test substance was not an ocular irritant (Consumer Product Testing Company 1990b).

Glyceryl Citrate/Lactate/Linoleate/Oleate

The ocular irritation potential of Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated using three female rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of one eye of each animal. At 24 h post instillation, the eyes were flushed with warm physiological saline solution. The conjunctivae, iris, and cornea were examined for any signs of ocular irritation at 24, 48, and 72 h post instillation. Ocular irritation was not observed in either of the three rabbits tested (Hüls AG 1996c).

Skin Irritation

Glyceryl Laurate

Kabara (1984) evaluated the skin irritation potential of a 20% Glyceryl Laurate emulsion using six albino rabbits. The test substance, 0.5 ml, was applied to both an abraded and intact skin site (clipped free of hair) on each animal, and each site was then covered with an occlusive patch. Patches were secured with adhesive tape, and the entire trunk of each animal was wrapped with an impervious material. The animals were immobilized during the 24-h contact period.

At 24 h and 72 h after patch removal, reactions at abraded and intact sites were scored according to the following scales: 0 (no erythema) to 4 (severe erythema to slight eschar formations); and 0 (no edema) to 4 (severe edema).

The primary irritation score for the group of six rabbits was 3.9, classifying the Glyceryl Laurate emulsion as a moderate skin irritant (Kabara 1984).

Henkel KgaA (1994) reported the results of a study to evaluate the skin irritation potential of undiluted Glyceryl Laurate using six rabbits. The test substance was applied (0.5 g under an occlusive patch) to dorsal skin of each animal. The test sites of three rabbits were shaved and those of the remaining three were scarified. Reactions were scored after 24 h and 72 h. Glyceryl Laurate induced minor erythema (mean score = 0.8) and edema (mean score = 0.9) in animals with intact skin. The scores for the three rabbits with scarified skin were not included.

Although details concerning the test protocol and study results were not included Unichema International (1997b) reported that Glyceryl Laurate was less irritating to the skin of rabbits, on an active for active basis, than sodium lauryl sulfate (SLS). Solutions of Glyceryl Laurate were equivalent in irritancy to SLS concentrations of approximately one fifth the strength.

Glyceryl Isostearate

Biogir S.A. Conseil Recherche (1989) conducted a study in which the skin irritation potential of Glyceryl Isostearate was evaluated using three New Zealand albino rabbits. The test substance (0.5 ml on hydrophilic gauze) was applied to skin, clipped free of hair, on the right side of each animal. Patches were secured with hypoallergenic microporous adhesive tape and then covered with elastic material that surrounded the animal's torso. After 4 h of contact, all patches were removed. A gauze square moistened with 0.5 ml of distilled water was applied to a control site on the left side of each animal according to the same procedure.

At 1, 24, 48, and 72 h post removal of the semiocclusive bandage, reactions were scored according to the following scales: 0 (no erythema) to 4 (severe erythema, with or without formation of scars and presence of a lesion representing a significant reaction such as a burn or necrosis); 0 (no edema) to 4 (severe

edema). Because slight irritation persisted beyond 72 h post removal, the animals were observed until all lesions had regressed completely.

Mild erythema was observed in two rabbits at 1, 24, and 48 h post removal. A more severe reaction (moderate irritation) was observed in the third rabbit; the reaction did not clear until day 5. Very mild edema was noted in two rabbits at 1 h post removal, and persisted to 48 h post removal in one rabbit. Slowly reversible, slight changes in the structure of the skin were also observed. It was concluded that Glyceryl Isostearate was not a skin irritant in albino rabbits (Biogir S.A. Conseil Recherche 1989).

The Institut Français de Recherches et Essais Biologiques (1977) evaluated the skin irritation potential of Glyceryl Isostearate using six male New Zealand albino white rabbits. A sterile absorbent gauze pad containing the test substance (0.5 ml) was applied to a scarified site on the right flank and an intact site on the left flank of each animal. Both sites had been clipped free of hair. Each gauze pad was secured with a non-allergenic, adhesive occlusive patch.

The patches remained in place for 23 h; reactions were scored at 24 and 72 h post application according to the following scales: 0 (no erythema) to 4 (severe erythema, crimson red, with slight eschar formation [injuries in depth]) and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond area of application). The primary irritation index (PII) was calculated after all scores had been recorded. Glyceryl Isostearate was classified as a nonirritant (PII = 0.21) (Institut Français de Recherches et Essais Biologiques [IFREB] 1977).

The Centre de Recherche et d'Elevage des Oncins (1975) evaluated a mixture consisting of Glyceryl Isostearate and glyceryl stearate, propylene glycol isostearate, propylene glycol stearate, ceteth-25, and oleth-25 in a skin irritation test using rabbits. The concentrations of each component were not stated. The mixture (0.5 ml, 20% in sterile water) was applied to an intact site and an abraded site (each 2 cm^2 and clipped free of hair) on each of six male New Zealand rabbits. A nonallergenic, adhesive patch was placed over each test site, and the trunk of each animal was wrapped with an adhesive plaster. Patches were removed at 24 h post application and reactions scored (at 24 h and 72 h) according to the scales indicated in the preceding paragraph. The mixture was classified as a slight irritant (PII = 0.92).

Glyceryl Rosinate

The skin irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using six New Zealand white rabbits. The test substance (0.5 ml) was applied to abraded and intact skin (two sites per animal), and sites were covered with occlusive patches for 24 h. The patches were secured with hypoallergenic cloth tape and the entire trunk of each animal was encased in an impermeable plastic, occlusive wrapping. Reactions were scored at 24 and 72 h post application according to the following scales: 0 (very slight erythema, barely perceptible) to 4 (severe erythema [beet redness] to slight eschar formation [injuries in depth]) and 1 (very slight edema, barely perceptible) to 4 (severe edema, area raised approximately 1 mm and extending beyond area of exposure). The mean scores at 24 and 72 h were averaged and a PII calculated. A PII of 3.40 (potential for severe irritation—warning label may be considered) was reported (Consumer Product Testing Company 1990c).

Glyceryl Citrate/Lactate/Linoleate/Oleate

In an acute dermal toxicity study summarized earlier in the report text, undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate (heated) was applied to the skin of Wistar rats (five males, five females). The test substance (dose = 2000 mg/kg; dose volume = 2.004 ml/kg) was applied to each animal using a gauze patch, and each patch was secured with a semiocclusive dressing for 24 h. Neither erythema nor edema was observed in any of the animals tested (Hüls AG 1996b).

Hüls AG (1996d) reported another study of the skin irritation potential of undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate using three rabbits (strain not stated). The test substance was applied to shaved, intact skin for 4 h. At 24 h post application, clearly circumscribed erythema and very mild to clear edema were observed. Barely perceptible to clearly circumscribed erythema and very mild edema were observed at 48 and 72 h post application. After day 6 post application, erythema and swelling were barely detectable. In one animal, a brown stain was noted at the application site; the skin surface was described as dry and squamous. Very slight erythema, dryness, and scaling were noted in all animals on day 8. These reactions were accompanied by slight swelling in one of the three animals. All reactions classified as erythema or edema had cleared by day 10 post application. Scaling was observed in one animal (day 10), but had cleared by day 14. The average score for erythema and scabbing (24, 48, and 72 h readings included) was 1.67. The average score for edema formation (24-, 48-, and 72-h readings included) was 1.11.

Comedogenicity

The comedogenicity of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using three male New Zealand white rabbits (3 months old). The test substance (0.1 ml) was applied to the internal base of the right ear of each rabbit 5 days per week for 3 weeks (15 applications per rabbit). Untreated left ears (internal base) served as controls. Test sites were evaluated for comedone formation and enlarged pores daily. Terminal biopsies of treated and control ears were performed. All specimens were graded for the extent of acanthosis, keratosis, and keratin ("plugging") according to the following scale: 0 (no different from untreated/treated control) to 3 (approximately 75% greater than untreated/treated control). At gross examination, erythema at the application site was noted in all three rabbits. At microscopic examination, all tissues were within normal histological limits. Follicular hyperkeratosis

(comedone formation) was not observed (Consumer Product Testing Company 1990d).

Skin Sensitization

Glyceryl Laurate

The Cosmetic, Toiletry, and Fragrance Association (CTFA) provided the results of a 1975 study of the skin sensitization potential of Glyceryl Laurate in a maximization test using guinea pigs.

Prior to study initiation, a preliminary irritation test (intradermal injection and topical application procedures) was performed using two groups of four males, respectively. In the intradermal injection test, the four animals were injected intradermally with Glyceryl Laurate (0.05% to 1% in 6% absolute alcohol/saline). Reactions described as faint, pink erythema predominated. In the topical application test, the other four males were tested with concentrations ranging from 5% to 25% in absolute alcohol. Scaling was observed in one guinea pig tested with 25% Glyceryl Laurate.

Ten guinea pigs (six males, four females) were tested in the maximization test. The animals were subjected to four sensitizing injections of 2% Glyceryl Laurate and then challenged with intradermal injections of 0.8% Glyceryl Laurate and topical applications of 25% Glyceryl Laurate. Four male guinea pigs served as controls. The grading scale for intradermal challenge reactions ranged from faint, pink erythema to deep, pink erythema. Topical challenge reactions were scored according to the following scale: ± (barely perceptible erythema) to ++++ (erythema–breakdown of surface–necrosis). Positive reactions were not observed in either of the ten animals tested. Glyceryl Laurate was classified as a nonsensitizer (CTFA 1975).

Kabara (1984) studied the skin sensitization potential of a 20% Glyceryl Laurate emulsion in a guinea pig maximization test. To induce sensitization, 10 animals were treated by intradermal injection in the shoulder region. At 7 days post injection, sensitization was boosted by placement of an occlusive patch over the injection site; an occlusive challenge patch was applied to the flank at 14 days post injection. Four additional guinea pigs were treated in a manner similar to that of the test group, except that the test substance was applied only during the challenge phase. Positive challenge reactions were observed in two test animals challenged with a 10% dilution of the test substance. No visible reactions were present in control animals challenged with a 10% dilution of the test substance or either test or control animals challenged with a 5% dilution.

A second challenge was initiated 7 days after the first. Positive reactions were observed in five test animals and two control animals challenged with a 10% dilution of the test substance. Positive reactions were also observed in four test animals challenged with a 5% dilution of the test substance; no reactions were present in the control group. It was concluded that because positive reactions were observed in test and control groups (after first and second challenge), it is likely that irritation, and not sensitization, was responsible for these observations (Kabara 1984).

Glyceryl Isostearate

CTFA reported the results of a 1985 study of the skin sensitization potential of Glyceryl Isostearate using a guinea pig maximization test procedure. Eighteen guinea pigs (10 test, 4 treated controls, and 4 untreated controls; strain not stated) were used. During induction, the animals were injected intradermally (0.1-ml injections) in the shoulder region with 2.5% Glyceryl Isostearate in a vehicle consisting of polyethylene glycol (PEG), microcrystalline cellulose (MCC), and Dobs/saline (dodecyl benzene sulfonate in physiological saline).

At 5 to 7 days after the last injection, an occlusive induction patch saturated with 100% Glyceryl Isostearate was maintained in contact with the injection site for 48 h. Intradermal injection reactions were scored according to the following scale: fp (faint pink erythema) to dp (deep pink erythema). The challenge phase was initiated 12 to 14 days after application of the induction patch. An occlusive challenge patch containing 50% Glyceryl Isostearate (in PEG and MCC) was applied to the skin for 24 h. Further challenges were made at weekly intervals, or longer, as required. Challenge reactions were scored according to the following scale at 24 and 48 h: 0 (no reaction) to 3 (marked erythema).

The four treated controls consisted of four guinea pigs that were tested according to the preceding study protocol, with the exception that Glyceryl Isostearate was omitted only from the intradermal and covered patch induction procedures. The untreated control group consisted of four previously untreated animals that were challenged with Glyceryl Isostearate according to the procedure described earlier.

The results of the first challenge yielded one positive reaction at 24 h and two positive reactions at 48 h. Following the second challenge, positive reactions were not noted at 24 or 48 h. The slight sensitization reactions noted following the first challenge were confirmed by results of the third challenge (CTFA 1985).

Glyceryl Citrate/Lactate/Linoleate/Oleate

Hüls AG (1996e) reported results of the skin sensitization potential of Glyceryl Citrate/Lactate/ Linoleate/Oleate using 20 guinea pigs. Ten guinea pigs served as controls. Any reactions, particularly those classified as erythema and edema, were assessed 30 and 54 h after the initiation of treatment. Undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate was tested during induction phases I, II, and III (dermal application) because the undiluted material did not induce skin irritation in a preliminary test.

During the fourth week of testing, a "trigger concentration" was determined for initiation treatment on three guinea pigs that were the same ages as those in the main test. The undiluted test substance was administered (dermal application) as the highest, nonirritating concentration.

Glyceryl Citrate/Lactate/Linoleate/Oleate did not induce systemic effects or any adverse effects on body weight gain. At 30 h post application in induction phases I, II, and III, skin irritation was not observed in the 20 test animals or 10 vehicle-control animals. "Trigger" treatment with the undiluted test substance did not induce erythema or edema of the right rear flank at 30 or 54 h post application in test or control animals. Also, in patch tests, the vehicle did not cause skin reactions in animals of the test or control group. It was concluded that Glyceryl Citrate/Lactate/Linoleate/Oleate did not induce sensitization in guinea pigs (Hüls AG 1996e).

Glyceryl Rosinate

Shao et al. (1993) conducted a study to investigate whether the esterification of rosin with glycerol or other polyalcohols would alter the allergenicity of rosin. The allergenicity of Glyceryl Rosinate was evaluated using three groups of 15 female Dunkin-Hartley guinea pigs.

During induction, the first group (group I) received four closed epidermal applications of 8.3% glyceryl triabietate (GTA) in petrolatum (abietic acid, esterified to yield this compound, is the main component of rosin) on days 0, 2, 7, and 9 and two injections of Freund's complete adjuvant (FCA) on day 7. In the second group (group II), the induction procedure (same protocol) consisted of four closed epidermal applications of 20% gum rosin and two injections of FCA. The control group was sham treated.

All three groups were challenged with the following: 0.93%, 2.8%, and 8.3% GTA; 10% glycerol esterified tall oil rosin (TORG), 20% gum rosin; and petrolatum vehicle control. Challenge patches (Finn chambers) were removed after 24 h, and reactions scored at 48 and 72 h post application. Study results (challenge phase, 72-h reading) are summarized below.

In group I, results indicated one positive reaction to 0.93% GTA; 2.8% GTA; 20% gum rosin; and petrolatum. The incidence of positive reactions in group II was as follows: 1 (8.3% GTA); 2 (10% TORG); 3 (0.93% and 2.8% GTA); and 9 (20% gum rosin). One positive reaction to 0.93% GTA and two positive reactions to 8.3% GTA were observed in the control group. Scores at 48 and 72 h were not significantly different from one another. It is important to note that in group II, the incidence of positive reactions to 10% TORG (two reactions) was less than that of 20% gum rosin (nine reactions). The esterification of rosin with glycerol, in effect, reduced the allergenicity of rosin. GTA was nonallergenic and did not cross-react with allergens in unmodified gum rosin (Shao et al. 1993).

This same laboratory evaluated the allergenicity of GTA and other esters of glycerol and abietic acid (Gäfvert et al. 1994). Products formed from the esterification of abietic acid (mentioned in the preceding study) with glycerol include: glyceryl triabietate (GTA); glyceryl 1,2-diabietate ($GDA_{1,2}$); glyceryl 1,3-diabietate ($GDA_{1,3}$); and glyceryl 1-monoabietate (GMA).

The allergenicity of these compounds was evaluated according to the procedure in the preceding study using female Dunkin-Hartley guinea pigs. Group I (14 animals) and Group II (15 animals) animals were induced with 3.3% GMA in petrolatum and 20% gum rosin in petrolatum, respectively. Petrolatum was applied to animals of Group III (control). The animals were challenged with the following: GMA (0.37%, 1.1%, and 3.3%); 5.7% $GDA_{1,3}$; 5.7% $GDA_{1,2}$; 8.3% GTA, and 10% unmodified gum rosin. Challenge reactions at 72 h post application were reported. All statistically significant findings are accompanied by p values.

In group I, GMA induced sensitization at concentrations of 0.37% (1 of 14 animals), 1.1% (4 of 14, $p < .05$), and 3.3% (6 of 14, $p < .01$). The incidence of sensitization reactions to GMA in group II was as follows: 0.37% GMA (1 of 15 animals), 1.1% (3 of 15), and 3.3% (2 of 15). No significant responses were noted when $GDA_{1,3}$ and $GDA_{1,2}$ were tested on animals that were sensitive to GMA. Gum rosin induced sensitization in 8 of 15 animals ($p < .01$) in group II and in 1 of 14 animals in group I. No significant cross-reactivity with GMA was noted in animals that were sensitive to unmodified gum rosin. Neither GTA nor petrolatum induced sensitization in either of the three groups (Gäfvert et al. 1994).

Phototoxicity and Photoallergy

Glyceryl Isostearate

The phototoxicity and photoallergenicity potentials of Glyceryl Isostearate was evaluated using 20 albino guinea pigs. The back and sides of each animal were divided into the following six treatment areas: test material + UVA, test material + UVB, test material alone, positive control (8-methoxypsoralen) + UVA, UVB alone, and UVA alone. Doses of the test material and positive control (dose for each = 0.02 ml/cm^2) were applied 30 min prior to irradiation. UV irradiations were performed using Philips tubes (TL 20W/09 for UVA and TL 20W/12 UV for UVB). Cutaneous reactions were evaluated at 24 h post treatment. Glyceryl Isostearate did not induce significant cutaneous reactions with or without UV irradiation. The positive control (8-methoxypsoralen) induced severe reactions (Unichema International 1997a).

Immunologic Activity

Glyceryl Laurate

The effect of Glyceryl Laurate on delayed-type hypersensitivity to sheep erythrocytes was evaluated using mice. The four groups (10 mice per group) of female ICR mice used in the study were designated as treated (T; two groups), control (C), and normal (N). The mice in groups T and C were injected subcutaneously (s.c.) with 0.05 ml/mouse of sheep red blood cells (SRBCs) (3×10^9 cells/ml). Injections were made into the right hind footpads. The mice in group T were then immediately injected intraperitoneally (i.p.) with a saline suspension of Glyceryl Laurate, and group C mice were injected with saline alone. On day 4, mice of groups T, C, and N were injected (s.c.) in the left hind footpads with SRBCs (0.05 ml/mouse). Left footpad

thickness was measured with a caliper 24 h later. The i.p. administration of Glyceryl Laurate did not cause significant enhancement of the immunological response. Mean footpad thickness was 4.20 ± 0.44 mm, compared to 4.23 ± 0.36 mm and 3.55 ± 0.23 mm for untreated mice and saline controls, respectively (Kabara et al. 1985).

The modulation of immune cell proliferation in vitro by Glyceryl Laurate was evaluated using lymphocytes obtained from murine spleens. Lymphocyte proliferation was stimulated at Glyceryl Laurate concentrations between 10^{-5} and 5 μg/ml per 5×10^5 lymphocytes. At concentrations greater than 5 μg/ml, Glyceryl Laurate inhibited lymphocyte proliferation and blocked the proliferative effects of the lymphocyte mitogens, phorbol myristate acetate and concanavalin A, and the toxic shock syndrome toxin-1 (potent T-cell mitogen). Furthermore, the results of experiments using purified immune cell subsets indicated that Glyceryl Laurate (0.1 μg/ml) optimally induced T-cell proliferation, but did not affect B cells. Glyceryl Laurate–induced T-cell proliferation was blocked by cyclosporin A (immunosuppressive drug) at concentrations as low as 20 ng/ml, suggesting that Glyceryl Laurate could be exerting its effect along the calcium-dependent inositol phospholipid, signal transduction pathway (Witcher, Novick, and Schlievert 1996).

In Vitro Hemolytic Activity

Glyceryl Laurate

Kato et al. (1971) evaluated the hemolytic activity of Glyceryl Laurate using sheep erythrocytes. The erythrocytes were washed with 0.86% NaCl and suspended in NaCl solution. Glyceryl Laurate was dissolved or suspended in NaCl solution at several dilutions (starting with 1 mg/ml), and an equal volume of the red blood cell suspension in NaCl was added. Hemolytic activity, expressed by the highest dilution in which hemolysis was observed, was determined after incubation for 4 h at 37°C. The highest dilution in which hemolysis was observed was a sevenfold dilution of the starting concentration of Glyceryl Laurate. Glyceryl Laurate had strong hemolytic activity.

GENOTOXICITY

Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated for its potential to induce reverse mutations in the following *Salmonella typhimurium* strains: TA 98, TA 100, TA 1535, and TA 1537. The Ames test (plate incorporation and preincubation methods) was used in this evaluation. Five concentrations of Glyceryl Citrate/Lactate/Linole-ate/Oleate (50 to 5000 μg/plate) were tested in triplicate both with and without metabolic activation. Tetrahydrofurane served as the solvent control, and the three positive controls were as follows: 2-nitrofluorene, sodium azide, and 9-aminoacridine. Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic (all strains) in the plate incorporation test or the preincubation test either with or without metabolic activation (Hüls AG 1996f).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, which is composed of diterpene resin acids. In studies on the mutagenicity of resin acids, only neoabietic acid (component of rosin) was mutagenic in the Ames/*Salmonella* assay (FDA 1988).

CARCINOGENICITY

Glyceryl Stearate was tested for tumor promoting activity (Saffioti and Shubik 1963) on the clipped dorsal skin of 20 female Swiss mice. One week after a single application of 9,10-dimethylbenz(a)anthracene (DMBA) (1% to 1.5% in mineral oil), 5% Glyceryl Stearate (in acetone) was applied to skin twice weekly. No tumors developed; slight epidermal hyperplasia at the site of application was noted.

Tumor Inhibition

Glyceryl Laurate

Kabara et al. (1985) evaluated the in vitro antitumor activity of Glyceryl Laurate using two leukemia cell lines, L-5178Y and L-1210. Leukemia cells were cultured (1.0×10^5 cells/ml, 48 h at 37°C) with various concentrations of the test substance, suspended in physiological saline containing 5.0% DMSO. Untreated cultures served as controls. The growth inhibitory effect was determined as the ratio of cell numbers in treated and control cultures at the end of the incubation period. Based on this ratio, the IC_{50} was obtained by probit diagramming analysis. The IC_{50} values were 50 and 62 mg/ml in L-1210 and L-5178Y cell lines, respectively. Thus, marked antitumor activity was demonstrated against both cell lines.

On the basis of the above results, these authors evaluated Glyceryl Laurate in a survival test using 5-week-old, female BDF_1 mice implanted intraperitoneally with L-1210 leukemia cells (1.0×10^5 cells/mouse). A suspension of the test substance in saline was injected i.p. into each animal once daily for five consecutive days (first injection, 24 h after tumor transplantation). One group of mice received daily injections of 30 mg/kg, and the other, daily injections of 100 mg/kg. Control mice were injected with saline.

Study results indicated that Glyceryl Laurate was ineffective in prolonging the life span of tumor-bearing mice. Survival times for test mice were 9.83 days (30 mg/kg dose group) and 9.66 days (100 mg/kg dose group). The survival time for control mice was also 9.83 days. The investigators stated that the in vivo inactivity of Glyceryl Laurate could have been due to the inappropriateness of the experimental conditions adopted, and that further tests should be performed using different routes of administration, dosages, or vehicles (Kabara et al. 1985).

In two earlier studies (Kato et al. 1969, 1971), the in vivo antitumor activity of Glyceryl Laurate in 5-week-old ddY mice (weights = 18 to 22 g) was evaluated using Ehrlich ascites tumor cells. In one study, 2×10^6 tumor cells were implanted i.p. into each of eight mice. Glyceryl Laurate was then administered i.p. daily for 5 successive days at doses of 2.5 mg/mouse/day

(2 mice) and 10 mg/mouse/day (2 mice). The four control mice were injected with tumor cells only. After 7 days, tumor growth and body weight gain were noted. Tumor growth was not observed in mice given either of the two doses. Survival was 27 and 24 days for the two mice dosed with 2.5 mg/day and 28 and >30 days for the two mice dosed with 10 mg/day. Tumor growth in four control mice was marked and survival was 13 to 17 days. Glyceryl Laurate inhibited tumor growth completely and increased the survival time of mice injected with tumor cells (Kato et al. 1969).

In a study by Kato et al. (1971), approximately one million tumor cells were implanted i.p. into 12 test mice (two groups of six) and six controls, and a solution or suspension of Glyceryl Laurate in 0.86% NaCl solution was administered i.p. daily for 5 successive days. The two test groups received doses of 2.5 and 10 mg/mouse/day, respectively, and control mice were injected with 0.2 ml of NaCl solution. After 7 days, tumor growth and body weight gain were noted. Tumor growth was marked in control mice (survival time = 16 days). However, no tumor growth was observed in either group of test mice. Survival times for 2.5 mg/day and 10 mg/day test mice were 26 and >29 days, respectively.

In an additional experiment, these authors evaluated the in vitro action of Glyceryl Laurate on Ehrlich ascites tumor. The hypothesis was that Glyceryl Laurate might have a specific affinity for the tumor cells, and, if strong enough, attack the cells. In vitro attack of the cells was measured using the viability of treated tumor cells. In the assay for viability, the viability of treated tumor cells (mixture of Glyceryl Laurate in phosphate-buffered saline with the tumor cell suspension) was determined by staining the cells with safranin dye. Glyceryl Laurate was tested at concentrations of 5, 50, and 500 μg/ml. The percentage of dead cells in the mixture was determined by counting the number of cells microscopically. Cell death (100%) was noted at concentrations of 50 and 500 μg/ml (Kato et al. 1971).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Studies on the reproductive and developmental toxicity of the Glyceryl Monoesters reviewed in this report were not found in the published literature. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are derived from rosin. As stated earlier, rosin is defined as the residue remaining when the volatile oil is distilled from turpentine or a product of the distillation, solvent extraction, or both, of the stumps or fallen trees of various species of *Pinus*. FDA (1988) reported that, following the administration of hexane extracts of *Pinus ponderosa* needles to mice by stomach tube, increased embryonic resorptions were observed. Recall that it is important to note that the following active components of the extracts tested, diterpene resin acids, were identified: pimaric acid, isopamaric acid, sandaracopimaric acid, palustric/levopimaric acid, abietic acid, dehydroabietic acid, and neoabietic acid. Abietic acid and dehydroabietic acid have been identified as main components of rosin.

CLINICAL ASSESSMENT OF SAFETY

Inhalation Toxicity

Glyceryl Caprylate/Caprate is used in hair sprays. Jensen and O'Brien (1993) reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition.

The determination of the health consequences of exposure to an aerosol requires an analysis of the inhalation and deposition of the aerosol within the human respiratory system. The toxic action of an aerosol may be related to the number of particles, their surface area, or the mass deposited. Many occupational diseases are associated with the deposition of particles within a certain region of the respiratory tract.

The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, $\mathbf{d_a}$, defined as the diameter of a sphere of unit density possessing the same terminal setting velocity as the particle in question.

Many particles present in the air do not enter the respiratory tract because of the size-selective sampling of the nose and the mouth. Still others are removed in the upper respiratory tract. The concept of size-selective air sampling calls for measurement of particles in industrial aerosols of the size that are associated with a specific health effect. For chemical substances present in inhaled air as suspensions of solid particles or droplets, the potential hazard depends on the particle size as well as on mass concentration. The American Conference of Governmental Industrial Hygenists (ACGIH) has defined three particle-size-selective threshold limit values (PSS TLVs) (ACGIH 1991): inhalable particulate mass TLVs (IPM TLVs) for those materials that are hazardous when deposited anywhere in the respiratory tract; thoracic particulate mass TLVs (TPM TLVs) for those materials that are hazardous when deposited anywhere within the lung airways and the gas-exchange region; and respirable particulate mass TLVs (RPM TLVs) for those materials that are hazardous when deposited anywhere in the gas-exchange region (Jensen and O'Brien 1993).

The mean aerodynamic diameter of 4.25 $\pm$ 1.5 μm of respirable particles above may be compared with diameters of anhydrous hair spray particles of 60 to 80 μm (typically, <1% are below 10 μm) and pump hair sprays with particle diameters of $\geq$80 μm (Bower 1999).

Skin Irritation

Glyceryl Rosinate

The skin irritation potential of a lipstick containing 1.0% Glyceryl Rosinate, as supplied, was evaluated using 12 volunteers (21 to 45 years old). All subjects were in good heath and free of any visible skin disease or anomaly. The lipstick was crushed (to mix the inner and outer layers) and applied to an

occlusive patch. Patches (one per subject) covered with the lipstick were applied to the back and remained in place for 24 h. Reactions were scored 3 days later according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]). A new patch containing the test substance was reapplied to the same site on each subject and removed after 24 h. Reactions were scored after patch removal and 24 h later. The grading period was followed by a second new patch application (24 h), and reactions were scored at the same intervals. The lipstick containing 1.0% Glyceryl Rosinate did not elicit an irritation response (all scores = 0) in either of the 12 subjects tested (Biosearch, Inc. 1992a).

Skin Sensitization

General

Human studies have indicated that the incidence of contact sensitization is dose dependent and that the induction of skin sensitization is dependent on the dose of a chemical per unit area of skin (Kimber, Gerberick, and Basketter 1999).

Glyceryl Laurate and Glyceryl Linoleate

Danisco Ingredients (1996), reported a study in which the skin irritation and sensitization potential of Glyceryl Laurate and Glyceryl Linoleate was evaluated using 91 healthy volunteers (males and females, 18 to 65 years old) in a modified Draize repeat-insult patch test. The study was classified as single-blind. Patches consisted of a 5 cm wide strip of Scanpor tape to which 10 "Finn-chambers" were fixed in pairs. The three glyceryl monoesters were tested at a concentration of 50% w/v in liquid paraffin. Glyceryl Linoleate (0.02 ml) was dispensed directly into individual Finn chambers. Glyceryl Laurate was heated to 60°C and 0.02 g was placed directly into individual Finn chambers; 0.02 ml liquid paraffin was dispensed onto a filter disc in the chamber. Liquid paraffin served as the negative control.

The 91 volunteers were divided into two groups, group 1 (39 subjects) and group 2 (52 subjects), respectively. In group 1, the first set of induction patches was applied to the upper back for 23 h and subsequent patch applications were 47 h in duration. The patch test schedule for these subjects was as follows: days 1, 2, 4, 7, 9, 11, 14, 16 and 18. In group 2, 47-h induction patch applications were made according to the following schedule: days 1, 3, 5, 8, 10, 12, 15, 17, and 19. In both groups, induction patches were applied to the same site, unless a reaction stronger than mild erythema was observed. Reactions were scored after patch removal according to the following scale: 0 (no visible reaction) to 5 (bullous reaction).

During the challenge phase, initiated on day 35, patches were applied to new sites on the upper back for 47 h. Challenge reactions were scored at 1 and 49 h after patch removal. Classification of either test substance as irritating was based on 10% of the induction scores defined as >1 (mild erythema). Sensitization was defined as a rapid response to challenge patch application, characterized by severe erythema and edema (usually with papules and/or vesicles).

Seventeen of the 91 subjects withdrew for reasons either unrelated to treatment (16 subjects) or because the patch was painful (1 subject). Seventy-four subjects (64 women, 10 men) completed the study. Glyceryl Linoleate did not induce skin irritation or sensitization. However, Glyceryl Laurate induced mild, erythematous reactions during induction in most of the subjects and questionable reactions during the challenge phase in seven subjects. During induction and challenge (1 and 49 h post removal) phases, reactions to Glyceryl Laurate ranged from 1 (mild erythema) to 2 (moderate erythema) (Danisco Ingredients 1996).

Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate

Danisco Ingredients (1999f) reported results of a study in which the skin irritation and sensitization potential of Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate was evaluated in a single-blind study using 93 healthy volunteers (ages between 18 and 65 years). Ten of the original 107 subjects withdrew for reasons unrelated to the conduct of the study. The repeat-insult patch test procedure (similar to procedure in preceding study) was a modification of the Draize test. Glyceryl Laurate was tested at a concentration of 25% in liquid paraffin oil, whereas Glyceryl Myristate and Glyceryl Oleate were each tested at a concentration of 50% in liquid paraffin oil. Liquid paraffin oil served as the control. Induction patches (Finn chambers on Scanpor tape) containing either of the three test substances or the control were applied to the upper back of each subject. The subjects were instructed to remove and discard the patches at the end of the 47-h contact period. This procedure was repeated (same sites) for a total of nine induction applications.

Test sites were evaluated prior to application of the next patch and 1 hour after patch removal on the last day of the induction phase according to the following scale: 0 (no visible reaction) to 5 (bullous reaction). Challenge patches were applied to the upper back (distant from induction site) of each subject on day 36. The patches were removed and discarded at the end of the 47-h contact period. Reactions were evaluated at 1 and 49 h after challenge patch removal.

Glyceryl Laurate (25% in liquid paraffin oil) induced moderate erythema (score = 2) in eight subjects during induction and in one subject during the challenge phase. Glyceryl Myristate and Glyceryl Oleate did not induce irritation or sensitization at a concentration of 50% in liquid paraffin oil. The investigators concluded that the three test substances did not induce sensitization during induction or challenge phases (Danisco Ingredients 1999f).

Glyceryl Caprate

The skin sensitization potential of 15% Glyceryl Caprate in paraffinium perl. DAB 10 (pharmaceutical grade) was evaluated in a modified Draize assay using 63 subjects, 58 of whom completed the study. During induction, the test substance was applied (0.025 ml, occlusive patches–Finn chamber) to the scapular region of the back three times per week (on Mondays, Wednesdays, and Fridays) for a total of 10 applications. At the end of each

48-h period (72 h on weekend), patches were removed and sites rinsed with distilled water. Reactions were scored according to the following scale: 0 (no reaction) to 4 (erythema, edema, and bullae). A 12-day nontreatment period was initiated after reactions to the 10th induction patch were scored. At the end of the 12-day period, occlusive challenge patches were applied to new sites on the scapular back for 48 h. Challenge reactions were scored at 48 and 72 h post application. The test substance did not induce irritation or sensitization reactions in any of the subjects tested (International Research Services, Inc. 1995).

Glyceryl Rosinate

Shao et al. (1993) patch tested eight dermatitis patients who had previously reacted to colophony (gum rosin) using Finn chambers with various rosins and rosin esters. Ten healthy subjects served as controls. Results indicated that the number of reactions to the rosin esters was lower, compared to the results for rosin. Five of eight patients had positive reactions to 10% tall oil rosin (in petrolatum), whereas four of eight patients had positive reactions to 20% glycerol-esterified tall oil rosin (in petrolatum). Also, seven of eight patients had positive reactions to 5% Portuguese gum rosin (in petrolatum) and three of eight patients had positive reactions to 20% glycerol-esterified gum rosin (in petrolatum). Additionally, neither of the eight subjects had positive reactions to glyceryl triabietate or petrolatum.

Positive reactions to each test substance ranged from + (erythema and infiltration) to +++ (erythema, infiltration, and vesicles). Because abietic acid is a main component of rosin and is easily oxidized to form contact allergens, the concentrations of this acid in the following rosin esters and rosins that were tested are indicated as follows: Portuguese gum rosin (42% abietic acid); tall oil rosin (55%); glycerol-esterified gum rosin (0.3%); and glycerol-esterified tall oil rosin (3.7%). It is important to note that the methylated oxidation product of abietic acid, 15-hydroperoxyabietic acid methyl ester (contact allergen) induced positive reactions in six of the eight patients tested and that this incidence was lower than that reported for Portuguese gum rosin (seven of eight patients). The results of this study indicated that esterification with glycerol reduced the allergenicity of rosin (Shao et al. 1993).

Gäfvert et al. (1994) evaluated the allergenicity of the following compounds (in petrolatum) in patients with contact allergy to gum rosin, 5% Portuguese gum rosin (GR), 10% tall oil rosin (TOR), 20% glycerol-esterified gum rosin (GGR), 20% glycerol-esterified tall oil rosin (TORG), 5.4% glyceryl-monoabietate (GMA), 9.5% glyceryl-1,2-diabietate ($GDA_{1,2}$), and 9.5% glyceryl-1,3-diabietate ($GDA_{1,3}$). $GDA_{1,2}$, $GDA_{1,3}$, and GMA are products that result from the esterification of abietic acid with glycerol (mentioned in preceding study). Except for patch tests with $GDA_{1,2}$ and $GDA_{1,3}$ (6 patients), 12 patients were used in the evaluation of each compound. Patch tests (Finn chambers) involved the application of each compound to the skin for 48 h. Reactions were scored at 72 h post application. Ten control subjects were patch tested according to the same procedure.

Results for the rosins and rosin esters were similar to those in the preceding study. Over half of the patients had reactions (++ to +++) to these compounds. Five of the 12 patients had positive reactions to GMA (++ to +++), and neither of the 6 patients had positive reactions to $GDA_{1,2}$, or $GDA_{1,3}$. The patch testing of an additional patient with the latter two compounds also yielded negative results. No reactions were observed in the 10 healthy control subjects. This study confirmed the contact sensitization potential of rosin and rosin esters in patients with contact allergy to gum rosin and identified glyceryl-1-monoabietate as a contact allergen (Gäfvert et al. 1994).

The Consumer Product Testing Company (1997) patch tested 53 subjects (males and females, 18 to 69 years old) with a test material consisting of 20% Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. PEGMODWP-20). (Because Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Glyceryl Rosinate in the test material is 10%.) Forty-nine of the original 53 subjects completed the study; 4 withdrew for reasons that were unrelated to testing.

Approximately 0.2 ml of the test material (contains 10% Glyceryl Rosinate) was applied to the upper back, between the scapulae, of each subject on Mondays, Wednesdays, and Fridays for a total of 10 induction applications. Sites were covered with a semiocclusive patch immediately after each application of the test material. Nontreatment periods of 24 h followed patch removals on Tuesdays and Thursdays. Saturday patch removals were followed by 48 h nontreatment periods. The induction phase was followed by a 2-week nontreatment period, after which a challenge patch was applied to the same site and a previously untreated site. Challenge reactions were scored at 24 and 48 h post application according to the following scale: 0 (no visible reaction) to 4+ (erythema and edema with vesiculation and ulceration). Induction reactions were also evaluated according to this grading scale.

One subject had a score of 2+ (well-defined erythema, possible presence of barely perceptible edema) during induction and at 24 and 48 h during the challenge phase (at new test site, but not at original site). At 72 h, the same subject also had a challenge reaction of 3+ (erythema and edema) at the new test site, but not at the original site. None of the remaining 48 subjects had induction or challenge reactions. It was concluded that the test material did not have the potential for inducing skin irritation and/or sensitization in this study (Consumer Product Testing Company 1997).

Ivy Laboratories (1996) evaluated the sensitization potential of a foundation containing 4% Glyceryl Rosinate using 28 healthy adult volunteers (13 males and 15 females; 18 to 46 years old). Twenty-five subjects completed the study; 3 subjects were removed for reasons that were unrelated to application of the test substance. Patches were applied to the upper outer arm,

volar forearm, or to the back of each subject. During induction, approximately 0.1 ml of 0.25% aqueous sodium lauryl sulfate (SLS) was applied under an occlusive patch (secured with occlusive tape) that was removed after 24 h. The foundation (0.1 ml on semiopen induction patch) was then applied to the test site for 48 h (or 72 h, i.e., over the weekend). If skin irritation was not observed at the time of patch removal, an occlusive patch containing 0.25% aqueous SLS was reapplied for 24 h. Patch removal was followed by reapplication of a fresh induction patch (semi-open) containing the foundation.

This sequence of SLS and test substance application was repeated for a total of five induction exposures. If irritation was observed at any time during induction, SLS pretreatment was discontinued and replaced with a 24 h nontreatment period between applications of the test substance. Following a 10-day nontreatment period, the challenge phase was initiated. Pretreatment with SLS was performed prior to challenge patch application. Approximately 0.1 ml of 5% aqueous SLS was applied, under an occlusive patch, to a fresh skin site for 1 h. After patch removal, a semiopen challenge patch containing 0.1 ml of the foundation was applied to the same site for 48 h. Challenge reactions were graded 1 h after patch removal and 24 h later according to the following scale: 0 (not sensitized) to 3 (strong sensitization, large vesiculobullous reaction).

Contact allergy was not observed in any of the subjects during either of the two grading periods (all scores = 0). It was concluded that the foundation containing 4% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1996).

The maximization assay described in the preceding study was also used to evaluate the sensitization potential of a blush containing 2% Glyceryl Rosinate. Twenty-seven healthy adult volunteers (11 males and 16 females;18 to 56 years old) were tested. Contact allergy was not observed in any of the subjects during either of the two grading periods (all scores = 0). It was concluded that the blush containing 2% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1997).

The sensitization potential of a lip gloss containing 2.0% Glyceryl Rosinate was evaluated using 27 healthy adult volunteers (7 males, 20 females; 18 to 60 years old). Basically, the same maximization assay procedure (indicated above), was used with the following modifications: Patches were applied to the upper outer arm of each subject. During induction, the application of 0.1 ml of 1% aqueous SLS (occlusive patch) was followed by the application of 0.1 g of the test material (site covered with occlusive tape, referred to as induction patch). Prior to initiation of the challenge phase, the challenge site (new site on opposite arm) was pre-treated with 0.1 ml of 10% aqueous SLS (under occlusive patch). Pretreatment was followed by application of the test substance (same site) under an occlusive challenge patch secured with occlusive tape. Contact allergy was not observed in any of the subjects during either of the two grading periods (all scores = 0), and there were no unusual or unexpected side effects. It was concluded that the lip gloss containing 2% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1990).

Biosearch, Inc. (1992b) evaluated the skin irritation and sensitization potential of a lipstick containing 1% Glyceryl Rosinate, as supplied, using 78 volunteers (16 to 55 years old). Eleven of the original 89 subjects withdrew from the study for personal reasons. All subjects selected for the study were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Approximately 0.15 g of the test substance was placed on an occlusive patch that was applied to the back of each subject for 24 h. Reactions were scored at 48 h post application according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]).

At the end of the grading period, a second patch was reapplied (same site) to each subject according to the same procedure. The test procedure was repeated on alternate days (Monday, Wednesday, and Friday) for a total of nine applications. Patches applied on Friday were removed on Saturday, and reactions were scored at 72 h post application. After a 2-week nontreatment period, a challenge patch containing the test substance was applied for 24 h to a new test site (adjacent to initial site) on each subject. Challenge reactions were scored at 48 and 72 h post application. Neither irritation nor sensitization reactions were observed in any of the subjects tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a sensitization response (Biosearch, Inc. 1992b).

Glyceryl Hydrogenated Rosinate

The Consumer Product Testing Company (2000) patch tested sixty subjects (males and females, 17 to 75 years old) with a test material consisting of 20% Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. Hydrogenated PEGMOD [20]). (Because Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Hydrogenated Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Hydrogenated Glyceryl Rosinate in the test material is 10%.) Fifty-one of the original 60 subjects completed the study, because 9 withdrew for reasons that were unrelated to testing.

A semiocclusive patch containing approximately 0.2 ml of the test material (contains 10% Hydrogenated Glyceryl Rosinate) was applied to the upper back, between the scapulae, of each subject on Mondays, Wednesdays, and Fridays for a total of nine, 24-h induction applications. Nontreatment periods of 24 h followed patch removals on Tuesdays and Thursdays. Saturday patch removals were followed by 48 h nontreatment periods. The induction phase was followed by a 2-week nontreatment period, after which a challenge patch was applied to a new test site, but not to the original site. Challenge reactions were scored at

24 and 72 h post application according to the following scale: 0 (no visible skin reaction) to 4 (severe erythema, possible edema, vesiculation, bullae and/or ulceration). The same scale was also used to evaluate induction reactions.

Neither skin irritation nor sensitization was observed in any of the subjects tested. It was concluded that the test substance did not not have the potential for inducing dermal irritation or allergic contact sensitization in this study (Consumer Product Testing Company 2000).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate

These are esters of glycerin and acids derived from rosin. In its reviews of rosin in color additive lakes, the FDA assessed the safety of various rosins (FDA 1988, 1994a, 1994b). The agency's findings are summarized below.

Although rosin has a history of use as a skin salve and as a soap, there were no toxicological data (e.g., from dermal irritation studies) that would support the safe use of rosin in contact with the skin or mucous membranes (e.g., in the lip area). Gum and wood rosins may be safely ingested; however, there are no data that support the safe use of rosin(s) as a substratum in color additive lakes intended for external uses (FDA 1988). In a more recent toxicology review, after considering that the "worst case" estimate for rosin content in lipsticks is 7.7% and that a more realistic estimate for lipstick rosin content is 0.6%, it was determined that, based on human patch test results, there appears to be little risk of irritant reactions due to rosin contained in lipsticks (FDA 1994a).

Furthermore, data submitted to FDA in 1994 indicated that lipsticks, blush, lipliner pencil, and nail polish containing rosinated lakes did not induce skin irritation in human subjects. Specifically, no skin irritation was observed when 197 subjects were patch tested (48-h single application) with blush products containing rosinated color additive lakes (9.3%) or when 10 subjects were tested with a lipstick product containing 1.07% rosinated color additive lakes in a phototoxicity test. Thus, FDA concluded that rosinated color additive lakes in cosmetic products at concentrations up to 9.3% do not present a health hazard due to irritation (FDA 1994b).

Skin irritation reactions to rosin/colophony have been reported; however, the intensity of these reactions is dependent upon the test concentration as well as the particular rosin that is being tested. In a human study on 60% colophony (Portuguese gum rosin), patch test results indicated that skin irritation could have been observed. However, in other studies, no evidence of skin irritation was found in more than 2300 subjects tested with 60% rosin or in 1132 patients patch tested with 20% rosin. Additionally, a number of commercially available, structurally modified rosin acids have been reported to induce dermal irritation. Most have an irritation threshold at concentrations greater than 10% (FDA 1994a).

FDA concluded that rosin/colophony can be classified as a moderate sensitizer. Sensitization to gum rosin exhibits a dose-response relationship (0.001% to 20%), indicating that sensitization can be minimized by reducing the concentration (details from the original study referenced in FDA's review of rosin are included in the next paragraph). It is important to note that positive allergic responses to rosin have been confirmed in both animal and human studies. Because of the allergenicity of rosin in human subjects, this compound is included in the standard 23-compound allergic contact dermatitis screen that is used by dermatologists (FDA 1994a).

FDA also considered results of a study by Karlberg (1988) using the method of Fregert (1981) in which patients with suspected rosin-allergy were patch tested with serial dilutions of Portuguese gum rosin in petrolatum according to the internationally accepted method for diagnosis of contact allergy by Fregert (1981). Finn chambers and Scanpor surgical tape were used. Patches were removed after 48 h of contact and reactions were scored at 72 h post application.

Twelve patients were tested with Portuguese gum rosin at concentrations ranging from 0.001% to 20%. Another group of 12 patients who had +++ reactions to 20% gum rosin in an earlier study was retested with two different preparations of Portuguese gum rosin (one in petrolatum) at concentrations ranging from 0.001% to 10%.

A clear dose-response relationship (with a maximum response at doses of 10% to 20%) was observed in the serial dilution test with 0.001% to 20% gum rosin (w/w) in petrolatum. The author stated that these results imply that a concentration of 10% gum rosin is worth considering for routine testing. The incidence of positive reactions to two different preparations of gum rosin in the second group of 12 patients is summarized as follows: 0.001% gum rosin (0 to 1 patient), 0.01% gum rosin (2 to 3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients), and 10% gum rosin (10 to 12 patients). In the results for 10% gum rosin, all but 2 patients were tested with both preparations of gum rosin (Karlberg 1988).

Overall, FDA concluded that there is little or no potential for dermal irritation reactions due to rosin at the concentrations used in lipsticks containing rosin lakes. Therefore rosin, at the concentrations that can be present in lipstick containing color additive rosin lakes, does not present a health hazard due to irritation. OCAC reports that unmodified rosin is a moderate sensitizer and can induce allergic reactions in sensitized individuals. At the concentration of rosin that can be present as a component of color additive lakes (up to 7%), rosin can cause sensitization in unsensitized individuals. It is possible that rosin is bound during the color laking process and is not available to induce sensitization. However, no information was available regarding the skin absorption and subsequent skin sensitization potential of rosin contained in color additive lakes. FDA recommended further studies be undertaken to address this issue (FDA 1994a).

FDA amended its conclusion after human skin sensitization data on various cosmetic products containing rosinated lakes of D&C Red No. 6, D&C Red No. 7, and D&C Red No. 34 at several different concentrations were received. FDA concluded that

the use of rosin as a substratum in color additive lakes is safe, up to rosinated color additive concentrations of 9.0% in cosmetics products. This conclusion was based on the observation that no skin sensitization or photoallergic reactions to cosmetic formulations containing rosinated color additives at concentrations up to 9.0% were noted in human subjects. The human data included a photoallergy test using 312 subjects and a composite of repeat insult patch tests on a total of 2,381 subjects (FDA 1994b).

FDA also included in its consideration the components of rosin. Abietic acid and dehydroabietic acid, resin acids, are the main component of rosin. Abietic acid was not considered a contact allergen and the risk of resin acids inducing contact sensitivity in workers exposed to tall oil-containing products was considered minimal (FDA 1988).

The later review noted that oxidation products of abietic and dehydroabietic acid (which can be formed during storage) have been found to be allergenic. Hydrogenation of rosin acid reduced the allergenic potency of these oxidized gum rosin. There may be cross sensitization between several oxidized rosin acids. The oxidation of rosin acids might be necessary in order to induce immunologic properties (FDA 1994a).

The FDA review also considered that peroxides and hydroperoxides of rosin acids can contribute to the sensitization potential of rosin. Specifically, the test results for nine synthesized oxidation products of abietic acid and other rosin acids indicated that 7-oxodehydroabietic acid; 13,14-epoxy abietic acid; and 8,12-peroxidodihydroabietic acid, (strongest sensitizer of the three) are moderate sensitizers. Furthermore, the sensitization potential of a mixture of oxidation products from the polar fraction was found to be as strong as that of the peroxido compound. Methyl ester, keto, hydroxy, and hydroxylated unsaturated ketone derivatives were weak to poor sensitizers (FDA 1994a).

Phototoxicity

Biosearch, Inc. (1992c) evaluated the phototoxicity of a lipstick containing 1.0% Glyceryl Rosinate, as supplied, using 10 volunteers (17 to 55 years old). All subjects were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Subjects on medication (especially medications suspected of causing photobiological reactions or medications with the potential for modifying the inflammatory response) were excluded. The subjects were classified as Fitzpatrick skin types I, II, and III. The degree of skin pigmentation did not significantly influence responses to UV light or interfere with the scoring of skin reactions. The test substance was applied (approximately 20 mg/site) to two sites on the back of each subject and spread to cover the areas uniformly. One of the test sites was irradiated with 0.5 MED (minimal erythemal dose, in seconds) of UVA and UVB light (continuous spectrum in UVA and UVB regions, 290 to 400 nm) between 30 and 60 min after application of the test substance. The MED was defined as the shortest exposure time at which erythema was first observed 20 ± 4 h after exposure. Irradiation with UVA and UVB light was followed by exposure to a total of 14 Joules/cm^2 of UVA. A 2 mm thick WG-345 Schott filter was interposed to eliminate UVB (290 to 320 nm) radiation from the ultraviolet source.

Reactions were scored at 24, 48, and 72 h post irradiation according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]). The second site to which the test substance had been applied was not irradiated and served as an irritation control. A third site served as the untreated, irradiated control. Skin irritation was not observed (score = 0) at control or irradiated sites in either of the ten subjects tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a phototoxicity response (Biosearch, Inc. 1992c).

Photoallergenicity

Biosearch, Inc. (1992d) evaluated the photoallergenicity of a lipstick containing 1% Glyceryl Rosinate, as supplied, using 26 volunteers (17 to 55 years old). Four of the original 30 subjects withdrew for personal reasons. All subjects were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Subjects on medication (especially medications suspected of causing photobiological reactions or medications with the potential for modifying the inflammatory response) were excluded. Skin types were variable and the degree of skin pigmentation did not significantly influence responses to UV light or interfere with the scoring of skin reactions. During the induction phase, each of the subjects received six applications of the test substance over a period of 3 weeks. For each application, approximately 0.15 g of the test substance was placed on an occlusive patch that was applied to the back for 24 h. Patches were applied on Tuesdays and Thursdays. After patch removal, each site was exposed to 2.0 MEDs of UVB radiation and 4 Joules/cm^2 of UVA radiation. The subjects were instructed to keep the back covered throughout the study to avoid exposure to natural or artificial sunlight. The challenge phase was initiated 18 days after the last induction exposure. Challenge patches containing the test substance were applied to two new, adjacent test sites for 24 h. After patch removal, reactions were scored according to the scale indicated in the preceding study.

One of the test sites was then exposed to a combination of 0.5 MED of UVB and 4 Joules/cm^2 of UVA light. The other site was not exposed to UVA light and served as the irritation control. The UV light control site was defined as an additional site that was not exposed to the test substance but was irradiated with 0.5 MED of UVB and 4 Joules/cm^2 of UVA light. Challenge sites were scored at 24, 48, and 72 h post-irradiation. No reaction (score = 0) was observed at control or test sites on any of the 26 volunteers tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a photoallergy response (Biosearch, Inc. 1992d).

Case Reports

A strong positive reaction was observed when a 35-year-old female patient with itchy, facial erythema was tested with 0.01% glyceryl monoisostearate. Reportedly, the itchy, facial erythema

resulted from the use of a foundation containing 1.77% glyceryl diisostearate. It is important to note that Glyceryl Monoisostearate was one of the impurities detected in glyceryl diisostearate (Tanaka, Shimizu, and Miyakawa 1993).

Glyceryl Monoisostearate (0.01% in petrolatum) induced ++ reactions (at 48 and 72 h) in an 18-year-old girl with a history of what was described as lip cream dermatitis (Hayakawa et al. 1987).

SAFETY INFORMATION ON ARACHIDONIC ACID

Information from the CIR Final Report on the safety of Arachidonic Acid in cosmetics (Andersen 1993) is summarized below.

Arachidonic Acid is an essential, polyunsaturated, fatty acid that is used as a surfactant-cleansing agent and a surfactant—emulsifying agent in cosmetic formulations. Arachidonic Acid is a liquid at room temperature, is soluble in alcohol, ether, and water, and absorbs in the ultraviolet B (UVB) range. Arachidonic Acid is well absorbed from the gastrointestinal tract and the circulatory system, it distributes rapidly into the lipid compartment of the body, and is rapidly converted to phospholipid by the liver. Arachidonic Acid can be metabolized by three different pathways: the cyclooxygenase, lipoxygenase, and cytochrome P450 systems.

Arachidonic Acid metabolites are involved in the inflammatory process. A chronic cellular imbalance of Arachidonic, γ-linolenic, and eicosapentaenoic acids, and of their respective eicosanoid derivatives, may have major health implications. Arachidonic Acid may alter the cutaneous immune response.

In a study in which Arachidonic Acid was applied to the pinnae of mice, an increase in pinnal thickness was observed. Microscopic effects were also observed throughout the study. Application of Arachidonic Acid to mouse skin produced edema and inflammation, with high doses possibly causing ulceration of the skin.

Arachidonic Acid did not produce teratogenic effects. Exogenous Arachidonic Acid appeared to help prevent the teratogenic effects caused by hyperglycemia and phenytoin. Subcutaneous administration to pregnant diabetic rats significantly reduced neural tube defects, cleft palate, and micrognathia. Arachidonic Acid has also dose-dependently reversed antimasculinization caused by a number of compounds. However, indomethacin has been found to stop the reversal of teratogenic effects by Arachidonic Acid.

Arachidonic Acid has mutagenic potential. Arachidonic Acid has increased the frequency of TG^r colonies, phagocyte-induced SCEs, chromosomal aberrations, thioether synthesis, MAL number, and the incorporation of [^{3}H]thymidine/mg cellular DNA.

In 24 h single insult patch tests, a formulation containing 0.04% Arachidonic Acid was not an irritant.

The CIR Expert Panel recognized that dermal absorption data were lacking and that such data were necessary before a determination of safety can be made. And based on the results of those studies, still further data may be needed. Because Arachidonic Acid may be involved in UV light-induced cutaneous immune suppression, immunomodulatory data may be requested (dependent on the results of the dermal absorption studies). In addition to immunomodulatory data, carcinogenicity, photocarcinogenicity, and human irritation, sensitization, and photosensitization data may also be requested.

Accordingly, the CIR Expert Panel found that the safety of this ingredient has not been documented and substantiated for cosmetic product use. The additional data needed were described as follows:

1. Dermal absorption data

Based on the results of the absorption studies, the Panel indicated there may be a need for the following data:

2. Immunomodulatory data
3. Carcinogenicity and photocarcinogenicity data
4. Human irritation, sensitization, and photosensitization data (Andersen 1993)

SUMMARY

The safety of the following 43 Glyceryl Monoesters in cosmetics is reviewed in this report: Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate.

According to one source, Glyceryl Monoesters are not pure monoesters, but are mostly mixtures with mono-, di-, and triesters in a ratio of approximately 4:4:2, respectively. Another source indicates that the guaranteed purity of commercial and conventional Monoglyceride (Glyceryl Monoester) is a minimum of 90%, meaning that impurities account for a maximum of 10% of the composition. The results of impurities analyses of 14 Glyceryl Monoesters indicated that only one, Glyceryl Palmitate/Stearate, contained (mono)glycerol diester at a concentration of 1.2%.

UV spectral analyses of 14 Glyceryl Monoesters indicated maximum absorbance at 238 or 239 nm.

Glyceryl Monoesters are used mostly as skin conditioning agents—emollients and/or surfactant—emulsifying agents in cosmetics. Frequency of use data provided by FDA in 1998 indicate that of the 43 ingredients in this safety assessment, the following 16 are used in cosmetics: Glyceryl Laurate, Glyceryl Alginate, Glyceryl Arachidonate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Cocoate, Glyceryl Hydroxystearate, Glyceryl Isostearate, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Palmitate, Glyceryl Myristate, Glyceryl Polyacrylate, Glyceryl Rosinate, and Glyceryl Undecylenate.

Concentration of use data received from the cosmetics industry in 1999 indicate that Glyceryl Monoesters are used at concentrations up to 12% in cosmetic products.

Glyceryl Monoesters have also been approved by FDA for use as direct or indirect food addtives. The Food Protection Committee of the National Academy of Sciences National Research Council Food and Nutrition Board concluded that there appears to be no reason to question the safety of mono-, di-, or triglycerides of lauric acid (i.e., Glyceryl Laurate, Glyceryl Dilaurate, or Glyceryl Trilaurate [Trilaurin]) as food additives.

Glyceryl Monoesters (monoglycerides) are metabolized to free fatty acids and glycerol, both of which are available for the resynthesis of triglycerides.

Glyceryl Laurate enhanced the penetration of drugs through cadaverous skin and hairless rat skin in vitro.

Lauricin (registered trademark for Glyceryl Laurate) has been described as having a wide spectrum of antimicrobial activity against diverse microbial species (viruses, fungi, molds, yeasts, and bacteria included).

A low-grade irritant response was observed following inhalation of an aerosol containing 10% Glyceryl Laurate by test animals.

An LD_{50} of >20,000 mg/kg was reported for rats dosed orally with Glyceryl Laurate. In other studies, neither Glyceryl Isostearate nor Glyceryl Citrate/Lactate/Linoleate/Oleate induced toxicity in rats that received a single oral dose of 2000 mg/kg. Similar results were reported in an acute dermal toxicity study in which 2000 mg/kg Glyceryl Citrate/Lactate/Linoleate/Oleate was administered to rats.

Undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was not toxic (LD_{50} > 5 g/kg) when administered orally to fasted Wistar albino rats (five males, five females; weight range 220 to 292 g). None of the animals died.

A no-effect level of 280 mg/m^3 was reported for Glyceryl Laurate in a short-term inhalation toxicity study involving rats. Rats were subjected to 14 1-hour exposures during a 3-week period. Neither gross nor microscopic lesions were noted in rats fed 25% Glyceryl Laurate in another short-term (10 weeks) study.

No test substance–related gross or microscopic changes were observed in albino rats fed a mixture of mono-, di-, and triglycerides containing 40% to 45% Glyceryl Laurate for two years.

Glyceryl Laurate had strong hemolytic activity in an in vitro assay using sheep erythrocytes.

Glyceryl Laurate, Glyceryl Isostearate, or Glyceryl Citrate/Lactate/Linoleate/Oleate were not classified as ocular irritants in rabbits. Undiluted, purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) also was not irritating to the eyes of rabbits.

Undiluted Glyceryl Laurate induced minor erythema and edema when applied (occlusive patches, single application) to intact skin of rabbits. In another study, single occlusive patch applications of 20% Glyceryl Laurate emulsion to abraded and intact skin caused moderate skin irritation in rabbits.

Overall, Glyceryl Isostearate was classified as nonirritating to the skin of rabbits in a study in which single, semiocclusive patch applications were made to intact skin. The most severe reaction (moderate irritation) did not clear until day 5 post removal. Glyceryl Isostearate was also classified as nonirritating to the skin of rabbits in another study in which single occlusive patch applications were made to intact and abraded skin sites.

A PII of 3.40 (potential for severe irritation—warning label may be considered) was reported in an occlusive patch test evaluating the skin irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) in rabbits. Follicular hyperkeratosis (comedone formation) was not observed in another study in which the same undiluted test substance was applied to the ears of rabbits.

Neither erythema nor edema was observed in rabbits after semiocclusive patches containing heated Glyceryl Citrate/Lactate/Linoleate/Oleate (single application) were applied to intact skin. In another study, Glyceryl Citrate/Lactate/Linoleate/Oleate (single applicatioin) induced clearly circumscribed erythema and very mild edema when applied to intact skin of rabbits. All reactions had cleared by day 10 post application.

The skin sensitization potential of Glyceryl Laurate was evaluated in the maximization test. Guinea pigs were subjected to four sensitizing injections of 2% Glyceryl Laurate and then challenged with intradermal injections of 0.8% Glyceryl Laurate and topical applications of 25% Glyceryl Laurate. No positive reactions were observed. In another maximization test, skin sensitization was induced in 2 of 10 guinea pigs challenged with a 10% dilution of 20% Glyceryl Laurate emulsion. When a second challenge was initiated 7 days after the first, positive reactions were observed in five animals. Positive reactions were also observed in four animals challenged with a 5% dilution of 20% Glyceryl Laurate emulsion. Because positive reactions were also noted in the control group after the first and second challenge, the results were attributed to skin irritation (but not sensitization) effects of the test substance.

Glyceryl Isostearate was also evaluated in the maximization test. After induction, ten guinea pigs were challenged with 50% Glyceryl Isostearate in polyethylene glycol (PEG) and microcrystalline cellulose (MCC). Two additional challenges were also conducted. The first challenge yielded one and two positive

reactions (all slight reactions) at 24 and 48 h, respectively. These results were confirmed by reactions observed after the third challenge.

The sensitization potential of Glyceryl Citrate/Lactate/Linoleate/Oleate in 20 guinea pigs was evualated using the Buehler method. Following the dermal application of undiluted test substance during induction and challenge phases, no evidence of irritation or sensitization was observed.

The reaction of rosin with glycerol to form two esterification products (glyceryl triabietate [GTA] and glycerol esterified tall oil rosin [TORG]), in effect, reduced the allergenicity of rosin. GTA results from the esterification of glycerol with abietic acid, the major component of rosin. The incidence of positive challenge reactions in 15 guinea pigs tested was as follows: 1 (8.3% GTA), 2 (10% TORG), 3 (0.93% and 2.8% GTA), and 9 (20% gum rosin). Glyceryl diabietate and glyceryl monoabietate induced either the same incidence or a higher incidence of sensitization in other experiments (similar test groups) in the same study.

No evidence of significant cutaneous reactions, with or without UV irradiation, was found when the photoxicity and photoallergenicity potential of Glyceryl Isostearate was evaluated using 20 guinea pigs.

In a study (using mice) investigating the effect of Glyceryl Laurate on delayed-type hypersensitivity to sheep erythrocytes, the test substance did not cause significant enhancement of the immunological response. In another study using lymphocytes from murine spleens, Glyceryl Laurate–induced T-cell proliferation was blocked by cyclosporin A (immunosuppressive drug) at concentrations as low as 20 ng/ml. These results suggest that Glyceryl Laurate could be exerting its effect along the calcium-dependent inositol phospholipid, signal transduction pathway.

In Ames plate incorporation and preincubation mutagenicity tests, Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic (with or without metabolic activation) to the following *Salmonella typhimurium* strains: TA 98, TA 100, TA 1535, and TA 1537. In studies on the mutagenicity of resin acids, only neoabietic acid (component of rosin) was mutagenic in the Ames/*Salmonella* assay. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, which is composed of diterpene resin acids.

Marked antitumor activity against two leukemia cell lines in vitro was observed in the presence of Glyceryl Laurate. A follow-up study to the preceding assay indicated that Glyceryl Laurate (i.p. injection, saline suspension) was ineffective in prolonging the lifespan of tumor-bearing BDF_1 mice that had been implanted i.p. with L-1210 leukemia cells. Doses of 30 and 100 mg/kg were injected daily for 5 consecutive days. In other experiments, the antitumor activity of Glyceryl Laurate against Ehrlich ascites tumor cells was demonstrated both in vivo and in vitro. In the two in vivo studies, Glyceryl Laurate (in saline) was injected i.p. into ddY mice that had been implanted i.p. with Ehrlich ascites tumor cells. Doses of 2.5 and 10.0 mg/mouse were injected daily for 5 successive days. Test results (both studies) indicated no tumor growth and increased survival time (compared to controls) at both doses.

The tumor promoting activity of Glyceryl Stearate on the clipped dorsal skin of Swiss mice was evaluated. One week after a single application of 9,10-dimethylbenz(*a*)anthracene (DMBA) (1% to 1.5% in mineral oil), 5% Glyceryl Stearate (in acetone) was applied to skin twice weekly. No tumors developed; slight epidermal hyperplasia at the site of application was noted.

Following the administration of hexane extracts of *Pinus ponderosa* needles to mice by stomach tube, increased embryonic resorptions were observed. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, and rosin is obtained from trees of various species of *Pinus*.

Glyceryl Laurate, Glyceryl Linoleate, and Glyceryl Palmitate were each tested at a concentration of 50% w/v, in liquid paraffin, in a repeat insult patch test (RIPT) (Finn chambers) involving 91 healthy human subjects. Glyceryl Linoleate did not induce skin irritation or sensitization in the 74 subjects who completed the study. Glyceryl Laurate induced mild, erythematous reactions during induction in most of the subjects and questionable reactions in seven subjects during the challenge phase. Reactions ranged from mild to moderate erythema (score = 2) during induction and challenge phases.

The skin irritation and sensitization potential of Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate was evaluated in a second RIPT (Finn chambers) using 107 healthy subjects, 93 of whom completed the study. Glyceryl Laurate was tested at a concentration of 25% in liquid paraffin oil, whereas Glyceryl Myristate and Glyceryl Oleate were tested at a concentration of 50% in paraffin oil. Glyceryl Laurate induced moderate erythema (score = 2) in eight subjects during induction and in one subject during the challenge phase. Glyceryl Myristate and Glyceryl Oleate did not induce irritation or sensitizatiion. Neither of the three test substances was considered a sensitizer. In another study, Glyceryl Caprylate (15%) did not induce skin irritation or sensitization in an RIPT involving 63 healthy subects, 58 of whom completed the study.

Two case reports indicated skin reactions to two cosmetic products containing Glyceryl Isostearate, as well as positive patch test reactions to this ingredient.

Skin irritation was not observed in 12 healthy volunteers patch tested (occlusive patches) with a lipstick containing 1.0% Glyceryl Rosinate. Neither skin irritation nor sensitization was observed in 78 healthy volunteers patch tested (occlusive patches) with the same product in a repeated insult patch test.

The contact sensitization potential of three product formulations containing Glyceryl Rosinate was evaluated in three maximization assays (healthy human subjects), respectively. Results were negative for the following three study groups: foundation containing 4.0% Glyceryl Rosinate (25 subjects), blush containing 2.0% Glyceryl Rosinate (27 subjects), and lip gloss containing 2.0% Glyceryl Rosinate (27 subjects).

Skin irritation and sensitization were observed in one of 49 subjects patch tested (RIPT, semiocclusive patches) with a material consisting of 20% Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. PEGMODWP-20). (Because Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Glyceryl Rosinate in the test material is 10%.) The challenge reaction was observed at the original test site, but not at the new site. It was concluded that the positive reaction observed was unique to that individual.

Neither skin irritation nor sensitization was observed in any of the 51 subjects patch tested (semiocclusive patches) with a material consisting of 20% Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. Hydrogenated PEGMOD [20]). (Because Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Hydrogenated Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Hydrogenated Glyceryl Rosinate in the test material is 10%.) The subjects were challenged at a new test site, but not at the original site.

Phototoxicity was not induced in a group of 10 healthy volunteers tested with a lipstick containing 1.0% Glyceryl Rosinate. Patches were not applied to test sites. Similarly, photoallergenicity was not induced in a group of 26 healthy volunteers patch tested (occlusive patches) with the same product in a repeat insult patch test.

Data on 12 patients suspected of having gum rosin allergy indicated that sensitization to Portuguese gum rosin exhibited a dose-response relationship (0.001% to 20%). In the same study, the incidence of positive reactions to Portuguese gum rosin in a second group of 12 patients with gum rosin allergy was summarized as follows: 0.001% gum rosin (0 to 1 patient), 0.01% gum rosin (2 to 3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients), and 10% gum rosin (10 to 12 patients). These data were based on patch tests with serial dilutions of Portuguese gum rosin in petrolatum.

The esterification of rosin with glycerol, in effect, reduced the allergenicity of rosin in dermatitis patients. Five of eight patients had positive reactions to 10% tall oil rosin in petrolatum, whereas four of eight patients had positive reactions to 20% glycerol-esterified tall oil rosin in petrolatum. Additionally, seven of eight patients had positive reactions to 5% Portuguese gum rosin in petrolatum and three of eight patients had positive reactions to 20% glycerol-esterified gum rosin in petrolatum.

Glyceryl-1-monoabietate was identified as a contact allergen in another study evaluating the allergenicity of rosin and its esterification products. Abietic acid (esterified to form glyceryl-1-monoabietate) is a main component of rosin, and, furthermore, clinical data indicate that it is easily oxidized to form contact allergens (e.g., 15-hydroperoxyabietic acid and its methyl ester). It is also important to note that oxidation products of abietic acid and dehydroabietic acid (also a main component of rosin) that can be formed during storage have been found to be allergenic.

FDA concluded that the use of rosin as a substratum in color additive lakes is safe up to rosinated color additive concentrations of 9.0% in cosmetic products. This conclusion was based on the observation that no skin sensitization or photoallergic reactions to cosmetic formulations containing rosinated color additives at concentrations up to 9.0% were noted in human subjects. The human data, submitted by CTFA, included a photoallergy test using 312 subjects and a composite of repeat-insult patch tests on a total of 2381 subjects.

Information from the earlier safety assessment of Arachidonic Acid is considered relevant, in that the concerns raised therein also apply to the safety assessment of Glyceryl Arachidonate. The CIR Expert Panel had concluded that the safety of Arachidonic Acid had not been documented and substantiated for cosmetic product use. Additional safety data that are needed include

1. Dermal absorption data

Based on the results of the absorption studies, the Panel indicated that there may be a need for the following data:

2. Immunomodulatory data
3. Carcinogenicity and photocarcinogenicity data
4. Human irritation, sensitization, and photosensitization data.

DISCUSSION

A primary concern regarding the safety of Glyceryl Monoesters is the possible presence of Glyceryl Diesters, and, specifically, the 1,2 diesters, which are known to have adverse effects. After reviewing impurities data on 14 Glyceryl Monoesters (90% pure), the Panel concluded that the level of 1,2-diacylglycerols (1,2 (mono)glycerol diester) in Glyceryl Monoesters is not sufficient to warrant any concern about effects on signal transduction and resulting effects on cell growth and proliferation that are associated with 1,2-diacylglycerol–induced activation of protein kinase C (PKC). The results of the impurities analysis indicated that only one of the 14 Glyceryl Monoesters, Glyceryl Palmitate/Stearate, contained (mono)glycerol diester.

Of approximately 4% of the (mono)glycerol diester content of Glyceryl Palmitate/Stearate, 29% is actually the 1,2 (mono)glycerol diester. Thus, the concentration of 1,2 (mono)glycerol diester in Glyceryl Palmitate/Stearate is approximately 1.2%. In addition, the Panel noted the absence of tumor promotion activity in a study using Glyceryl Stearate. The Panel noted that if 1.2% represents the maximum concentration of this impurity in cosmetic grade Glyceryl Monoester, then the concentration of 1,2-diacylglycerol in cosmetics would be significantly less, considering that current use concentration data from the cosmetics industry indicate that product concentrations of Glyceryl Monoesters range from 0.1% to 12%.

Given that Glyceryl Laurate is known to enhance the skin penetration of other chemicals, but that data are not available on the

penetration enhancement activity of other Glyceryl Monoesters, the Panel agreed that the manufacturers should consider the skin penetration enhancement potential of all Glyceryl Monoesters when formulating cosmetic products to ensure safety.

The Expert Panel previously stated that the available inhalation toxicity data are insufficient for addressing the Panel's concern over the use of Glyceryl Monoesters in aerosolized products, which relates to the potential surfactant activity of these ingredients on the lungs. After further review of this issue, focusing primarily on the use of Glyceryl Caprylate/Caprate in hair sprays, the Panel determined that Glyceryl Caprylate/Caprate can be used safely in these products, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of anhydrous hair sprays (60 to 80 μm) and pump hair sprays (>80 μm) was large compared to the median aerodynamic diameter of 4.25 $\pm$ 1.5 μm for a respirable particulate mass.

Though mammalian genotoxicity data on the Glyceryl Monoesters were not available, the Panel concluded that they are not likely genotoxic agents based on the chemical structures of these compounds and negative Ames test data. Limited carcinogenicity data were negative, and data on the Glyceryl Monoester, Glyceryl Stearate indicated that 5% Glyceryl Stearate in acetone was not a tumor promoter in Swiss mice. These data, combined with the observation that maximum use concentrations of Glyceryl Monoesters associated with most (but not all) of the product type categories for cosmetics are $\leq$5%, led the Panel to discount any carcinogenic risk.

The Panel expressed specific concerns relating to the safety of Glyceryl Rosinate, Glyceryl Hydrogenated Rosinate, Glyceryl Collagenate, and Glyceryl Arachidonate in cosmetics, based on the specific chemical with which glycerin is esterified.

Glyceryl Rosinate is defined as the monoester of glycerin and mixed long-chain acids derived from rosin, and Glyceryl Hydrogenated Rosinate is defined as the monoester of glycerin and hydrogenated mixed long-chain acids derived from rosin. The Panel recognizes the potential for contamination of cosmetic grade samples of Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate with rosin, a moderate sensitizer. The Panel also noted that abietic acid, the main component of rosin, is easily oxidized to form contact allergens such as 15-hydroperoxyabietic acid and its methyl ester; glyceryl-1-monoabietic acid. Moderating this concern are data indicating that the sensitization potential of rosin is reduced by esterification with glycerol.

The Panel determined that this concern could be adequately addressed by establishing a concentration limit for Glyceryl Rosinate in cosmetic products that is based on the highest test concentration in human skin sensitization studies that did not induce sensitization. Skin irritation and sensitization were observed in 1 of 49 subjects patch tested (semiocclusive patches) with a trade mixture containing 10% Glyceryl Rosinate. In the other human study, neither skin irritation nor sensitization was observed in any of the 51 subjects patch tested (semiocclusive patches) with a trade mixture containing 10% Glyceryl Hydrogenated Rosinate. After reviewing these negative data and considering that the highest reported use concentrations of Glyceryl Rosinate at 10% in an eyebrow pencil and up to 12% in a mascara (products applied to the eyebrows or eyelashes), the Panel agreed that Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate could be considered safe as used in cosmetic products. The Panel reasoned that any sensitization potential associated with Glyceryl Rosinate or Glyceryl Hydrogenated Rosinate at a concentration of 10% or 12% in a semiocclusive patch test would be significantly reduced in cosmetic products in which the mode of application results in minimal contact with the skin and does not involve any form of occlusion.

After reviewing the positive skin irritation study (rabbits, occlusive patches) on an undiluted trade mixture containing 50% Glyceryl Rosinate and 50% octyldodecyl myristate, the Panel agreed that the irritation potential of this material would be significantly reduced under the conditions of cosmetic use (i.e., dilution to current use concentrations of Glyceryl Rosinate and absence of occlusion).

The Panel noted that the photosensitization potential of Glyceryl Monoesters in cosmetics is not an issue, based on the negative UV absorption data on 14 ingredients and human photoallergenicity data on a cosmetic product containing 1% Glyceryl Rosinate that were provided.

Because protein found in cartilage and other connective tissues in animals is the source of collagen, the Expert Panel stipulates that Glyceryl Collagenate should be free of infectious agents.

The CIR Expert Panel has issued a Final Report with an insufficient data conclusion on Arachidonic Acid. Because it is likely that Glyceryl Arachidonate will be hydrolyzed to Arachidonic Acid, the Panel noted that the data needed for completion of the safety assessment on Arachidonic Acid are also applicable to Glyceryl Arachidonate. Dermal absorption data are needed. Based on the results of the absorption studies, the Panel indicated that there may be a need for the following data: immunomodulatory data; carcinogenicity and photocarcinogenicity data; and human irritation, sensitization, and photosensitization data.

CONCLUSIONS

Based on the available animal and clinical data included in this report, the CIR Expert Panel concludes that the following Glyceryl Monoesters are safe as cosmetic ingredients in the present practices of use and concentration: Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl

Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Gyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate.

The Panel also concludes that the available data are insufficient to support the safety of Glyceryl Arachidonate in cosmetic formulations.

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Amended Safety Assessment of Acrylates Copolymers as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 126 acrylates copolymers; 56 of these ingredients were previously reviewed by the Panel, and 70 are reviewed herein for the first time. Many of these ingredients are reported to have several functions in cosmetics, with the function of film former being the most commonly reported cosmetic function for members of this family; many of the ingredients also may function in cosmetics as viscosity increasing agents. The Panel reviewed relevant new data, including frequency and concentration of use, and considered the data from previous CIR reports. The Panel concluded the 126 acrylates copolymers named in this report are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

INTRODUCTION

CIR published the Final Report on the Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients in 2002.[1] Based on the available data, the Panel concluded that the acrylates copolymers named in that report are safe for use in cosmetics when formulated to avoid irritation.

According to its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years. As part of the re-review process, in addition to reassessing the existing conclusion, CIR also determines whether other ingredients are appropriate for inclusion in the re-review document. The Panel determined that it is appropriate to include all the copolymers (including crosslinked copolymers (i.e., crosspolymers)) prepared from monomers that comprise, in part, acrylic acid and/or methacrylic acid; the methyl, ethyl, propyl, or butyl ester(s) of these acids; or the salts of one or both of these two acids, with a few exceptions, as described below. Based on this rationale, the 126 ingredients described below, and listed in Table 1, are included in this re-review.

Some of the ingredients deemed appropriate for inclusion have previously been reviewed by CIR in other assessments. In 2017, the Panel published a safety assessment with the conclusion that 23 crosslinked alkyl acrylates included in the safety assessment are safe in the present practices of use and concentration, except when polymerized in benzene.[2] Acrylates C10-30 Alkyl Acrylate Crosspolymer may be polymerized in benzene, and the available data were insufficient to make a determination of safety, specifically with regard to carcinogenicity, for this ingredient when polymerized in benzene. Accordingly, this assessment only addresses the safety of Acrylates C10-30 Alkyl Acrylate Crosspolymer when polymerized in solvents other than benzene.

In 2011, the Panel published a safety assessment of Polymethyl Methacrylate (PMMA), Methyl Methacrylate Crosspolymer, and Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer, and concluded that these ingredients are safe in the practices of use and concentration that were described in the report.[3] The Food and Drug Administration (FDA) had made a determination of safety of PMMA use in several medical devices, which included human and animal safety data. The Panel used that information as the basis of safety of PMMA and related polymers as used in cosmetics.

Another report on similar ingredients is the 1982 CIR Final Report on the Safety Assessment of Carbomers-934, -910, -934P, 940, -941, and -962; the Panel concluded that these ingredients are safe in the present practices of use and concentration that were described in that report.[4] These ingredient names no longer exist as INCI names. Instead, they are now identified in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*) as technical names for one ingredient, Carbomer.[5] In 2003, the Panel reaffirmed that Carbomer is safe as used.[6]

In addition to the ingredients that have been previously reviewed by the Panel, an additional 70 acrylates copolymers that have not yet been reviewed are named in the *Dictionary*.[5] These ingredients are also included in this safety assessment.

The Panel determined that it was appropriate to exclude five ingredients that were part of the initial safety assessment on the Acrylates Copolymers in this re-review because they are either already part of a recent or a concurrent safety assessment. Sodium Styrene/Acrylates Copolymer and Styrene/Acrylates Copolymer were reviewed in 2014 (and found safe as used in cosmetics),[7] and the safety of Acrylates/VP Copolymer, Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer, and VP/Dimethyl-aminoethylmethacrylate Copolymer are part of the concurrent safety assessment of Vinylpyrrolidone Polymers.

According to the *Dictionary*, the ingredients included in this report have an array of functions in cosmetics, with the function of film former being the most commonly reported cosmetic function for members of this family (Table 2).[5] Many of the ingredients also may function in cosmetics as viscosity increasing agents.

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

Excerpts from the summaries of previous reports on Acrylates Copolymer and related ingredients, and all other previously-reviewed ingredients, are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or the summary section.) Additionally, the Discussions from these reports are also included in this document. For complete and detailed information, please refer to the original documents, which are available on the CIR website (https://www.cir-safety.org/ingredients). Please note that information on the monomers is found in several of the original reports, but not in this document.

Much of the new data included in this safety assessment was published by Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS).[8-14] Please note that NICNAS provides summaries of information generated by industry, and it is that summary data that are brought into this safety assessment when NICNAS is cited.

CHEMISTRY

Definition and Structure

The definitions and structures of the ingredients included in this report are provided in Table 2.

Copolymers are polymers synthesized from two or more different monomers, and crosspolymers are copolymers that are crosslinked (i.e., individual polymer chains are connected by bridging molecules [crosslinking agents]).[2] As stated in the Introduction, this report comprises a large number of copolymers and crosspolymers, most of which are prepared from monomers that include, in part, acrylic acid and/or methacrylic acid; the methyl, ethyl, propyl, or butyl ester(s) of these acids; or the salts of one or both of these two acids (Figure 1).

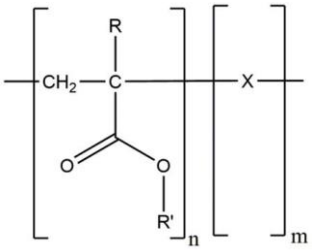


Figure 1. Acrylates copolymers, wherein R is hydrogen or methyl; R' is hydrogen, methyl, ethyl, propyl, butyl, or a salt cation (e.g., sodium); and X is one or more co-monomer residues.

However, a few of these ingredients are the polymerization products of monomers that comprise acrylate esters that are not methyl, ethyl, propyl, or butyl; but instead, these esters are the products of different alkoxyl or polyalkoxyl groups (Figure 1). Also, these other ingredients are all essentially homopolymers.

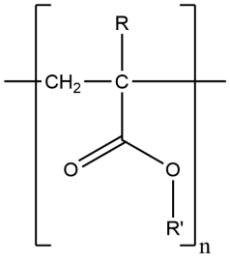


Figure 2. Other polyacrylates, wherein R is hydrogen or methyl; and R' is alkoxyl or polyalkoxyl (e.g., PEG-23).

Physical and Chemical Properties

From the Safety Assessment of Crosslinked Alkyl Acrylates[2]

Crosslinked polymers are generally less chemically reactive and less soluble (if not totally insoluble) than their respective non-crosslinked counterparts. Because of the manner in which these polymers are created and the mixture of monomers and cross-linking agents that can be used, 2 polymers that have the same INCI name can have very different physical consistencies.

Physical and chemical properties of several acrylates copolymers are described in Table 3. Primarily, physical form is identified therein.

Methods of Manufacture

From the Original Safety Assessment of Acrylates Copolymers[1]

Linear polymers of acrylic acid are produced by combining the monomer with a free-radical initiator, which is generally largely consumed by the reaction. The size of the polymer is determined by controlling the environment in which the polymerization occurs. Polymers of acrylic acid are characterized by their average molecular weight, but many species of greater and lesser molecular weight are present and unreacted monomer and catalysts can also be present. Additionally, hydroquinone and monomethyl ester of hydroquinone are often incorporated into acrylic acid and its esters as an inhibitor.[1]

Specific method of manufacture information for several ingredients is found in the original report.

From the Safety Assessment of Crosslinked Alkyl Acrylates[2]

Cross-linked alkyl acrylates are typically produced via free radical, head-to tail chain propagation polymerization. Ethyl acetate + cyclohexane, water, n-hexane, and benzene are all named as solvents.

From the Safety Assessment of PMMA and related ingredients[3]

The manufacturing process for PMMA beads used in medical devices and in cosmetic products is the same. The only difference is the size of the PMMA spheres, which are provided according to the specifications of the purchaser. Polymethyl methacrylate beads or powders in cosmetics are precipitated out from a polymerization reaction. The average bead size can be controlled within the 4 to 50 µm specifications. In nail products, polymer powders are made from methyl or ethyl methacrylate or their copolymers.

From the Safety Assessment of [Carbomer][4]

Carbomer is manufactured by reflux polymerization of acrylic acid in an inert solvent in the presence of a catalyst. In doing this, a closed system, free of oxygen and water, is used.

Acrylates Copolymer

Acrylates Copolymer, as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate, with a quantitative composition described as poly(ethyl acrylate-co-methyl methacrylate) 2:1, is produced by emulsion polymerization.[15] A redox-initiated polymerization of the monomers ethyl acrylate and methyl methacrylate occurs through the use of a free radical donor redox initiator system. Polyethylene glycol monostearyl ether is used as an emulsifier in the process, and an alkyl mercaptan is used as a chain modifying agent. At the end of the process, an emulsifier is added to reduce foaming. Residual monomers and excess water are removed by water vapor distillation, and the pH of the reaction mixture is adjusted with sodium hydroxide.

A similar emulsion polymerization process is used to synthesize Acrylates Copolymer as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid, with a quantitative composition described as poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 in an aqueous (aq.) medium.[16] Polymerization is by means of a free radical initiator. Sodium lauryl sulfate (SLS) and polysorbate 80 are used as emulsifiers, and an alkyl mercaptan is used as a chain-modifying agent. Small amounts of dimethicone (polydimethyl siloxane) are added to reduce foam formation. Water vapor distillation removes the residual monomers to a level of less than 100 mg/kg total. After the reaction product is cooled and filtered, the dry substance content is approximately 30%.

Composition/Impurities

From the Original Safety Assessment of Acrylates Copolymers[1]

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

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

From the Safety Assessment of Crosslinked Alkyl Acrylates[2]

Small amounts of residual monomer and/or solvent may be present in the crosspolymers.

From the Safety Assessment of PMMA and related ingredients[3]

The impurity of concern in PMMA is the monomer, methyl methacrylate (MMA). Analysis of PMMA beads used in cosmetic formulations found MMA to be present at < 100 ppm. The Nail Manufacturers Council reported that the residual monomer is typically < 1.5%; averages of 0.7% and 1.2% have been reported. Residual MMA in Methyl Methacrylate Crosspolymer is similar to that found in PMMA, i.e., < 100 ppm.

From the Safety Assessment of [Carbomer][4,6]

Reported impurities for the Carbomer resins include water, benzene, propionic acid, acetic acid, acrylic acid, heavy metals, iron, arsenic, and lead. The Panel calls attention to the presence of benzene as an impurity in Carbomer and recommends that every effort be made to reduce it to the lowest possible value. However, when the safety of Carbomer was reassessed in 2003, the Panel acknowledged the industry practice of removing benzene from Carbomer.

Acrylates Copolymer

Specifications for Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate) state that it contains < 100 mg/kg total monomer (sum of methyl methacrylate and ethyl acrylate); 0.7% residual emulsifier (polyethylene glycol monostearyl ether); < 0.5% ethanol; and < 0.1% methanol.[17] Additionally, limits on heavy metals are: < 2 mg/kg arsenic; < 2 mg/kg lead; < 2 mg/kg mercury; < 10 mg/kg zinc; and < 10 mg/kg copper.

Approximately 0.3% SLS and 1.2% polysorbate 80, both w/w based on the solid substance, are residual in the polymer as a result of the emulsion polymerization process used to synthesize Acrylates Copolymer as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid.[16]

Acrylates/Steareth-20 Methacrylate Copolymer

Acrylates/Steareth-20 Methacrylate Copolymer contains < 100 ppm residual monomer.[18]

Polyacrylate-1 Crosspolymer

Polyacrylate-1 Crosspolymer is reported to be 99% pure.[12] (No other details were available.)

VA/Butyl Maleate/Isobornyl Acrylate Copolymer

A copolymer of vinyl acetate, butyl maleate and isobornyl acrylate in ethanol is reported to be at least 95.3% pure.[8] Impurities are reported as < 0.4% acetone dimethylformaldehyde; < 0.1% vinyl acetate; < 0.1% monobutyl maleate; and < 0.1% isobornyl acrylate. The maximum percentage of low molecular weight species (molecular weight < 1000) is < 2%.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this report is evaluated based on data received from the US 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. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to information received from the VCRP and the Council survey, 66 of the 126 ingredients assessed in this report are in use.[19-25] Carbomer has the highest frequency of use; according to 2018 VCRP data, it is used in 6434 cosmetic formulations (with 6175 uses under the name Carbomer and 259 uses listed under various tradenames), and most of these uses (5336) are in leave-on products (Table 4).[25] Acrylates Copolymer and Acrylate/C10-30 Alkyl Acrylate Crosspolymer (solvent not specified) have the next highest frequencies of use, with 3177 and 3135 reported uses, respectively. Many of the other in-use acrylates copolymers have hundreds of use, although some have just a few.

The results of concentration of use surveys conducted by the Council in 2018 indicate that Acrylates Copolymer has the highest maximum use concentration; it is used at up to 98.6% in nail extenders; use in product categories other than nail products is not as high, but Acrylates Copolymer is used at up to 25% in products that result in dermal contact (face and neck products).[19] Ingredients with the next highest reported concentrations of use are Acrylates/VA Copolymer (at 50%, in "other" skin care formulations)[19] and Polymethyl Methacrylate (at up to 44.6%, in face powders).[23]

Numerous ingredients named in this report have been reviewed previously by the Panel. For many of the previously-reviewed ingredients, the frequency of use has increased since the time of the original review, with some increases being quite significant. For example, the frequency of use of Acrylates Copolymer increased from 227 uses in 1998[1] to 3177 uses in 2018,[25] and the frequency of use of Carbomer increased from 1504 uses in 2001[6] to 6434 uses in 2018.[25] Concentrations of use were not reported by the FDA at the time of the original assessment of Acrylates Copolymer and related ingredients, so it is not known if the concentrations of use have changed for those ingredients. For the other previously-reviewed ingredients, there were no notable increases in concentrations of use.

It should be noted that that the original report on Polymethyl Methacrylate stated this ingredient was used as beads in cosmetic products. However, based on environmental concerns, the use of microbeads in cosmetics is being phased out in many jurisdictions, including the US.[26] Microbeads include the Polymethyl Methacrylate beads described in the 2011 report.

In some cases, reports of uses were received from the FDA VCRP, but no concentration of use data were provided. For example, Potassium Carbomer is reported to be used in 73 formulations, but no use concentration data were submitted in response to the Council survey. In several other cases, no uses were reported to the VCRP, but a maximum use concentration was provided by industry. It should be presumed that for those ingredients, there is at least one use in each category for which a concentration was reported.

Many of the acrylates copolymers are used in products that can be used near the eye (e.g., 30% Acrylates/Ethylhexyl Acrylate Copolymer in mascara),[20] or are used in products that could result in incidental ingestion (e.g., 16.1% Polymethyl Methacrylate in lipstick formulations).[23] Additionally, some of these ingredients are used in cosmetic sprays and could possibly be inhaled; for example, VA/Butyl Maleate/Isobornyl Acrylate Copolymer is reported to be used at a maximum concentration of 10% in aerosol hair sprays). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent

diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[27,28] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[29,30] Sodium Polyacrylate has reported use in an aerosol deodorant at a concentration of 2.9%.[19] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[30] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Additionally, some of the acrylates copolymers are reportedly used in loose powders; for example, Polymethyl Methacrylate is used at concentrations up to 44.6% in face powders,[23] and could possibly be inhaled. 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.[31-33]

The acrylates copolymers that are not reported to be in use, according to 2018 FDA VCRP and 2018 Council survey data, are listed in Table 5.

With the exception of AMP-Acrylates Copolymer, the acrylates copolymers described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).[34] AMP-Acrylates Copolymer is restricted by a maximum secondary amine content of 5% in ready for use preparations.

Non-Cosmetic

From the Safety Assessment of PMMA and related ingredients[3]

Polymethyl methacrylate bone cement has been approved by the FDA as a class II (special controls) medical device that requires premarket notification and adherence to standards. Polymethyl methacrylate beads are incorporated into collagen as dermal fillers. Intraocular lenses are made of PMMA.

Several of the ingredients reviewed in this report are approved for use as secondary direct food additives or as indirect food additives. (See Table 6.) Additionally, Polymethyl Acrylate is a prior-sanctioned food ingredient as a substances used in the manufacture of paper and paperboard products used in food packaging. [21CFR181.30]

Acrylates Copolymer

Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate[15] and as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid[16]) is used as an excipient in the preparations for oral tablets as a glazing/coating agent to permit the pH-independent delayed release of active ingredients.

TOXICOKINETIC STUDIES

Dermal Penetration

From the Safety Assessment of PMMA and related ingredients[3]

Polymethyl methacrylate-based cosmetic ingredients are large molecules and remain in particulate form (dispersed) in final preparations and thus will not likely cross the stratum corneum to induce systemic toxicity.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Oral

Acrylates Copolymer

Five male rats were administered 55 - 75 mg/animal of Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate; supplied as a dried film labeled with ^{14}C with a specific activity of 0.17 µCi/mg) by gavage.[15] Urine and feces were collected for 5 days prior to dosing (to establish background radioactivity levels), and for 7 days following dosing. Animals were then killed, and tissue samples were collected and assessed for radioactivity. An additional 9 male rats were also given a single oral dose of the test article, and 3 animals were killed 1, 3, or 14 days after dosing, and tissue samples were collected. The mean total recovery of radioactivity over a period of 5 days following administration of the labeled substance was in excess of 90% of the administered dose. More than 97% of the radioactivity was recovered in the feces, primarily with 48 h of dosing. Little radioactivity (0.0092%) was excreted in the urine. Levels of radioactivity in the blood and tissues did not significantly differ between treated and control animals. The researchers concluded that less than 0.02% of the administered test article was absorbed from the gastrointestinal tract, and that any material that was absorbed was rapidly excreted.

Three groups of 4 male and 4 female Sprague-Dawley rats were dosed by gavage for 13 days with Acrylates Copolymer (as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid; dose not stated), followed by a single dose of radiolabeled test material (10 µCi per animal; ^{14}C-labeled at the free carboxyl group of the methacrylic acid moiety).[16] One group was killed at 24 h, and one at 72 h, after the last dose. The last group was kept for 10 days, and urine and feces were collected. The majority of the dose was excreted in the feces; with 94% collected within 72 h of dosing. Little or no radioactivity (< 0.1%) was recovered in urine. Tissues and tissue contents accounted for < 0.01% of the total recovery, and levels of radioactivity in the carcass were below limits of detection.

TOXICOLOGICAL STUDIES

From the Safety Assessment of PMMA and related ingredients[3]

The Panel saw no need to review systemic toxicity data on PMMA and related polymers applied to the skin as the safety of this route of exposure can be extrapolated from data on use of these polymers as medical devices, which had already been reviewed and found safe by the FDA.

Acute Toxicity Studies

From the Original Safety Assessment of Acrylates Copolymers[1]

The following LD_{50} values were reported for Acrylates Copolymer: > 16 g/kg (dermal, rabbits), > 16 ml/kg (dermal), >9 g/kg (dermal), 9 g/kg (dermal, rats), > 5.2 mg/l (rats). Ethylene/Acrylic Acid Copolymer had a" low order of acute toxicity" following dermal and oral administration to rats; the oral LD_{50} was > 5 g/kg. The oral LD_{50} for rats of an ammonium salt of Ethylene/Acrylic Acid was 41.5 ml/kg. In an acute inhalation study, 0 of 6 rats exposed to an aqueous emulsion of the ammonium salt of Ethylene/Acrylic Acid polymer died. The dermal LD_{50} for rabbits and the oral LD_{50} for rats of Vinyl Acetate/Maleate/Acrylate Copolymer solution was > 5 g/kg. For rats, the oral LD_{50} values of Polyacrylic Acid and Sodium Polyacrylate were 2.5 and > 40 g/kg, respectively; and 0.34 and 2.59 ml/kg, respectively, for male rats.

From the Safety Assessment of Crosslinked Alkyl Acrylates[2]

Little toxicity data were available. Acute dermal toxicity data for Acrylates/C10-30 Alkyl Acrylate Crosspolymer and Acrylates/Vinyl Neodecanoate Crosspolymer in rabbits (LD_{50}s > 2.0 g/kg and > 5.0 g/kg, respectively) and oral LD_{50} values in rats for Acrylates/C10-30 Alkyl Acrylate Crosspolymer (>10 g/kg), Acrylates/ Vinyl Isodecanoate Crosspolymer (2 g/kg), Acrylates/Vinyl Neodecanoate Crosspolymer (> 5 g/kg), and Sodium Acrylates Crosspolymer-2(> 2 g/kg indicated that these ingredients are not very toxic. Additionally, the inhalation LC_{50} of Acrylates/Vinyl Neodecanoate Crosspolymer in rats is > 16.34 mg/l air (1 h).

From the Safety Assessment of [Carbomer][4]

Acute oral studies with rats, guinea pigs, mice, and dogs showed that Carbomer has low toxicity when ingested. The inhalation LC_{50} of Carbomer in albino rats was 1.71 mg/l. The dermal LD_{50} of rats exposed to Carbomer was > 3 g/kg.

The acute toxicity studies summarized here are described in Table 7. Dermal LD_{50}s of > 2 g/kg[13] and > 5 g/kg[14] were reported for Acrylates Copolymer in rats, and in rabbits, an LD_{50} of > 2 g/kg was reported for VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol.[8] The dermal LD_{50}s of Acrylates/Beheneth-25 Methacrylate Copolymer[10] and Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%) in rats[14] were > 5 g/kg. Acute oral studies were conducted on Acrylates Copolymer; the LD_{50}s in rats and dogs were > 25.2 g dry copolymer/kg bw and > 7.95 g dry copolymer/kg bw, respectively.[15] In oral studies in rats, LD_{50}s of > 5 g/kg were reported for Acrylates/ Beheneth-25 Methacrylate Copolymer,[10] Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%),[14] and VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol.[8] For Polyacrylate-1 Crosspolymer, the oral LD_{50} in rats was > 2 g/kg.[12] In an acute inhalation study in rats, a 4-h exposure resulted in an LC_{50} of > 3960 mg/l Acrylates Copolymer.[15]

Short-Term Toxicity Studies

From the Original Safety Assessment of Acrylates Copolymers[1]

Pulmonary lesions were observed in rats used in short-term inhalation studies of acrylic acid polymers.

From the Safety Assessment of [Carbomer][4]

Feeding of rats with doses up to 5.0 g/kg/day Carbomer (49 days) and of rats and dogs with up to 5.0% Carbomer in the diet (21 days) resulted in lower than normal body weights.

Oral

Acrylates Copolymer

Groups of 10 male and 10 female rats were dosed by gavage with 500, 1000, and 2000 mg/kg bw/day of dry Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate) for 35 days.[15] Two recovery groups of 5 males and 5 females were dosed with 0 or 2000 mg dry copolymer/kg bw/d and were used for a recovery period of 14 days without dosing. The control group received distilled water. No animals died during the study. Differences in hematology and clinical chemistry parameters and in organ weights that were observed between treated and control animals were not considered related to the test article because a dose-response was not observed. There were no changes in urinary parameters reported. The no-observed-adverse effect level (NOAEL) was 2000 mg/kg bw/day.

In a 28-day study, groups of 3 male and 3 female Göttingen minipigs were administered Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate) via coating on cellulose pellets containing 22.7% copolymer.[15] The animals received the coated cellulose pellets at dose levels of 500, 1000, and 2000 mg/kg bw/d, which corresponded to dose levels of 113, 227, and 454 mg/kg bw/d expressed as dry copolymer. Clinical signs were observed and feed consumption was measured daily, body weights were measured weekly, and hematology, clinical chemistry, urinalysis, and fecal parameters were evaluated. No treatment-related deaths were observed. There were no toxicologically relevant changes in body weight, food consump-

tion, clinical observations, ophthalmoscopy, clinical pathology, urinalysis, fecal analysis, or in organ weights. Microscopic examination revealed instances of mucosal/submucosal edema in the cecum and colon of one male receiving 454 mg dry copolymer/kg bw/d and in the caecum of one male dosed at 227 mg dry copolymer/kg bw/d; the researcher commented that the influence of the high doses is unclear, and the finding may be a physiological reaction of the intestine to the high amounts of non-soluble or non-degradable particles resulting in osmotic imbalance. No toxicological relevance was attributed to this change. Centrilobular yellow/brown pigmentation and mild fibrosis was apparent in the liver of a single female dosed at 454 mg dry copolymer/kg bw/d. The NOAEL was determined to be 227 mg dry copolymer/kg bw/d.

Subchronic Toxicity Studies

From the Original Safety Assessment of Acrylates Copolymers[1]

In a subchronic inhalation toxicity study of Acrylates Copolymer, alveolar histiocytosis was observed at a concentration of 30 mg/m^3. Pulmonary lesions were observed in rats used in subchronic inhalation studies of acrylic acid polymers.

From the Safety Assessment of [Carbomer][4]

Subchronic feeding of rats and dogs with up to 5.0% Carbomer in the diet (90 days) resulted in lower than normal body weights. In rats fed Carbomer at dietary levels of 5.0% for 90 days, absolute liver weights and liver to body and brain weight ratios were reduced, but no pathological changes were observed.

Chronic Toxicity Studies

From the Original Safety Assessment of Acrylates Copolymers[1]

In a chronic inhalation study of respirable polyacrylate particles, compound-related pulmonary lesions were not observed.

From the Safety Assessment of [Carbomer][4]

Rats fed Carbomer at dietary levels of 0.1%, 0.5%, or 5.0% for 6.5 months exhibited various organ weight changes. In dogs fed 0.5 or 1.0 g/kg/day Carbomer for 6.5 months, gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver were observed. In another study, there were no significant effects in dogs fed up to 1.0 g/kg/day Carbomer for 32 months.

Oral

Acrylates Copolymer

A 40% Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate) dispersion was sprayed onto powdered diet at a ratio of 1:10, and the coated diet was mixed with basal diet and administered to groups of 20 male and 20 female Sprague-Dawley rats for 26 wks.[15] Once mixed with basal diet, the dose levels were 500 and 2000 mg dry copolymer/kg bw/day. A control group of 20 males and 20 females received diet prepared by spraying with water and subsequent drying. The test was performed in accord with the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 408. Clinical signs were evaluated and feed consumption was measured daily, body weights were determined weekly, and clinical chemistry, hematology, and urinalysis parameters were evaluated at several intervals. All animals were killed at study termination. None of the animals died during the study, and no clinical signs of toxicity were observed. No treatment-related findings were observed. The NOAEL was ≥ 2000 mg dry copolymer/ kg bw/day.

A similar study was conducted using coated pellets containing approximately 22.7% Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate), and the pellets were placed into gelatin capsules and administered to groups of 4 male and 4 female Beagle dogs for 26 wks.[15] The dose levels used were 50, 125, and 250 mg dry copolymer/kg bw/d, which were equivalent to 200, 500, and 1000 mg test material/kg bw/d. A control group of 4 males and 4 females were given empty capsules. An additional 3 male and 3 female animals were included with both the control and high dose groups, and these animals were allowed to recover for 3 wks after the termination of dosing. Examinations were made as described above. High-dose animals had lower body weight gains as compared to controls, and the difference became statistically significant at wk 12. Males of the low- and mid-dose groups had slightly lower body weights compared to controls; no changes were observed in the body weights of females of these groups. Relative heart and right thyroid weights in treated females were increased, but these changes were not considered treatment-related because no differences were observed microscopically. Other observations were not considered toxicologically significant, and the NOAEL was determined to be 250 mg dry copolymer/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

From the Original Safety Assessment of Acrylates Copolymers[1]

Reproductive effects were not observed in a study in which rats were dosed orally with 4500- or 90,000-Da molecular weight (MW) Sodium Polyacrylate. In this study, groups of 30 gravid rats were dosed with up to 3000 mg/kg/day of the low MW test article in distilled water on days 6-15 of gestation, and the animals were killed on day 19 of gestation. Groups of 28-29 gravid rats were dosed with up to 1125 mg/kg/day of the high MW test article in distilled water; 8 animals/group were dosed on days 6-13 of gestation and killed on day 13, and the remaining animals in each high MW-test article group were dosed on days 6-15 of gestation, and killed on day 10 of gestation.

Oral

Acrylates Copolymer

Two studies were conducted in which an Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate) dispersion was sprayed onto powdered diet at a ratio of 1:10, and the coated diet was mixed with basal diet for testing.[15] In the first study, groups of 20 mated female Wistar rats were fed 0, 500, or 2000 mg dry copolymer/ kg bw/day on days 6 through 15 of gestation, and the gravid rats were killed on day 19 of gestation. In the second study, groups of 10 mated female New Zealand White rabbits were given the same dosages on days 6 to 18 of gestation, and killed on day 29 of gestation. There were no signs of maternal toxicity in rats or rabbits, and there were no reproductive or developmental effects observed for either species. The NOAELs for dams and fetuses were 2000 mg/kg bw/day in both rats and rabbits.

GENOTOXICITY STUDIES

From the Original Safety Assessment of Acrylates Copolymers[1]

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

From the Safety Assessment of Crosslinked Alkyl Acrylates[2]

The little genotoxicity data that were available for the crosslinked alkyl acrylates reported negative results in Ames tests.

The genotoxicity studies summarized here are described in Table 8. Acrylates Copolymer (comprised of various monomer combinations) was not genotoxic in Ames tests (up to 5000 µg dry copolymer/plate), mouse lymphoma L5178Y cell mutation assays (up to 6250 µg dry copolymer/ml), or a chromosomal aberration assay (up to 9000 µg dry copolymer/ml in human lymphocytes), and it was not genotoxic in the mouse micronucleus test in which mice were dosed with up to 2000 mg dry copolymer/kg bw.[13,15,16] Acrylates/Hydroxyesters Acrylates Copolymer (in a product containing < 50%) was also not mutagenic in the Ames test.[14] Details were missing from many of these studies.

CARCINOGENICITY STUDIES

Published carcinogenicity studies on the acrylates copolymers were not discovered in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

From the Original Safety Assessment of Acrylates Copolymers[1]

In dermal irritation studies using rabbits, Acrylates Copolymer was non- to mildly irritating. In one study, it produced signs of an irritant property. However, in a study in which the patches adhered to the skin, very slight to well-defined erythema, and severe erythema in one animal, were observed at 72 hours. A mixture containing 30% Ammonium Acrylates Copolymer was practically nonirritant, and an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer produced minor irritation. Acrylates/VA Copolymer produced moderate to severe but reversible dermal irritation, Vinyl Acetate/ Maleate/Acrylate Copolymer solution had a primary irritation index of 4.4. Sodium Polyacrylate did not produce irritation. Acrylates Copolymer was not a sensitizer to guinea pigs in maximization studies or a Buehler sensitization test.

A 25% aq. dilution of Acrylates Copolymer was not an irritant or a sensitizer in a human repeated insult patch test (HRIPT; 47 subjects). In clinical testing, Acrylates Copolymer, 30% solids, was not an irritant or sensitizer, and neither was Acrylates Copolymer (100% solids) tested as a 15% solution in ammonia water or a 25% solution in acetone. Undiluted Sodium Polyacrylate did not produce irritation or sensitization in 50 subjects.

From the Safety Assessment of Crosslinked Alkyl Acrylates[2]

In an alternative method study, Acrylates/Vinyl Neodecanoate Crosspolymer was predicted to be a nonirritant. Studies in rabbits, guinea pigs, and humans reported no to slight irritation with undiluted and weak sensitization with 2% aq, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, no irritation with Acrylates Crosspolymer at 30% in olive oil, and no irritation or sensitization with Sodium Acrylates Crosspolymer 2 (concentration not specified). Mostly, human testing with undiluted Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Acrylates Crosspolymer, and Acrylates/Ethylhexyl Acrylate Crosspolymer, up to 2.5% aq. Acrylates/Vinyl Isodecanoate Crosspolymer, 1% aq. dilutions of formulations containing 2% Acrylates/Vinyl Neodecanoate Crosspolymer, and formulations containing up to 2.6% Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymers do not indicate any dermal irritation or sensitization. The only exception was a weak irritant response noted during an intensified Shelanski HRIPT with undiluted Acrylates/C10-30 Alkyl Acrylate Crosspolymer.

While the residual monomer (MMA) has the potential to induce sensitization, the levels in these ingredients were reported to be well below the levels that would induce sensitization to MMA, thus resolving the Panel's concern about sensitization.

From the Safety Assessment of PMMA and related ingredients[3]

PMMA was not a dermal irritant to rabbits. PMMA was not irritating or sensitizing at 6.8% in an HRIPT test using 52 participants. The same result was obtained in another HRIPT test of PMMA at 2.0% (n = 106).

From the Safety Assessment of [Carbomer][4]

Rabbits showed minimal skin irritation when tested with 100% Carbomer. Clinical studies with Carbomer and its various salts showed low potential for skin irritation and sensitization at concentrations of 0.5%, 5%, 10%, and 100%. When tested on humans at 1.0% concentration, Carbomer and its various salts also demonstrated low potential for skin irritation and sensitization. Further, formulations containing up to 0.25% Carbomer demonstrated low potential for human skin irritation, sensitization, phototoxicity, and photo-contact allergenicity.

The dermal irritation and sensitization studies summarized here are described in Table 9; details were not available for many of the studies. In animal studies, Acrylates/Beheneth-25 Methacrylate Copolymer[10] and Acrylates/Hydroxyesters Acrylates Copolymer (in a product containing < 50%)[14] were classified as slightly irritating to rabbit skin. Acrylates Copolymer[13,15] and VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol[8] were not irritating to rabbit skin. Acrylates Copolymer was not classified as a sensitizer in a local lymph node assay (LLNA),[13] or in a Buehler test using guinea pigs.[15] VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol, tested neat, was not irritating or sensitizing in a Buehler test in guinea pigs [8] In clinical testing, VA/Butyl Maleate/Isobornyl Acrylate Copolymer (as a slurry in ethanol) produced slight erythema in 20% of the 25 subjects tested in a 48-h patch test.[8] In an HRIPT, Acrylates/Hydroxyesters Acrylates Copolymer (as a product containing < 50%) was not a sensitizer, and it was concluded that VA/Butyl Maleate/Isobornyl Acrylate Copolymer in 10% ethanol not likely to be a sensitizer (109 subjects); erythema was observed in a few subjects at both induction and challenge.[8]

Phototoxicity/Photosensitization

Human

VA/Butyl Maleate/Isobornyl Acrylate Copolymer

The phototoxicity of VA/Butyl Maleate/Isobornyl Acrylate Copolymer was evaluated in 10 fair-skinned subjects.[8] Patches with 0.2 ml of the copolymer in 10% ethanol were applied to both volar forearms of each subject for 24 h. One arm was irradiated with long-wave ultraviolet (UVA) for 15 minutes (total dose = 3.3 J); an untested site on this arm served as an irradiated control. The other arm was not irradiated and was protected from light, including sunlight, by either a mitten or a long sleeve. Immediately after irradiation and at 48 and 72 h, both arms were graded for reactions. Minimal erythema at the test site, which occurred immediately after irradiation, was observed in one subject; no other reactions were reported. It was concluded that the test article "is not likely to be phototoxic in humans" at the concentration tested.

In a photosensitization study, 24-h patches applied with 0.2 ml of VA/Butyl Maleate/Isobornyl Acrylate Copolymer in 10% ethanol were applied to both volar forearms of 28 fair-skinned subjects twice a week for 3 wks.[8] At 24 hours, the test sites of both arms were examined and graded. One arm was then irradiated with ultraviolet UVA for 15 minutes, followed by medium-wave ultraviolet (UVB) irradiation. The dose of UVB irradiation administered was determined separately for each subject and was based on skin type and the minimal erythema dose (MED), which was established on the control arm prior to the first irradiation. The MED used in the study was set at the lesser of either the time that was sufficient to achieve a 1.0 score, or 120 seconds. An untreated site on the irradiated arm served as the irradiated control. Each test site was graded immediately after irradiation. The other treated arm was not irradiated. After a 2–wk non-treatment period, challenge patches were applied to previously untreated sites for 24 h, and the irradiated arm was exposed to UVA only.

During induction, transient effects such as minimal erythema, slight edema, and tanning were observed; most of the responses reported were seen at the irradiated treated and non-treated sites. No responses were reported on the non-irradiated arm. Following challenge, 3 subjects exhibited positive responses on the treated and irradiated arm, including minimal erythema, slight edema, skin dryness, or a combination of these symptoms. Two of these subjects also showed similar symptoms on the treated but non-irradiated arm. No reactions were observed on the non-treated irradiated forearm. It was concluded that VA/Butyl Maleate/ Isobornyl Acrylate Copolymer in 10% ethanol was "not likely to be photoallergenic or photosensitizing."

OCULAR IRRITATION STUDIES

From the Original Safety Assessment of Acrylates Copolymers[1]

In two chorioallantoic membrane vascular assays (CAMVAs), Acrylates Copolymer was predicted to be non-irritating, and in two bovine corneal opacity and permeability (BCOP) test, it was predicted to be a mild irritant. In ocular irritation studies using rabbits, Acrylates Copolymer was generally non- to mildly irritating. In two other studies, Acrylates Copolymer (containing 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively) was an eye irritant but not corrosive according to OECD guidelines, by considered minimally irritating according to the methods of Kay and Calandra. A mixture containing 30% Ammonium Acrylates Copolymer was practically nonirritating. An aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer produced trace corneal injury. Acrylates/VA Copolymer produced severe but reversible ocular irritation, and Vinyl Acetate/Maleate/ Acrylate Copolymer solution produced moderate to severe but reversible ocular irritation. In a Draize eye test, the greatest tolerated concentration of Sodium Polyacrylate was 13% to 20% and 20% to 30% for unrinsed and rinsed eyes, respectively. In an irritant

threshold test, the greatest concentration of Sodium Polyacrylate that did not produce irritation in three or more of five rabbits was 2%.

From the Safety Assessment of Crosslinked Alkyl Acrylates[2]

Alternative test methods for ocular irritation indicated that Acrylates/Vinyl Isodecanoate Crosspolymer and a formulation containing 1% Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer are not likely ocular irritants. In studies using rabbits, undiluted Acrylates/C10-30 Alkyl Acrylate Crosspolymer produced minimal to moderate irritation, and it was considered a borderline irritant in unrinsed rabbit eyes. Acrylates Crosspolymer, at 50% in olive oil, and Sodium Acrylates Crosspolymer 2 did not appear to be ocular irritants in rabbit eyes.

From the Safety Assessment of PMMA and related ingredients[3]

In an EpiOcular test, PMMA had a Draize ocular irritation score of 0. PMMA was mildly irritating in rabbit eyes.

From the Safety Assessment of [Carbomer][4]

Rabbits showed zero to moderate eye irritation when tested with Carbomer and/or its various salts at concentrations of 0.20 - 100%.

The ocular irritation studies summarized here are described in Table 10. All of the studies were performed in rabbits; details were not available for several of the studies. Acrylates Copolymer was not an ocular irritant in one study,[15] and was slightly irritating in another.[13] Acrylates/Beheneth-25 Methacrylate Copolymer[10] and Acrylates/Hydroxyesters Acrylates Copolymer (as a product containing < 50%)[14] were slightly irritating to rabbit eyes, and VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol (tested undiluted) was a moderate to severe eye irritant.[8]

CLINICAL STUDIES

Occupational Exposure

From the Original Safety Assessment of Acrylates Copolymers[1]

In examining the effects of workplace exposures, employees exposed to a variety of acrylic polymer dusts (as well as other materials) did not have an excess of chest x-ray abnormalities, especially those suggestive of diffuse pulmonary fibrosis. Additionally, they did not have an excess of pulmonary function testing (PFT) abnormality.

SUMMARY

The Panel has previously issued a Final Report on Acrylates Copolymer and 33 Related Cosmetic Ingredients in 2002, concluding that the acrylates copolymers named in that report are safe for use in cosmetics when formulated to avoid irritation. The Panel also reviewed the safety of numerous similar ingredients in several other reports. The Panel determined that it is appropriate to include all the copolymers in one assessment, including crosslinked copolymers (i.e., crosspolymers) prepared from monomers that comprise, in part, acrylic acid and/or methacrylic acid; the methyl, ethyl, propyl, or butyl ester(s) of these acids; or the salts of one or both of these two acids. Additionally, the Panel determined that three acrylates copolymers that were included in the original report should be excluded here because these are already under review in a concurrent safety assessment. As a result, this is a safety assessment of 126 similar copolymers that are commonly reported to function as film formers and viscosity increasing agents.

According to FDA VCRP data and the results of the Council use survey, 66 of the 126 ingredients assessed in this report are in use. According to VCRP data, Carbomer has the highest frequency of use; it is reported to be used in 6434 cosmetic formulations, and most of these uses (5336) are in leave-on products. Acrylates Copolymer and Acrylate/C10-30 Alkyl Acrylate Crosspolymer (solvent not specified) also have very high frequency of use, with 3177 and 3135 reported uses, respectively.

The results of concentration of use surveys conducted by the Council in 2018 indicate that Acrylates Copolymer has the highest maximum use concentration; it is used at up to 98.6% in nail extenders; use in product categories other than nail products is not as high, but Acrylates Copolymer is used at up to 25% in products that result in dermal contact (face and neck products). Ingredients with the next highest reported concentrations of use are Acrylates/VA Copolymer (at 50%, in "other" skin care formulations) and Polymethyl Methacrylate (at up to 44.6%, in face powders).

In ADME studies of Acrylates Copolymer (either as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate or as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid), most of the test substance was excreted in the feces. Very little radioactivity was recovered in the urine or in the carcass.

Dermal LD_{50}s of > 2 g/kg and > 5 g/kg were reported for Acrylates Copolymer in rats, and in rabbits, an LD_{50} of > 2 g/kg was reported for VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol. The dermal LD_{50}s of Acrylates/ Beheneth-25 Methacrylate Copolymer and Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%) in rats were > 5 g/kg. Acute oral studies were conducted on Acrylates Copolymer; the LD_{50}s in rats and dogs were > 25.2 g dry copolymer/kg bw and > 7.95 g dry copolymer/kg bw, respectively. In oral studies in rats, LD_{50}s of > 5 g/kg were reported for Acrylates/Beheneth-25 Methacrylate Copolymer, Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%), and VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol. For Polyacrylate-1 Crosspolymer, the oral LD_{50} in rats was > 2 g/kg. In an acute inhalation study of Acrylates Copolymer in rats, the LC_{50} was > 3960 mg/l.

In a gavage study, rats were dosed with 500, 1000, and 2000 mg/kg bw/day of dry Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate) for 35 days. There were no notable findings, and the NOAEL was 2000 mg/kg bw/day. In a 28-day dietary study in which rats were fed Acrylates Copolymer-coated cellulose pellets at a dose up to 2000 mg/kg bw/d. There were no toxicologically relevant changes in body weight, food consumption, clinical observations, ophthalmoscopy, clinical pathology, urinalysis, fecal analysis, or in organ weights. In this study, the NOAEL was determined to be 227 mg dry copolymer/kg bw/d. In similar studies in which rats and dogs were fed Acrylates Copolymer-coated pellets for 26 weeks, the NOAEL was ≥ 2000 mg dry copolymer/kg bw/day for rats, and it was determined to be 250 mg dry copolymer/kg bw/d for dogs. These were the highest doses tested in the 26 wk studies.

In two dietary studies in which an Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate) dispersion was sprayed onto powdered diet and administered at a dose up to 2000 mg dry copolymer/kg bw/day and fed to pregnant rats (on days 6 – 15 of gestation) and rabbits (on days 6 – 18 of gestation), there were no signs of maternal toxicity in rats or rabbits, and there were no reproductive or developmental effects observed for either species. The NOAELs for dams and fetuses were 2000 mg/kg bw/day in both rats and rabbits.

Acrylates Copolymer (comprised of various monomer combinations) was not genotoxic in Ames tests (up to 5000 µg dry copolymer/plate), mouse lymphoma L5178Y cell mutation assays (up to 6250 µg dry copolymer/ml), or a chromosomal aberration assay (up to 9000 µg dry copolymer/ml in human lymphocytes), and it was not genotoxic in the mouse micronucleus test in which mice were dosed with up to 2000 mg dry copolymer/kg bw. Acrylates/Hydroxyesters Acrylates Copolymer (in a product containing < 50%) also was not mutagenic in the Ames test.[14] Details were not available for many of these studies.

Carcinogenicity data were neither found in the published in the publically available literature, nor were unpublished studies submitted.

In animal studies, Acrylates/Beheneth-25 Methacrylate Copolymer and Acrylates/Hydroxyesters Acrylates Copolymer (in a product containing < 50%) were classified as slightly irritating to rabbit skin. Acrylates Copolymer and VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol were not irritating to rabbit skin. Acrylates Copolymer was not classified as a sensitizer in a LLNA, or in a Buehler test using guinea pigs. VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol, tested neat, was not irritating or sensitizing in a Buehler test in guinea pigs. In clinical testing, VA/Butyl Maleate/Isobornyl Acrylate Copolymer (as a slurry in ethanol) produced slight erythema in 20% of the 25 subjects tested in a 48-h patch test. In an HRIPT, Acrylates/Hydroxyesters Acrylates Copolymer (as a product containing < 50%) was not a sensitizer, and it was concluded that VA/Butyl Maleate/Isobornyl Acrylate Copolymer in 10% ethanol not likely to be a sensitizer (109 subjects); erythema was observed in a few subjects at both induction and challenge.

In study in which the phototoxicity of VA/Butyl Maleate/Isobornyl Acrylate Copolymer in 10% ethanol was evaluated in 10 fair-skinned subjects following 24 h patches, it was concluded that the test article "is not likely to be phototoxic in humans." In a similar test in which 24-h patches were applied to 28 fair-skinned subjects twice a week for 3 wks, VA/Butyl Maleate/Isobornyl Acrylate Copolymer in 10% ethanol was "not likely to be photoallergenic or photosensitizing."

Ocular irritation studies were performed in rabbits; details were not available for several of the studies. Acrylates Copolymer was not an ocular irritant in one study, and was slightly irritating in another. Acrylates/Beheneth-25 Methacrylate Copolymer and Acrylates/Hydroxyesters Acrylates Copolymer (as a product containing < 50%) were slightly irritating to rabbit eyes, and VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol (tested undiluted) was a moderate to severe eye irritant.

DISCUSSION

In accordance with its procedures, CIR evaluates the conclusions of previously-issued reports approximately every 15 years. In 2002, the Panel reviewed the safety of Acrylates Copolymer and 33 related cosmetic ingredients, and concluded that those ingredients were safe for use in cosmetics when formulated to avoid irritation. The Panel has issued three other reports on related copolymers and crosspolymers prepared from monomers that comprise, in part, acrylic acid or methacrylic acid (as well as appropriate salts and esters of these acids). In addition to those acrylates copolymers previously reviewed, the Panel determined that it was appropriate to include 70 acrylates copolymers that have not yet been reviewed. Subsequently, there are a few copolymers that fit the description for this family that are not included in this report because they were recently included in other reports, and there are some that will warrant a review of their own in in the near future because of frequency of use.

The Panel recognized the large number of ingredients in this safety assessment, and the fact that these polymers comprise many different monomeric building blocks. Nonetheless, these polymers are uniformly large molecules and are produced in chemical reactions that leave very little residual monomer. Despite differences in chemical composition, these ingredients have highly similar chemical and physical properties and similar cosmetic uses. For these reasons, the Panel concluded that it is reasonable to consider these ingredients as a group, and the collection of these 126 ingredients in one report enables the assembly of reinforcing and complementary test data.

Acrylates Copolymer is used at up to 98.6% in nail extenders; however, concentrations of use in products that result in dermal exposure are lower (i.e., 50% or less). Because these copolymers are generally large molecules, significant dermal absorption is not expected. Therefore, topical application of these ingredients is not expected to result in systemic toxicity. Additionally, the existing data support a lack of sensitization potential; consequently, the Panel was satisfied that the data included in this report (as well as those data described in the previous reports) supported the safety of the acrylates copolymers as used in cosmetics.

The Panel noted that in the original report on Polymethyl Methacrylate (2011), this ingredient was reported to be used in microbeads in cosmetic products. Environmental concerns fall outside of the Panel's purview of review of personal safety in the use of cosmetic formulations. However, based on environmental concerns, the use of microbeads in cosmetics is being phased out in many jurisdictions, including the US.

The Panel discussed the concern of residual monomer that might be present in these polymers. In most cases, taking into consideration the low amount of residual monomer in the polymers, the Panel was not concerned that the presence of residual monomer would result in adverse effects. However, the Panel did stress that manufacturers should continue to use good manufacturing processes to ensure the amount of residual monomer is kept to a minimum.

The Panel also discussed the issue of residual solvent that might be present. Again, the Panel stressed that the amount of residual solvent should be minimized. However, the Panel was particularly concerned with polymerization in benzene. It cannot be predicted with certainty what quantity of benzene would be volatilized/leached from a polymer during manufacture, formulation, or use; while some benzene is inevitably volatilized during manufacture, some benzene may be trapped in the polymer matrix and may leach out during formulation and use. Because of this uncertainty, the Panel stipulated that these ingredients should not be polymerized in benzene.

The Panel remarked that the potential exists for dermal irritation with the use of products formulated using the ingredients named in this assessment. Therefore, the Panel specified that products containing the acrylates copolymers named in this assessment must be formulated to be non-irritating.

Finally, because some of the acrylates copolymers are used in cosmetic sprays and powders (e.g., VA/Butyl Maleate/Isobornyl Acrylate Copolymer is reported to be used at a maximum concentration of 10% in aerosol hair sprays and Polymethyl Methacrylate is used at concentrations up to 44.6% in face powders) and could possibly be inhaled, the Panel discussed the issue of potential inhalation toxicity. As discussed in the initial assessment on Acrylates Copolymer, the acrylic acid monomer can be a nasal irritant; however, exposure to the monomer from use of these polymers in cosmetic formulations would be less than the established threshold limit value for nasal irritation. Also, the Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the following 126 acrylates copolymers are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

Acrylates Copolymer
Acrylates Crosspolymer
Acrylates Crosspolymer-3
Acrylates Crosspolymer-4
Acrylates Crosspolymer-5*
Acrylates/Ammonium Methacrylate Copolymer
Acrylates/Beheneth-25 Methacrylate Copolymer
Acrylates/Beheneth-25 Methacrylate/Steareth-30 Methacrylate Copolymer*
Acrylates/C10-30 Alkyl Methacrylate Copolymer
Acrylates/C10-30Alkyl Acrylate Crosspolymer
Acrylates/C12-13 Alkyl Methacrylates/Methoxyethyl Acrylate Crosspolymer*
Acrylates/C12-22 Alkyl Methacrylate Copolymer
Acrylates/C26-28 Olefin Copolymer*
Acrylates/C5-8 Alkyl Acrylate Copolymer*
Acrylates/Ceteareth-20 Methacrylate Crosspolymer*
Acrylates/Ceteareth-20 Methacrylate Crosspolymer-2*
Acrylates/Ceteth-20 Methacrylate Copolymer*
Acrylates/Ethylhexyl Acrylate Copolymer
Acrylates/Ethylhexyl Acrylate Crosspolymer
Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer*
Acrylates/Hydroxyesters Acrylates Copolymer
Acrylates/Hydroxyethyl Acrylate/Lauryl Acrylate Copolymer*
Acrylates/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer*
Acrylates/Laureth-25 Methacrylate Copolymer*
Acrylates/Lauryl Methacrylate Copolymer*
Acrylates/Lauryl Methacrylate/Tridecyl Methacrylate Crosspolymer*
Acrylates/Methoxy PEG-4 Methacrylate Copolymer*
Acrylates/Methoxy PEG-15 Methacrylate Copolymer*
Acrylates/Methoxy PEG-23 Methacrylate Copolymer
Acrylates/Methoxy PEG-90 Methacrylate Crosspolymer*
Acrylates/Palmeth-25 Acrylate Copolymer
Acrylates/PEG-4 Dimethacrylate Crosspolymer*
Acrylates/Steareth-20 Methacrylate Copolymer
Acrylates/Steareth-20 Methacrylate Crosspolymer
Acrylates/Steareth-30 Methacrylate Copolymer
Acrylates/Steareth-50 Acrylate Copolymer*
Acrylates/Stearyl Methacrylate Copolymer
Acrylates/VA Copolymer
Acrylates/VA Crosspolymer
Acrylates/Vinyl Isodecanoate Crosspolymer
Acrylates/Vinyl Neodecanoate Crosspolymer
Acrylic Acid/C12-22 Alkyl Acrylate Copolymer*
Acrylic Acid/Stearyl Acrylate Copolymer

Allyl Methacrylate/Glycol Dimethacrylate Crosspolymer*
Allyl Methacrylates Crosspolymer
Ammonium Acrylates Copolymer
Ammonium Acrylates/Ethylhexyl Acrylate Copolymer*
Ammonium Acrylates/Methyl Styrene/Styrene Copolymer
Ammonium Polyacrylate
Ammonium Styrene/Acrylates Copolymer
Ammonium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer*
Ammonium VA/Acrylates Copolymer*
AMP-Acrylates Copolymer
Behenyl Methacrylate/t-Butyl Methacrylate Copolymer
Butyl Acrylate/Cyclohexyl Methacrylate Copolymer*
Butyl Acrylate/Ethylhexyl Methacrylate Copolymer*
Butyl Acrylate/Glycol Dimethacrylate Crosspolymer
Butyl Acrylate/Hydroxyethyl Methacrylate Copolymer*
Butyl Methacrylate/Acryoyloxy PG Methacrylate Copolymer*
C12-22 Alkyl Acrylate/Hydroxyethylacrylate Copolymer
C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer*
Calcium Potassium Carbomer*
Carbomer
Cyclohexyl Methacrylate/Ethylhexyl Methacrylate Copolymer*
Ethylene/Acrylic Acid Copolymer
Ethylene/Acrylic Acid/VA Copolymer*
Ethylene/Calcium Acrylate Copolymer*
Ethylene/Magnesium Acrylate Copolymer*
Ethylene/Methacrylate Copolymer
Ethylene/Sodium Acrylate Copolymer
Ethylene/Zinc Acrylate Copolymer*
Ethylhexyl Acrylate/Methoxy PEG-23 Methacrylate/Vinyl Acetate Copolymer*
Ethylhexyl Acrylate/Methyl Methacrylate Copolymer
Glycol Dimethacrylate Crosspolymer*
Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer*
Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer*
Lauryl Acrylate Crosspolymer
Lauryl Acrylate/VA Copolymer*
Lauryl Acrylate/VA Crosspolymer*
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer
Methacrylic Acid/PEG-6 Methacrylate/PEG-6 Dimethacrylate Crosspolymer*
Methacryloyl Ethyl Betaine/Acrylates Copolymer
Methoxy PEG-23 Methacrylate/Glyceryl Diisostearate Methacrylate Copolymer
Methyl Methacrylate Crosspolymer
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer
Methyl Methacrylate/PEG/PPG-4/3 Methacrylate Crosspolymer
PEG/PPG-5/2 Methacrylate/Methacrylic Acid Crosspolymer*
Poly C10-30 Alkyl Acrylate
Poly(Methoxy PEG-9 Methacrylate)*
Polyacrylate-14
Polyacrylate-29*
Polyacrylate-34*
Polyacrylate-1 Crosspolymer
Polyacrylic Acid
Polybutyl Acrylate*
Polybutyl Methacrylate*
Polyethylacrylate
Polyhydroxyethylmethacrylate*
Polyisobutyl Methacrylate*
Polymethyl Acrylate
Polymethyl Methacrylate
Polypropyl Methacrylate*
Polystearyl Methacrylate*
Potassium Acrylate Crosspolymer*
Potassium Acrylates Copolymer
Potassium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Potassium Acrylates/Ethylhexyl Acrylate Copolymer*
Potassium Aluminum Polyacrylate*
Potassium Carbomer
Potassium Polyacrylate*
Sodium Acrylate/Acrolein Copolymer*
Sodium Acrylate/Vinyl Alcohol Copolymer
Sodium Acrylates Copolymer
Sodium Acrylates Crosspolymer-2
Sodium Acrylates/Beheneth-25 Methacrylate Crosspolymer*
Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Sodium Acrylates/Ethylhexyl Acrylate Copolymer*
Sodium Acrylates/Vinyl Isodecanoate Crosspolymer
Sodium Carbomer
Sodium Polyacrylate
Sodium Polymethacrylate
Steareth-10 Allyl Ether/Acrylates Copolymer
Stearyl/Lauryl Methacrylate Crosspolymer*
Styrene/Acrylates/Ammonium Methacrylate Copolymer
VA/Butyl Maleate/Isobornyl Acrylate Copolymer

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

TABLES

Table 1. List of 126 ingredients included in this re-review

Acrylates Copolymer
Acrylates Crosspolymer
Acrylates Crosspolymer-3
Acrylates Crosspolymer-4
Acrylates Crosspolymer-5
Acrylates/Ammonium Methacrylate Copolymer
Acrylates/Beheneth-25 Methacrylate Copolymer
Acrylates/Beheneth-25 Methacrylate/Steareth-30 Methacrylate Copolymer
Acrylates/C10-30 Alkyl Methacrylate Copolymer
Acrylates/C10-30Alkyl Acrylate Crosspolymer
Acrylates/C12-13 Alkyl Methacrylates/Methoxyethyl Acrylate Crosspolymer
Acrylates/C12-22 Alkyl Methacrylate Copolymer
Acrylates/C26-28 Olefin Copolymer
Acrylates/C5-8 Alkyl Acrylate Copolymer
Acrylates/Ceteareth-20 Methacrylate Crosspolymer
Acrylates/Ceteareth-20 Methacrylate Crosspolymer-2
Acrylates/Ceteth-20 Methacrylate Copolymer
Acrylates/Ethylhexyl Acrylate Copolymer
Acrylates/Ethylhexyl Acrylate Crosspolymer
Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer
Acrylates/Hydroxyesters Acrylates Copolymer
Acrylates/Hydroxyethyl Acrylate/Lauryl Acrylate Copolymer
Acrylates/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Acrylates/Laureth-25 Methacrylate Copolymer
Acrylates/Lauryl Methacrylate Copolymer
Acrylates/Lauryl Methacrylate/Tridecyl Methacrylate Crosspolymer
Acrylates/Methoxy PEG-4 Methacrylate Copolymer
Acrylates/Methoxy PEG-15 Methacrylate Copolymer
Acrylates/Methoxy PEG-23 Methacrylate Copolymer
Acrylates/Methoxy PEG-90 Methacrylate Crosspolymer
Acrylates/Palmeth-25 Acrylate Copolymer
Acrylates/PEG-4 Dimethacrylate Crosspolymer
Acrylates/Steareth-20 Methacrylate Copolymer
Acrylates/Steareth-20 Methacrylate Crosspolymer
Acrylates/Steareth-30 Methacrylate Copolymer
Acrylates/Steareth-50 Acrylate Copolymer
Acrylates/Stearyl Methacrylate Copolymer
Acrylates/VA Copolymer
Acrylates/VA Crosspolymer
Acrylates/Vinyl Isodecanoate Crosspolymer
Acrylates/Vinyl Neodecanoate Crosspolymer
Acrylic Acid/C12-22 Alkyl Acrylate Copolymer
Acrylic Acid/Stearyl Acrylate Copolymer
Allyl Methacrylate/Glycol Dimethacrylate Crosspolymer
Allyl Methacrylates Crosspolymer
Ammonium Acrylates Copolymer
Ammonium Acrylates/Ethylhexyl Acrylate Copolymer
Ammonium Acrylates/Methyl Styrene/Styrene Copolymer
Ammonium Polyacrylate
Ammonium Styrene/Acrylates Copolymer
Ammonium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer
Ammonium VA/Acrylates Copolymer
AMP-Acrylates Copolymer
Behenyl Methacrylate/t-Butyl Methacrylate Copolymer
Butyl Acrylate/Cyclohexyl Methacrylate Copolymer
Butyl Acrylate/Ethylhexyl Methacrylate Copolymer
Butyl Acrylate/Glycol Dimethacrylate Crosspolymer
Butyl Acrylate/Hydroxyethyl Methacrylate Copolymer
Butyl Methacrylate/Acryoyloxy PG Methacrylate Copolymer
C12-22 Alkyl Acrylate/Hydroxyethylacrylate Copolymer
C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer
Calcium Potassium Carbomer
Carbomer
Cyclohexyl Methacrylate/Ethylhexyl Methacrylate Copolymer
Ethylene/Acrylic Acid Copolymer
Ethylene/Acrylic Acid/VA Copolymer
Ethylene/Calcium Acrylate Copolymer
Ethylene/Magnesium Acrylate Copolymer
Ethylene/Methacrylate Copolymer
Ethylene/Sodium Acrylate Copolymer
Ethylene/Zinc Acrylate Copolymer
Ethylhexyl Acrylate/Methoxy PEG-23 Methacrylate/Vinyl Acetate Copolymer
Ethylhexyl Acrylate/Methyl Methacrylate Copolymer
Glycol Dimethacrylate Crosspolymer
Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer
Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Lauryl Acrylate Crosspolymer
Lauryl Acrylate/VA Copolymer
Lauryl Acrylate/VA Crosspolymer
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer
Methacrylic Acid/PEG-6 Methacrylate/PEG-6 Dimethacrylate Crosspolymer
Methacryloyl Ethyl Betaine/Acrylates Copolymer
Methoxy PEG-23 Methacrylate/Glyceryl Diisostearate Methacrylate Copolymer
Methyl Methacrylate Crosspolymer
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer
Methyl Methacrylate/PEG/PPG-4/3 Methacrylate Crosspolymer
PEG/PPG-5/2 Methacrylate/Methacrylic Acid Crosspolymer
Poly C10-30 Alkyl Acrylate
Poly(Methoxy PEG-9 Methacrylate)
Polyacrylate-14
Polyacrylate-29
Polyacrylate-34
Polyacrylate-1 Crosspolymer
Polyacrylic Acid
Polybutyl Acrylate
Polybutyl Methacrylate
Polyethylacrylate
Polyhydroxyethylmethacrylate
Polyisobutyl Methacrylate
Polymethyl Acrylate
Polymethyl Methacrylate
Polypropyl Methacrylate
Polystearyl Methacrylate
Potassium Acrylate Crosspolymer
Potassium Acrylates Copolymer
Potassium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Potassium Acrylates/Ethylhexyl Acrylate Copolymer
Potassium Aluminum Polyacrylate
Potassium Carbomer
Potassium Polyacrylate
Sodium Acrylate/Acrolein Copolymer
Sodium Acrylate/Vinyl Alcohol Copolymer
Sodium Acrylates Copolymer
Sodium Acrylates Crosspolymer-2
Sodium Acrylates/Beheneth-25 Methacrylate Crosspolymer
Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Sodium Acrylates/Ethylhexyl Acrylate Copolymer
Sodium Acrylates/Vinyl Isodecanoate Crosspolymer
Sodium Carbomer
Sodium Polyacrylate
Sodium Polymethacrylate
Steareth-10 Allyl Ether/Acrylates Copolymer
Stearyl/Lauryl Methacrylate Crosspolymer
Styrene/Acrylates/Ammonium Methacrylate Copolymer
VA/Butyl Maleate/Isobornyl Acrylate Copolymer

Ingredients in blue type were included in the original Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients[1]
Ingredients in green type were reviewed in the Safety Assessment of Cross-Linked Alkyl Acrylates[2]
Ingredients in pink type were reviewed in the safety assessment of Polymethyl Methacrylate and other ingredients[3]
The ingredient in gray type was reviewed in the safety assessment of Carbomers[4]
Prior to this assessment, the ingredients in black type had not yet been reviewed by CIR

Table 2. Definitions, Structures, and Functions of the ingredients reviewed in this report[5]

Ingredients (CAS Nos.)*	Definitions and Structures	Function(s)
Acrylates Copolymer 159666-35-0; 25035-69-2; 25212-88-8; 25685-29-4	a copolymer of two or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	adhesives; artificial nail builders; binders; dispersing agents - nonsurfactant; film formers; hair fixatives; skin-conditioning agents - emollient; skin-conditioning agents - miscellaneous
Acrylates Crosspolymer 26794-61-6; 74464-10-1	a copolymer of acrylic acid, methacrylic acid or one of its simple esters, crosslinked with glycol dimethacrylate	absorbents
Acrylates Crosspolymer-3	a copolymer of acrylic acid, methacrylic acid or one of its simple esters, crosslinked with trimethylolpropane triacrylate and trimethylolpropane diallyl ether	film formers; hair fixatives; viscosity increasing agents - aqueous
Acrylates Crosspolymer-4	a copolymer of acrylic acid, methacrylic acid or one of its simple esters, crosslinked with trimethylolpropane triacrylate	emulsion stabilizers; film formers; surfactants - dispersing agents; viscosity increasing agents - aqueous
Acrylates Crosspolymer-5	a copolymer of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with an allyl ether of pentaerythritol	viscosity increasing agents - aqueous
Acrylates/Ammonium Methacrylate Copolymer	a copolymer of ammonium methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers; hair fixatives
Acrylates/Beheneth-25 Methacrylate Copolymer	a copolymer of the ester of methacrylic acid and Beheneth-25 and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	viscosity increasing agents - aqueous
Acrylates/Beheneth-25 Methacrylate/Steareth-30 Methacrylate Copolymer	a copolymer of beheneth-25 methacrylate, steareth-30 methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers
Acrylates/C10-30 Alkyl Methacrylate Copolymer	the copolymer of C10-30 alkyl methacrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	viscosity increasing agents - aqueous
Acrylates/C10-30Alkyl Acrylate Crosspolymer	a copolymer of C10-30 alkyl acrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with an allyl ether of sucrose or an allyl ether of pentaerythritol	emulsion stabilizers; viscosity increasing agents - aqueous; viscosity increasing agents - nonaqueous
Acrylates/C12-13 Alkyl Methacrylates/Methoxy-ethyl Acrylate Crosspolymer	a copolymer of C12-13 alkyl methacrylates, methoxyethyl acrylate, and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with vinyloxazoline	hair fixatives
Acrylates/C12-22 Alkyl Methacrylate Copolymer	the copolymer of C12-22 alkyl methacrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	film formers
Acrylates/C26-28 Olefin Copolymer	a polymer of C26-28 olefins and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - nonaqueous
Acrylates/C5-8 Alkyl Acrylate Copolymer	copolymer of C5-8 alkyl acrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	emulsion stabilizers; film formers; viscosity increasing agents - aqueous
Acrylates/Ceteareth-20 Methacrylate Crosspolymer	copolymer of the ester of methacrylic acid and Ceteareth-20 and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters, crosslinked with ethylene glycol dimethacrylate	viscosity increasing agents - aqueous
Acrylates/Ceteareth-20 Methacrylate Crosspolymer-2	a copolymer of the ester of methacrylic acid and ceteareth-20 and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters, crosslinked with diallyl maleate	bulking agents; chelating agents; emulsion stabilizers; opacifying agents; viscosity increasing agents - aqueous
Acrylates/Ceteth-20 Methacrylate Copolymer	a copolymer formed from the ester of methacrylic acid and ceteth-20 , and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - aqueous
Acrylates/Ethylhexyl Acrylate Copolymer	a copolymer of ethylhexyl acrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	film formers
Acrylates/Ethylhexyl Acrylate Crosspolymer	a copolymer of 2-ethylhexylacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with ethylene glycol dimethacrylate	binders
Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer	a copolymer of 2-ethylhexyl acrylate, glycidyl methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with triethylene glycol dimethacrylate	film formers

Table 2. Definitions, Structures, and Functions of the ingredients reviewed in this report[5]

Ingredients (CAS Nos.)*	Definitions and Structures	Function(s)
Acrylates/Hydroxyesters Acrylates Copolymer 25035-89-6	a copolymer of one or more monomers consisting of acrylic acid, methacrylic acid, or their simple esters, and one or more monomers of hydroxyacrylate esters	film formers
Acrylates/Hydroxyethyl Acrylate/Lauryl Acrylate Copolymer	a copolymer of hydroxyethyl acrylate, lauryl acrylate, and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	film formers
Acrylates/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	a copolymer of hydroxyethyl acrylate, butyl acrylate and methoxyethyl acrylate	film formers
Acrylates/Laureth-25 Methacrylate Copolymer	the copolymer of laureth-25 methacrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	viscosity increasing agents - aqueous
Acrylates/Lauryl Methacrylate Copolymer	a copolymer of lauryl methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers
Acrylates/Lauryl Methacrylate/Tridecyl Methacrylate Crosspolymer	a copolymer of lauryl methacrylate, tridecyl methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with vinyloxazoline	film formers
Acrylates/Methoxy PEG-4 Methacrylate Copolymer	a copolymer of methoxy PEG-4 methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	hair conditioning agents
Acrylates/Methoxy PEG-15 Methacrylate Copolymer	a copolymer of methoxy PEG-15 methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	dispersing agents - nonsurfactant
Acrylates/Methoxy PEG-23 Methacrylate Copolymer	a copolymer of methoxy PEG-23 methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	film formers
Acrylates/Methoxy PEG-90 Methacrylate Crosspolymer 957645-61-3	a copolymer of methoxy PEG-90 methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked by glycol dimethacrylate	skin protectants
Acrylates/Palmeth-25 Acrylate Copolymer	a copolymer of the ester of acrylic acid and ethoxylated palm alcohol with an average of 25 moles of ethylene oxide and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - aqueous
Acrylates/PEG-4 Dimethacrylate Crosspolymer 50657-38-0	a copolymer of one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked by PEG-4 dimethacrylate	film formers
Acrylates/Steareth-20 Methacrylate Copolymer	a copolymer of the ester of methacrylic acid and steareth-20 and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - aqueous
Acrylates/Steareth-20 Methacrylate Crosspolymer	a copolymer of steareth-20 methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with an allyl ether of pentaerythritol or an allyl ether of trimethylolpropane	dispersing agents - nonsurfactant; film formers
Acrylates/Steareth-30 Methacrylate Copolymer 75760-37-1	a copolymer of the ester of methacrylic acid and steareth-30 and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	viscosity increasing agents - aqueous
Acrylates/Steareth-50 Acrylate Copolymer	a copolymer of the ester of acrylic acid and steareth-50 and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - aqueous
Acrylates/Stearyl Methacrylate Copolymer	a copolymer of stearyl methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	emulsion stabilizers; viscosity increasing agents - aqueous
Acrylates/VA Copolymer	a copolymer of vinyl acetate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers; hair fixatives
Acrylates/VA Crosspolymer	a copolymer of vinyl acetate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with triallylisocyanurate	film formers
Acrylates/Vinyl Isodecanoate Crosspolymer	a copolymer of the ester of vinyl isodecanoate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with polyalkenyl polyether	dispersing agents - nonsurfactant; emulsion stabilizers; viscosity increasing agents - aqueous
Acrylates/Vinyl Neodecanoate Crosspolymer	a copolymer of vinyl neodecanoate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with an allyl ether of trimethylolpropane or pentaerythritol	emulsion stabilizers; film formers; viscosity increasing agents - aqueous
Acrylic Acid/C12-22 Alkyl Acrylate Copolymer	a copolymer of acrylic acid and C12-22 alkyl acrylate	binders; emulsion stabilizers; viscosity increasing agents - nonaqueous

Table 2. Definitions, Structures, and Functions of the ingredients reviewed in this report[5]

Ingredients (CAS Nos.)*	Definitions and Structures	Function(s)
Acrylic Acid/Stearyl Acrylate Copolymer 36120-03-3	a polymer of acrylic acid and stearyl acrylate monomers	emulsion stabilizers; film formers; surfactants - emulsifying agents
Allyl Methacrylate/Glycol Dimethacrylate Crosspolymer 779327-42-3	a highly crosslinked polymer of allyl methacrylate and ethylene glycol dimethacrylate	oral care agents; skin protectants; skin-conditioning agents - emollient; skin-conditioning agents - miscellaneous
Allyl Methacrylates Crosspolymer 182212-41-5	a copolymer of allyl methacrylates crosslinked with glycol dimethacrylate	emulsion stabilizers; opacifying agents; viscosity increasing agents - nonaqueous
Ammonium Acrylates Copolymer	the ammonium salt of a polymer of two or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers; viscosity increasing agents - aqueous
Ammonium Acrylates/Ethylhexyl Acrylate Copolymer	a copolymer of ethylhexyl acrylate and the ammonium salt of one or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters	film formers
Ammonium Acrylates/Methyl Styrene/Styrene Copolymer	a copolymer consisting of ammonium acrylate, methyl styrene and styrene monomers	film formers
Ammonium Polyacrylate 9003-03-6	the ammonium salt of Polyacrylic Acid	emulsion stabilizers; film formers
Ammonium Styrene/Acrylates Copolymer	the ammonium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters	dispersing agents - nonsurfactant; film formers
Ammonium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	ammonium salt of Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	film formers
Ammonium VA/Acrylates Copolymer	the ammonium salt of a polymer of vinyl acetate and two or more monomers consisting of acrylic acid, methacrylic acid or their simple ester	binders; dispersing agents - nonsurfactant; film formers; hair fixatives
AMP-Acrylates Copolymer 1203962-19-9	the aminomethyl propanol salt of Acrylates Copolymer	film formers
Behenyl Methacrylate/t-Butyl Methacrylate Copolymer	a copolymer of behenyl methacrylate and t-butyl methacrylate monomers	film formers
Butyl Acrylate/Cyclohexyl Methacrylate Copolymer	a copolymer of butyl acrylate and cyclohexyl methacrylate	film formers
Butyl Acrylate/Ethylhexyl Methacrylate Copolymer	a copolymer of butyl acrylate and 2-ethylhexyl methacrylate monomers	film formers; hair fixatives
Butyl Acrylate/Glycol Dimethacrylate Crosspolymer	a homopolymer of butyl acrylate crosslinked with glycol dimethacrylate	absorbents; film formers
Butyl Acrylate/Hydroxyethyl Methacrylate Copolymer	a copolymer consisting of n-butyl acrylate and 2-hydroxyethyl methacrylate monomers	film formers
Butyl Methacrylate/Acryoyloxy PG Methacrylate Copolymer 1431551-12-0	a polymer of butyl methacrylate and acryloyloxy propylene glycol methacrylate monomers	film formers
C12-22 Alkyl Acrylate/Hydroxyethylacrylate Copolymer	a copolymer of C12-22 alkyl acrylate and hydroxyethylacrylate	binders; emulsion stabilizers; viscosity increasing agents - nonaqueous
C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer	a copolymer of C8-22 alkyl acrylate and methacrylic acid crosslinked with hexanediol diacrylate	film formers; hair fixatives; hair-waving/straightening agents
Calcium Potassium Carbomer	the calcium potassium salt of Carbomer	emulsion stabilizers; film formers; viscosity increasing agents - aqueous
Carbomer 9003-01-4; 9007-16-3; 9007-17-4; 9062-04-8; 76050-42-5	a homopolymer of acrylic acid crosslinked with an allyl ether of pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene	emulsion stabilizers; viscosity increasing agents - aqueous
Cyclohexyl Methacrylate/Ethylhexyl Methacrylate Copolymer 82227-04-1	a copolymer of cyclohexyl methacrylate and ethylhexyl methacrylate	film formers
Ethylene/Acrylic Acid Copolymer 9010-77-9	a copolymer of ethylene and acrylic acid monomers	binders; film formers; viscosity increasing agents - nonaqueous
Ethylene/Acrylic Acid/VA Copolymer 26713-18-8	a copolymer of ethylene, acrylic acid and vinyl acetate monomers	binders; film formers; viscosity increasing agents - nonaqueous
Ethylene/Calcium Acrylate Copolymer 26445-96-5	a copolymer of ethylene and calcium acrylate monomers	binders; film formers
Ethylene/Magnesium Acrylate Copolymer 27515-37-3	a copolymer of ethylene and magnesium acrylate monomers	binders; film formers
Ethylene/Methacrylate Copolymer 25103-74-6	a copolymer of ethylene and methyl methacrylate monomers	film formers
Ethylene/Sodium Acrylate Copolymer 25749-98-8; 25750-82-7	a copolymer of ethylene and sodium acrylate monomers	binders; film formers; viscosity increasing agents - aqueous

Table 2. Definitions, Structures, and Functions of the ingredients reviewed in this report[5]

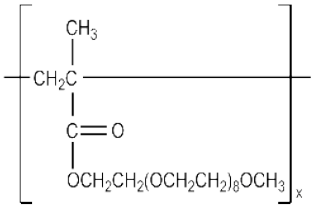
Ingredients (CAS Nos.)*	Definitions and Structures	Function(s)
Ethylene/Zinc Acrylate Copolymer 28208-80-2; 59650-68-9	a copolymer of ethylene and zinc acrylate monomers	film formers
Ethylhexyl Acrylate/Methoxy PEG-23 Methacrylate/Vinyl Acetate Copolymer 137455-77-7	a copolymer of methoxy PEG-23 methacrylate, vinyl acetate, and ethylhexyl acrylate	hair fixatives
Ethylhexyl Acrylate/Methyl Methacrylate Copolymer	a copolymer of ethylhexyl acrylate and methyl methacrylate	film formers
Glycol Dimethacrylate Crosspolymer	a crosslinked polymer of glycol dimethacrylate	slip modifier
Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer	a crosslinked copolymer of vinyl alcohol and glycol dimethacrylate	film formers
Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	the copolymer of hydroxyethyl acrylate and methoxyethyl acrylate	film formers
Lauryl Acrylate Crosspolymer	a polymer of lauryl acrylate crosslinked with divinylbenzene	hair fixatives
Lauryl Acrylate/VA Copolymer	a copolymer of lauryl acrylate and vinyl acetate monomers	film formers
Lauryl Acrylate/VA Crosspolymer	a copolymer of lauryl acrylate and vinyl acetate crosslinked with divinylbenzene	abrasives
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	a crosslinked copolymer of lauryl methacrylate and ethylene glycol dimethacrylate monomers	film formers; hair fixatives
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer	a copolymer of lauryl methacrylate and sodium methacrylate crosslinked with ethylene glycol dimethacrylate	slip modifiers; surface modifiers
Methacrylic Acid/PEG-6 Methacrylate/PEG-6 Dimethacrylate Crosspolymer	a copolymer of methacrylic acid and PEG-6 methacrylate crosslinked with PEG-6 dimethacrylate	film formers
Methacryloyl Ethyl Betaine/Acrylates Copolymer	a polymer of methacryloyl ethyl betaine and two or more monomers of methacrylic acid or its simple esters	dispersing agents - nonsurfactant; film formers; hair fixatives
Methoxy PEG-23 Methacrylate/Glyceryl Diisostearate Methacrylate Copolymer	a copolymer of methoxy PEG-23 methacrylate and glyceryl diisostearate methacrylate monomers	skin protectants
Methyl Methacrylate Crosspolymer 25777-71-3	a copolymer of methyl methacrylate crosslinked with glycol dimethacrylate	bulking agent; film former; viscosity increasing agent - nonaqueous
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer 25777-71-3	a crosslinked copolymer of methyl methacrylate and ethylene glycol dimethacrylate monomers	film formers
Methyl Methacrylate/PEG/PPG-4/3 Methacrylate Crosspolymer	a random copolymer of methyl methacrylate and PEG/PPG-4/3 methacrylate crosslinked with ethylene glycol dimethacrylate	film formers
PEG/PPG-5/2 Methacrylate/Methacrylic Acid Crosspolymer	copolymer of methacrylic acid and polyethylene glycol, polypropylene glycol methacrylate containing an average of 5 moles of ethylene oxide and 2 moles of propylene oxide, crosslinked with glycol dimethacrylate	film formers
Poly C10-30 Alkyl Acrylate	a polymer of the ester of acrylic acid and C10-30 alcohol	binders; emulsion stabilizers; viscosity increasing agents - nonaqueous
Poly(Methoxy PEG-9 Methacrylate)	the polymer that conforms generally to the formula: 	film formers; skin-conditioning agents - humectant; skin-conditioning agents - occlusive
Polyacrylate-14	a copolymer of PEG-25 C10-30 alkyl ether methacrylate, PEG-20 PPG-5 allyl ether and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film former
Polyacrylate-29	A copolymer of stearyl methacrylate, methoxy PEG-9 methacrylate and methacrylic acid	film formers; skin-conditioning agents - miscellaneous; surfactants - emulsifying agents
Polyacrylate-34	a copolymer of octoxy PEG-8 PPG-6 methacrylate, PPG-9 methacrylate, PPG-6 acrylate and 2-methoxyethylacrylate monomers	hair fixative
Polyacrylate-1 Crosspolymer	a copolymer of one or more simple esters of acrylic or methacrylic acid, C1-4 dialkylamino C1-6 alkyl methacrylate, PEG/PPG-30/5 allyl ether, PEG 20-25 C10-30 alkyl ether methacrylate, hydroxy C2-6 alkyl methacrylate crosslinked with ethylene glycol dimethacrylate	film formers; hair conditioning agents; hair fixatives; viscosity increasing agents - aqueous

Table 2. Definitions, Structures, and Functions of the ingredients reviewed in this report[5]

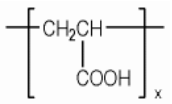
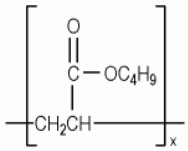
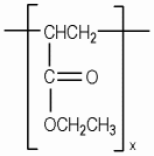
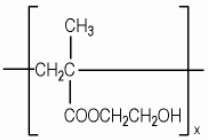
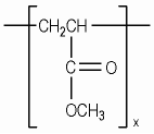
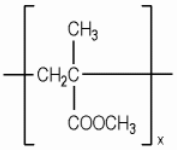
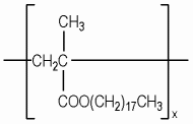
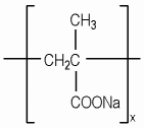
Ingredients (CAS Nos.)*	Definitions and Structures	Function(s)
Polyacrylic Acid 9003-01-4	the polymer of acrylic acid that conforms generally to the formula: 	binders; emulsion stabilizers; film formers; viscosity increasing agents - aqueous
Polybutyl Acrylate 9003-49-0	a polymer of n-butyl acrylate that conforms generally to the formula: 	binders; film formers
Polybutyl Methacrylate 9003-63-8	the homopolymer of butyl methacrylate	film formers
Polyethylacrylate 9003-32-1	the polymer of ethyl acrylate that conforms generally to the formula: 	binders; dispersing agents - nonsurfactant; film formers; hair fixatives
Polyhydroxyethylmethacrylate 25249-16-5	the organic compound that conforms to the formula: 	binders
Polyisobutyl Methacrylate 9011-15-8	the homopolymer of isobutyl methacrylate	film formers
Polymethyl Acrylate 9003-21-8	the polymer that conforms to the formula: 	film formers
Polymethyl Methacrylate 9011-14-7	the polymer of methyl methacrylate that conforms to the formula: 	bulking agents; film formers
Polypropyl Methacrylate	the homopolymer of propyl acrylate	film formers
Polystearyl Methacrylate	the polymer of stearyl methacrylate that conforms to the formula: 	film formers
Potassium Acrylate Crosspolymer 86416-97-9 (sodium salt)	the potassium salt of a polymer of acrylic acid crosslinked with *N*,*N*'-methylenebisacrylamide	absorbents; slip modifiers
Potassium Acrylates Copolymer	the potassium salt of a polymer consisting of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers
Potassium Acrylates/C10-30 Alkyl Acrylate Crosspolymer	the potassium salt of Acrylates/C10-30 Alkyl Acrylate Crosspolymer	film formers
Potassium Acrylates/Ethylhexyl Acrylate Copolymer	the potassium salt of Acrylates/Ethylhexyl Acrylate Copolymer	film formers
Potassium Aluminum Polyacrylate	a mixture of the potassium and aluminum salts of Polyacrylic Acid	absorbents; binders; viscosity increasing agents - aqueous
Potassium Carbomer	the sodium salt of Carbomer	emulsion stabilizers; film formers; viscosity increasing agents - aqueous

Table 2. Definitions, Structures, and Functions of the ingredients reviewed in this report[5]

Ingredients (CAS Nos.)*	Definitions and Structures	Function(s)
Potassium Polyacrylate 25608-12-2	the potassium salt of Polyacrylic Acid	emulsion stabilizers; viscosity increasing agents - aqueous
Sodium Acrylate/Acrolein Copolymer	a polymer consisting of sodium acrylate and acrolein monomers	binders; film formers; viscosity increasing agents - aqueous
Sodium Acrylate/Vinyl Alcohol Copolymer 27599-56-0; 58374-38-2	a polymer of sodium acrylate and vinyl alcohol monomers	binders; emulsion stabilizers; film formers; viscosity increasing agents - aqueous
Sodium Acrylates Copolymer 25549-84-2	the sodium salt of a polymer consisting of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers; viscosity increasing agents - aqueous
Sodium Acrylates Crosspolymer-2	the sodium salt of a copolymer of acrylic acid, methacrylic acid or one or more of its simple esters crosslinked with ethylene glycol diglycidyl ether	absorbents
Sodium Acrylates/Beheneth-25 Methacrylate Crosspolymer	the sodium salt of a copolymer of acrylic acid, methacrylic acid or one or more of its simple esters and beheneth-25 methacrylate, crosslinked with methylene bis-acrylamide	dispersing agents - nonsurfactant; skin-conditioning agents - miscellaneous; viscosity increasing agents - aqueous
Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer	the sodium salt of Acrylates/C10-30 Alkyl Acrylate Crosspolymer	film formers
Sodium Acrylates/Ethylhexyl Acrylate Copolymer	a copolymer of ethylhexyl acrylate and the sodium salt of one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers
Sodium Acrylates/Vinyl Isodecanoate Crosspolymer	the sodium salt of Acrylates/Vinyl Isodecanoate Crosspolymer	dispersing agents - nonsurfactant; emulsion stabilizers; viscosity increasing agents - aqueous
Sodium Carbomer 1401207-41-7; 73298-57-4	sodium salt of Carbomer	emulsion stabilizers; film formers; viscosity increasing agents - aqueous
Sodium Polyacrylate 25549-84-2; 9003-04-7	the sodium salt of Polyacrylic Acid	absorbent; emulsion stabilizer; film former; hair fixative; skin-conditioning agent - emollient; viscosity increasing agent - aqueous
Sodium Polymethacrylate 25086-62-8; 54193-36-1	the polymer that conforms generally to the formula: 	binders; emulsion stabilizers; film formers; viscosity increasing agents - aqueous
Steareth-10 Allyl Ether/Acrylates Copolymer 109292-17-3	a copolymer of the allyl ether of steareth-10 and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers; viscosity increasing agents - nonaqueous
Stearyl/Lauryl Methacrylate Crosspolymer	a copolymer of stearyl methacrylate and lauryl methacrylate crosslinked with ethylene glycol dimethacrylate	skin-conditioning agents - miscellaneous
Styrene/Acrylate/Ammonium Methacrylate Copolymer	a polymer of styrene, ammonium methacrylate and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters	dispersing agents - nonsurfactant; film formers
VA/Butyl Maleate/Isobornyl Acrylate Copolymer	a copolymer of vinyl acetate, butyl maleate and isobornyl acrylate monomers	film formers

***Ingredients in blue type were included in the original Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients[1]**
Ingredients in green type were reviewed in the Safety Assessment of Cross-Linked Alkyl Acrylates[2]
Ingredients in pink type were reviewed in the safety assessment of Polymethyl Methacrylate and other ingredients[3]
The ingredient in gray type was reviewed in the safety assessment of Carbomers[4]
Prior to this assessment, the ingredients in black type had not yet been reviewed by CIR

Table 3. Physical and Chemical Properties

Property	Value	Reference
Acrylates Copolymer		
Physical Form	white beads [as 2-propenoic acid, 2-methyl-, polymer with butyl 2-methyl-2-propenoate, ethyl 2-methyl-2-propenoate and ethyl 2-propenoate] liquid in commercial form; forms a film when dried	13 15,16
Color	milky white	15,16
Odor	"characteristic"	15,16
Molecular Weight (g/mol)	100,000 (wt avg) [as 2-propenoic acid, 2-methyl-, polymer with butyl 2-methyl-2-propenoate, ethyl 2-methyl-2-propenoate and ethyl 2-propenoate] 600,000 (avg) [as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate] 280,000 (avg) [as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid]	13 15 16
Density/Specific Gravity (@ 20 ºC)	1.37 – 1.047 [as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate]	17
Water Solubility (g/L)	miscible in water	15,16
Acrylates/Beheneth-25 Methacrylate Copolymer		
Physical Form	opaque flowing dispersion	10
Color	white	10
Melting Point (ºC)	> 100	10
Water Solubility (@ pH 2 – 3) (@ pH 6 – 8)	insoluble soluble	10
Acrylates/C12-22 Alkyl Methacrylate Copolymer		
Physical Form	aq. emulsion	9
Odor	acrylic	9
Water Solubility (g/L @ 20 ºC)	1000	9
Acrylates/Hydroxyesters Acrylates Copolymer		
Physical Form	emulsion	35
Color	white	14
Molecular Weight (g/mol)	~ 60,000	35
Acrylates/Palmeth-25 Acrylate Copolymer		
Physical Form	opaque emulsion	11
Color	white	11
Water Solubility (g/L @ 20 ºC)	1000	11
Acrylates/Steareth-20 Methacrylate Copolymer		
Physical Form	liquid	18
Color	milky white	18
Polyacrylate-1 Crosspolymer		
Physical Form	solid	12
Color	pale brown	12
Density (kg/m^3 @ 25 ºC)	1160	12
Melting Point (ºC)	47.35	12
VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol		
Physical Form	clear viscous liquid	8
Odor	ethanolic	8
Molecular Weight (g/mol)	79,000 – 154,000 (wt avg)	8
Vapor pressure (mmHg @ 20ºC)	44.48	8
Water Solubility (g/L)	< 1; if the ethanol is allowed to evaporate, the remaining polymer is stated to be water insoluble	8

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Acrylates Copolymer				**Acrylates Crosspolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**	**2011[2]**	**2018[21]**	**2011[2]**
Totals*	**3177**	**227**	**0.00025-98.6**	******	**5**	**2**	**0.15-4.5**	**0.1-4**
Duration of Use								
Leave-On	*2050*	*207*	*0.00025-98.6*	**	*5*	*2*	*1-4.5*	*0.1-4*
Rinse-Off	*1106*	*20*	*0.00052-4.2*	**	*NR*	*NR*	*0.15-2.7*	*0.3-0.8*
Diluted for (Bath) Use	*21*	*NR*	*0.9-2.4*	**	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	702	33	0.00025-18.4	**	1	NR	1	0.8
Incidental Ingestion	453	36	0.0003-3	**	NR	NR	NR	4
Incidental Inhalation-Spray	53; 107[a]; 58[b]	3; 5[a]; 3[b]	0.36-4.9; 0.12-2.6[a]	**	1[a]; 2[b]	NR	NR	NR
Incidental Inhalation-Powder	45; 58[b]	35; 3[b]	0.015-1.4; 0.045-25[c]	**	2[b]	NR	NR	2
Dermal Contact	1884	104	0.00025-25	**	4	2	1-4.5	0.1-4
Deodorant (underarm)	2[a]	3[a]	NR	**	NR	NR	NR	NR
Hair - Non-Coloring	184	3	0.00052-4.9	**	NR	NR	NR	NR
Hair-Coloring	17	14	0.36-3.6	**	NR	NR	0.15	NR
Nail	436	53	0.54-98.6	**	1	NR	NR	NR
Mucous Membrane	1297	36	0.0003-4.2	**	NR	NR	2.2-2.7	4
Baby Products	14	NR	0.26-1.4	**	NR	NR	NR	NR
	Acrylates Crosspolymer-3				**Acrylates Crosspolymer-4**			
	2018[25]		**2018[20]**		**2018[25]**		**2018[20]**	
Totals*	**4**		**1.6**		**16**		**3.1**	
Duration of Use								
Leave-On	*3*		*1.6*		*NR*		*3.1*	
Rinse-Off	*1*		*NR*		*16*		*NR*	
Diluted for (Bath) Use	*NR*		*NR*		*NR*		*NR*	
Exposure Type								
Eye Area	1		NR		NR		NR	
Incidental Ingestion	NR		NR		NR		NR	
Incidental Inhalation-Spray	2[a]		1.6[a]		NR		NR	
Incidental Inhalation-Powder	NR		NR		NR		3.1[c]	
Dermal Contact	NR		NR		16		NR	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	3		1.6		NR		NR	
Hair-Coloring	NR		NR		NR		NR	
Nail	NR		NR		NR		NR	
Mucous Membrane	NR		NR		16		NR	
Baby Products	NR		NR		NR		NR	
	Acrylates/Ammonium Methacrylate Copolymer				**Acrylates/Beheneth-25 Methacrylate Copolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**		**2018[20]**	
Totals*	**26**	**1**	**0.00063-10**	******	**91**		**0.05-1.7**	
Duration of Use								
Leave-On	*11*	*1*	*0.002-10*	**	*53*		*0.3-1.7*	
Rinse-Off	*15*	*NR*	*0.00063-0.0025*	**	*37*		*0.05-1*	
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*1*		*NR*	
Exposure Type								
Eye Area	NR	1	NR	**	NR		NR	
Incidental Ingestion	1	NR	NR	**	NR		NR	
Incidental Inhalation-Spray	4[a]; 3[b]	NR	NR	**	48[a]		1.7; 0.95-1.1[a]	
Incidental Inhalation-Powder	3[b]	NR	0.002[c]	**	NR		0.3-0.8[c]	
Dermal Contact	25	NR	0.00063-0.005	**	34		0.3-8	
Deodorant (underarm)	NR	NR	NR	**	NR		NR	
Hair - Non-Coloring	NR	NR	NR	**	46		0.05-1.7	
Hair-Coloring	NR	NR	NR	**	11		0.2-1	
Nail	NR	NR	10	**	NR		NR	
Mucous Membrane	7	NR	0.00062	**	10		NR	
Baby Products	NR	NR	NR	**	NR		NR	

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Acrylates/C10-30 Alkyl Methacrylate Copolymer				**Acrylates/C10-30Alkyl Acrylate Crosspolymer (†polymerized in solvents other than benzene)**			
	2018[25]		**2018[20]**		**2018[25]**	**2011[2] †**	**2018[21] †**	**2011[2] †**
Totals*	**NR**		**0.0001-1.1**		**3135**	**1696**	**0.000045-3**	**0.0002-5**
Duration of Use								
Leave-On	*NR*		*0.0001-1.1*		*2577*	*1365*	*0.000045-3*	*0.0002-5*
Rinse-Off	*NR*		*0.0005-0.001*		*546*	*313*	*0.1-1.8*	*0.002-5*
Diluted for (Bath) Use	*NR*		*NR*		*12*	*18*	*0.15*	*1*
Exposure Type								
Eye Area	NR		NR		215	132	0.12-0.9	0.003-2
Incidental Ingestion	NR		NR		1	3	0.6	0.5
Incidental Inhalation-Spray	NR		0.0001		176; 1167[a]; 770[b]	70[a]	0.08-2; 0.11-0.2[a]	0.03-2
Incidental Inhalation-Powder	NR		NR		77[b]; 4[c]	6	0.000045-0.6; 0.07-2[c]	0.0002-0.1
Dermal Contact	NR		0.15-0.3		2992	1591	0.000045-3	0.0002-5
Deodorant (underarm)	NR		NR		3[a]	1[a]	0.15-0.5 (not spray) 0.2 (spray)	0.001[a]
Hair - Non-Coloring	NR		0.0001-1.1		95	77	0.19-2	0.1-2
Hair-Coloring	NR		NR		35	11	0.19-1.8	0.4-5
Nail	NR		NR		8	9	0.05-1	0.1-1
Mucous Membrane	NR		NR		175	111	0.15-0.6	0.002-3
Baby Products			0.15		17	10	0.3	0.2
	Acrylates/C12-22 Alkyl Methacrylate Copolymer				**Acrylates/Ethylhexyl Acrylate Copolymer**			
	2018[25]		**2018[20]**		**2018[25]**		**2018[20]**	
Totals*	**9**		**0.23-1.4**		**60**		**0.25-30**	
Duration of Use								
Leave-On	*9*		*0.23-1.4*		*60*		*0.25-30*	
Rinse-Off	*NR*		*NR*		*NR*		*NR*	
Diluted for (Bath) Use	*NR*		*NR*		*NR*		*NR*	
Exposure Type								
Eye Area	1		0.23		53		0.9-30	
Incidental Ingestion	NR		NR		NR		NR	
Incidental Inhalation-Spray	5[a]; 1[b]		1; 0.9[a]		NR		NR	
Incidental Inhalation-Powder	1[b]		0.45-1.4[c]		NR		0.25[c]	
Dermal Contact	9		0.23-1.4		19		0.25-20.1	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	NR		NR		NR		NR	
Hair-Coloring	NR		NR		NR		NR	
Nail	NR		NR		2		NR	
Mucous Membrane	NR		NR		NR		NR	
Baby Products	NR		NR		NR		NR	
	Acrylates/Ethylhexyl Acrylate Crosspolymer				**Acrylates/Hydroxyesters Acrylates Copolymer**			
	2018[25]	**2011[2]**	**2018[21]**	**2011[2]**	**2018[25]**	**1998[1]**	**2018[19]**	**1998[1]**
Totals*	**3**	**NR**	**1-5.4**	**4-6**	**35**	**NR**	**0.71-6**	******
Duration of Use								
Leave-On	*3*	*NR*	*1-5.4*	*4-6*	*30*	*NR*	*0.71-6*	**
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*5*	*NR*	*NR*	**
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	**
Exposure Type								
Eye Area	NR	NR	NR	6	8	NR	0.8	**
Incidental Ingestion	1	NR	NR	NR	NR	NR	NR	**
Incidental Inhalation-Spray	NR	NR	NR	NR	15; 5[a]; 1[b]	NR	0.71-6	**
Incidental Inhalation-Powder	NR	NR	1-3.1; 4.5[c]	NR	NR	NR	NR	**
Dermal Contact	NR	NR	1-5.4	4-6	2	NR	NR	**
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	**
Hair - Non-Coloring	NR	NR	NR	NR	25	NR	0.71-6	**
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	**
Nail	2	NR	NR	NR	NR	NR	NR	**
Mucous Membrane	1	NR	NR	NR	NR	NR	NR	**
Baby Products	NR	NR	NR	NR	NR	NR	NR	**

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Acrylates/Methoxy PEG-23 Methacrylate Copolymer				**Acrylates/Palmeth-25 Acrylate Copolymer**			
	2018[25]		**2018[20]**		**2018[25]**		**2018[20]**	
Totals*	**NR**		**0.4-1.4**		**9**		**0.53-1.3**	
Duration of Use								
Leave-On	*NR*		*0.4-1.4*		*2*		*NR*	
Rinse-Off	*NR*		*NR*		*7*		*0.53-1.3*	
Diluted for (Bath) Use	*NR*		*NR*		*NR*		*NR*	
Exposure Type								
Eye Area	NR		NR		NR		NR	
Incidental Ingestion	NR		NR		NR		NR	
Incidental Inhalation-Spray	NR		1.4; 0.4[a]		1[b]		NR	
Incidental Inhalation-Powder	NR		NR		1[b]		NR	
Dermal Contact	NR		NR		6		1.3	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	NR		0.4-1.4		NR		NR	
Hair-Coloring	NR		NR		3		0.53	
Nail	NR		NR		NR		NR	
Mucous Membrane	NR		NR		2		NR	
Baby Products	NR		NR		NR		NR	
	Acrylates/Steareth-20 Methacrylate Copolymer				**Acrylates/Steareth-20 Methacrylate Crosspolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**	**2011[2]**	**2018[21]**	**2011[2]**
Totals*	**65**	**35**	**0.06-2**	******	**4**	**NR**	**0.37-2.3**	**0.1-2**
Duration of Use								
Leave-On	*22*	*10*	*0.06-0.5*	**	*2*	*NR*	*2.3*	*0.1-2*
Rinse-Off	*43*	*24*	*0.3-2*	**	*2*	*NR*	*0.37-1.6*	*1*
Diluted for (Bath) Use	*NR*	*1*	*NR*	**	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	2	NR	0.11-0.21	**	NR	NR	NR	NR
Incidental Ingestion	1	NR	NR	**	NR	NR	NR	NR
Incidental Inhalation-Spray	2; 4[a]; 9[b]	2; 7[a]	0.06-0.5	**	1[a]; 1[b]	NR	2.3[a]	NR
Incidental Inhalation-Powder	9[b]	NR	0.09[c]	**	1[b]	NR	NR	NR
Dermal Contact	36	14	0.06-1.8	**	1	NR	1.6	0.1-1
Deodorant (underarm)	NR	NR	NR	**	NR	NR	NR	NR
Hair - Non-Coloring	19	15	0.45-0.5	**	1	NR	2.3	2
Hair-Coloring	9	5	0.54-2	**	2	NR	0.37	NR
Nail	NR	1	NR	**	NR	NR	NR	NR
Mucous Membrane	7	2	0.3	**	NR	NR	NR	1
Baby Products	1	2	NR	**	NR	NR	NR	NR
	Acrylates/Steareth-30 Methacrylate Copolymer				**Acrylates/Stearyl Methacrylate Copolymer**			
	2018[25]		**2018[20]**		**2018[25]**		**2018[20]**	
Totals*	**NR**		**0.03-2.1**		**NR**		**0.014-0.04**	
Duration of Use								
Leave-On	*NR*		*0.03-0.87*		*NR*		*0.014-0.04*	
Rinse-Off	*NR*		*1.8-2.1*		*NR*		*0.02-0.04*	
Diluted for (Bath) Use	*NR*		*NR*		*NR*		*NR*	
Exposure Type								
Eye Area	NR		0.03		NR		NR	
Incidental Ingestion	NR		NR		NR		NR	
Incidental Inhalation-Spray	NR		0.2-0.6; 0.87[a]		NR		0.014-0.04[a]	
Incidental Inhalation-Powder	NR		NR		NR		NR	
Dermal Contact	NR		0.15-2.1		NR		0.04	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	NR		0.2-0.87		NR		0.014-0.04	
Hair-Coloring	NR		NR		NR		NR	
Nail	NR		NR		NR		NR	
Mucous Membrane	NR		2.1		NR		NR	
Baby Products	NR		NR		NR		NR	

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Acrylates/VA Copolymer				**Acrylates/VA Crosspolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**		**2018[20]**	
Totals*	**1**	**NR**	**2.5-50**	******	**1**		**25**	
Duration of Use								
Leave-On	*1*	*NR*	*2.5-50*	**	*1*		*25*	
Rinse-Off	*NR*	*NR*	*NR*	**	*NR*		*NR*	
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*NR*		*NR*	
Exposure Type								
Eye Area	1	NR	2.5	**	NR		NR	
Incidental Ingestion	NR	NR	NR	**	NR		NR	
Incidental Inhalation-Spray	NR	NR	NR	**	NR		NR	
Incidental Inhalation-Powder	NR	NR	NR	**	NR		NR	
Dermal Contact	NR	NR	50	**	NR		NR	
Deodorant (underarm)	NR	NR	NR	**	NR		NR	
Hair - Non-Coloring	NR	NR	NR	**	NR		NR	
Hair-Coloring	NR	NR	NR	**	NR		NR	
Nail	NR	NR	NR	**	1		25	
Mucous Membrane	NR	NR	NR	**	NR		NR	
Baby Products	NR	NR	NR	**	NR		NR	
	Acrylates/Vinyl Isodecanoate Crosspolymer				**Acrylates/Vinyl Neodecanoate Crosspolymer**			
	2018[25]	**2011[2]**	**2018[21]**	**2011[2]**	**2018[25]**	**2011[2]**	**2018[21]**	**2011[2]**
Totals*	**30**	**33**	**0.2-0.4**	**0.2-0.5**	**14**	**10**	**NR**	**2**
Duration of Use								
Leave-On	*22*	*25*	*0.25-0.4*	*0.3-0.5*	*3*	*4*	*NR*	*2*
Rinse-Off	*8*	*8*	*0.2*	*0.2-0.5*	*5*	*4*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*6*	*2*	*NR*	*NR*
Exposure Type								
Eye Area	1	NR	NR	NR	1	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	8[a]; 10[b]	NR	0.34-0.4[a]	0.4	2[a]	NR	NR	NR
Incidental Inhalation-Powder	10[b]	NR	0.25[c]	NR	NR	NR	NR	NR
Dermal Contact	30	33	0.2-.0.4	0.2-0.5	14	10	NR	2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	10	6	NR	2
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Acrylic Acid/Stearyl Acrylate Copolymer				**Allyl Methacrylates Crosspolymer**			
	2018[25]		**2018[20]**		**2018[25]**	**2011[2]**	**2018[21]**	**2011[2]**
Totals*	**NR**		**0.1-2**		**31**	**48**	**0.0034-2**	**0.003-2**
Duration of Use								
Leave-On	*NR*		*0.1-2*		*27*	*44*	*0.0034-2*	*0.003-2*
Rinse-Off	*NR*		*0.25*		*4*	*4*	*0.075-1*	*0.1*
Diluted for (Bath) Use	*NR*		*NR*		*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR		NR		NR	4	0.0034	4
Incidental Ingestion	NR		NR		7	16	0.034	16
Incidental Inhalation-Spray	NR		0.1; 2[a]		7[a]; 4[b]	2[a]	1[a]	2[a]
Incidental Inhalation-Powder	NR		NR		4[b]	2	2; 0.4-2[c]	2
Dermal Contact	NR		NR		23	31	0.0034-2	31
Deodorant (underarm)	NR		NR		NR	NR	NR	NR
Hair - Non-Coloring	NR		0.1-2		1	NR	NR	NR
Hair-Coloring	NR		NR		NR	NR	NR	NR
Nail	NR		NR		NR	NR	NR	NR
Mucous Membrane	NR		NR		7	16	0.034	16
Baby Products	NR		NR		NR	NR	NR	NR

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Ammonium Acrylates Copolymer				**Ammonium Acrylates/Methyl Styrene/Styrene Copolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**		**2018[20]**	
Totals*	**60**	**21**	**0.0057-19.5**	******	**5**		**0.9**	
Duration of Use								
Leave-On	*60*	*21*	*0.3-19.5*	**	*5*		*0.9*	
Rinse-Off	*NR*	*NR*	*0.0057-0.046*	**	*NR*		*NR*	
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*NR*		*NR*	
Exposure Type								
Eye Area	47	21	0.8-19.5	**	5		0.9	
Incidental Ingestion	NR	NR	NR	**	NR		NR	
Incidental Inhalation-Spray	1[b]	NR	NR	**	NR		NR	
Incidental Inhalation-Powder	1[b]	NR	NR	**	NR		NR	
Dermal Contact	20	3	0.0057-19.5	**	5		0.9	
Deodorant (underarm)	NR	NR	NR	**	NR		NR	
Hair - Non-Coloring	NR	NR	NR	**	NR		NR	
Hair-Coloring	NR	NR	NR	**	NR		NR	
Nail	10	NR	0.3-7.8	**	NR		NR	
Mucous Membrane	NR	NR	NR	**	NR		NR	
Baby Products	NR	NR	NR	**	NR		NR	
	Ammonium Polyacrylate				**Ammonium Styrene/Acrylates Copolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**	**1998[1]**	**2018[19]**	**1998[1]**
Totals*	**15**	**NR**	**0.000001-1.8**	******	**2**	**NR**	**0.052-16.5**	******
Duration of Use								
Leave-On	*14*	*NR*	*0.00018-1.8*	**	*2*	*NR*	*0.052-16.5*	**
Rinse-Off	*1*	*NR*	*0.000001-0.0005*	**	*NR*	*NR*	*NR*	**
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*NR*	*NR*	*NR*	**
Exposure Type								
Eye Area	2	NR	0.0022	**	1	NR	NR	**
Incidental Ingestion	NR	NR	NR	**	NR	NR	NR	**
Incidental Inhalation-Spray	3[a]; 6[b]	NR	NR	**	1[a]	NR	NR	**
Incidental Inhalation-Powder	6[b]	NR	0.00018[c]	**	NR	NR	0.052	**
Dermal Contact	14	NR	0.000001-1.8	**	2	NR	0.052	**
Deodorant (underarm)	NR	NR	NR	**	NR	NR	NR	**
Hair - Non-Coloring	NR	NR	NR	**	NR	NR	NR	**
Hair-Coloring	NR	NR	NR	**	NR	NR	NR	**
Nail	1	NR	NR	**	NR	NR	16.5	**
Mucous Membrane	1	NR	NR	**	NR	NR	NR	**
Baby Products	NR	NR	NR	**	NR	NR	NR	**
	AMP-Acrylates Copolymer				**Behenyl Methacrylate/t-Butyl Methacrylate Copolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**		**2018[20]**	
Totals*	**31**	**NR**	**0.00084-8**	******	**5**		**NR**	
Duration of Use								
Leave-On	*28*	*NR*	*0.00084-8*	**	*5*		*NR*	
Rinse-Off	*3*	*NR*	*0.51*	**	*NR*		*NR*	
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*NR*		*NR*	
Exposure Type								
Eye Area	1	NR	0.3	**	2		NR	
Incidental Ingestion	NR	NR	NR	**	3		NR	
Incidental Inhalation-Spray	12; 14[a]	NR	0.44-8; 0.00084-1.1[a]	**	NR		NR	
Incidental Inhalation-Powder	NR	NR	NR	**	NR		NR	
Dermal Contact	1	NR	0.035-0.64	**	2		NR	
Deodorant (underarm)	NR	NR	NR	**	NR		NR	
Hair - Non-Coloring	29	NR	0.00084-8	**	NR		NR	
Hair-Coloring	NR	NR	NR	**	NR		NR	
Nail	1	NR	NR	**	NR		NR	
Mucous Membrane	NR	NR	NR	**	3		NR	
Baby Products	NR	NR	NR	**	NR		NR	

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Butyl Acrylate/Glycol Dimethacrylate Crosspolymer				**C12-22 Alkyl Acrylate/Hydroxyethylacrylate Copolymer**			
	2018[25]	**2011[2]**	**2018[21]**	**2011[2]**	**2018[25]**		**2018[20]**	
Totals*	**1**	**NR**	**4.2-10**	**NR**	**NR**		**3**	
Duration of Use								
Leave-On	*1*	*NR*	*4.2-10*	*NR*	*NR*		*3*	
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*		*NR*	
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*		*NR*	
Exposure Type								
Eye Area	NR	NR	8.3-8.5	NR	NR		NR	
Incidental Ingestion	NR	NR	NR	NR	NR		NR	
Incidental Inhalation-Spray	1[a]	NR	NR	NR	NR		NR	
Incidental Inhalation-Powder	NR	NR	4.2	NR	NR		NR	
Dermal Contact	1	NR	4.2-10	NR	NR		3	
Deodorant (underarm)	NR	NR	NR	NR	NR		NR	
Hair - Non-Coloring	NR	NR	NR	NR	NR		NR	
Hair-Coloring	NR	NR	NR	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	
	C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer				**Carbomer**			
	2018[25]	**2011[2]**	**2018[21]**	**2011[2]**	**2018[25] #**	**2001[6] ##**	**2018[22]**	**2001[6]**
Totals*	**2**	**NR**	**NR**	**NR**	**6434**	**1504**	**0.00001-15**	**0.001-2**
Duration of Use								
Leave-On	*2*	*NR*	*NR*	*NR*	*5336*	*1167*	*0.0012-15*	*0.001-2*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*1093*	*330*	*0.00001-2.5*	*0.003-2*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*5*	*7*	*0.18-0.3*	*0.1-1*
Exposure Type								
Eye Area	NR	NR	NR	NR	301	65	0.2-1.5	0.2-2
Incidental Ingestion	NR	NR	NR	NR	95	6	0.048-9	0.1-0.7
Incidental Inhalation-Spray	1[b]	NR	NR	NR	16; 2565[a]; 1870[b]	50; 347[a]; 412[b]	0.003-1; 0.048-2.5[a]	0.3-1; 0.003-2[a]; 0.05-1[b]
Incidental Inhalation-Powder	1[b]	NR	NR	NR	2; 1870[b]; 30[c]	1; 412[b]; 5[c]	0.0012-0.88 0.1-15[c]	0.3; 0.05-1[b]; 0.2-0.8[c]
Dermal Contact	1	NR	NR	NR	5601	1335	0.00001-15	0.001-2
Deodorant (underarm)	NR	NR	NR	NR	3[a]	NR	0.25 (not spray) 0.18 (spray)	NR
Hair - Non-Coloring	1	NR	NR	NR	490	96	0.0084-2.5	0.3-1.5
Hair-Coloring	NR	NR	NR	NR	222	57	0.2-2.5	0.7-2
Nail	NR	NR	NR	NR	12	7	0.003-0.87	0.2-2
Mucous Membrane	NR	NR	NR	NR	200	26	0.048-9	0.003-2
Baby Products	NR	NR	NR	NR	36	15	0.15-0.69	0.2-0.8
	Ethylene/Acrylic Acid Copolymer				**Ethylene/Methacrylate Copolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**	**1998[1]**	**2018[19]**	**1998[1]**
Totals*	**316**	**6**	**0.001-16.5**	******	**60**	**5**	**0.0003-0.83**	******
Duration of Use								
Leave-On	*306*	*6*	*0.001-16.5*	**	*60*	*5*	*0.0003-0.83*	**
Rinse-Off	*NR*	*NR*	*0.001-0.5*	**	*NR*	*NR*	*NR*	**
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*NR*	*NR*	*NR*	**
Exposure Type								
Eye Area	181	NR	0.001-16.5	**	29	NR	0.0003-0.74	**
Incidental Ingestion	3	NR	NR	**	NR	NR	0.3-0.59	**
Incidental Inhalation-Spray	18[a]; 7[b]	NR	0.25	**	2[a]; 1[b]	NR	NR	**
Incidental Inhalation-Powder	23; 7[b]	NR	0.5; 0.001-8[c]	**	9; 1[b]	NR	0.3;0.037-0.53[c]	**
Dermal Contact	298	6	0.001-16.5	**	42	5	0.037-0.83	**
Deodorant (underarm)	NR	NR	NR	**	NR	NR	NR	**
Hair - Non-Coloring	1	NR	NR	**	NR	NR	NR	**
Hair-Coloring	NR	NR	NR	**	NR	NR	NR	**
Nail	4	NR	4	**	NR	NR	NR	**
Mucous Membrane	3	NR	NR	**	NR	NR	0.3-0.59	**
Baby Products	NR	NR	NR	**	NR	NR	NR	**

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Ethylene/Sodium Acrylate Copolymer				**Ethylhexyl Acrylate/Methyl Methacrylate Copolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**		**2018[20]**	
Totals*	**1**	**1**	**NR**	******	**5**		**7**	
Duration of Use								
Leave-On	*NR*	*1*	*NR*	**	*5*		*7*	
Rinse-Off	*1*	*NR*	*NR*	**	*NR*		*NR*	
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*NR*		*NR*	
Exposure Type								
Eye Area	NR	1	NR	**	5		NR	
Incidental Ingestion	NR	NR	NR	**	NR		NR	
Incidental Inhalation-Spray	NR	NR	NR	**	NR		NR	
Incidental Inhalation-Powder	NR	NR	NR	**	NR		NR	
Dermal Contact	1	1	NR	**	5		7	
Deodorant (underarm)	NR	NR	NR	**	NR		NR	
Hair - Non-Coloring	NR	NR	NR	**	NR		NR	
Hair-Coloring	NR	NR	NR	**	NR		NR	
Nail	NR	NR	NR	**	NR		NR	
Mucous Membrane	NR	NR	NR	**	NR		NR	
Baby Products	NR	NR	NR	**	NR		NR	
	Lauryl Acrylate Crosspolymer				**Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer**			
	2018[25]		**2018[20]**		**2018[25]**	**2011[2]**	**2018[21]**	**2011[2]**
Totals*	**NR**		**1.2**		**99**	**63**	**1.1-3.2**	**0.06-3**
Duration of Use								
Leave-On	*NR*		*1.2*		*90*	*56*	*1.1-3.2*	*0.06-3*
Rinse-Off	*NR*		*NR*		*9*	*7*	*NR*	*0.2-3*
Diluted for (Bath) Use	*NR*		*NR*		*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR		NR		25	9	NR	0.1-3
Incidental Ingestion	NR		NR		19	8	1.3	0.06-2
Incidental Inhalation-Spray	NR		1.2[a]		6; 2[b]	NR	NR	0.3
Incidental Inhalation-Powder	NR		NR		6; 2[b]	8	1.1; 3[c]	0.01-1
Dermal Contact	NR		NR		79	53	1.1-3.2	0.06-3
Deodorant (underarm)	NR		NR		NR	1[a]	NR	0.3[a]
Hair - Non-Coloring	NR		1.2		NR	NR	NR	NR
Hair-Coloring	NR		NR		NR	NR	NR	NR
Nail	NR		NR		1	1	NR	NR
Mucous Membrane	NR		NR		19	8	1.3	0.06-2
Baby Products	NR		NR		NR	NR	NR	NR
	Lauryl Methacrylate/Sodium Methacrylate Crosspolymer				**Methacryloyl Ethyl Betaine/Acrylates Copolymer**			
	2018[25]	**2011[2]**	**2018[21]**	**2011[2]**	**2018[25]**	**1998[1]**	**2018[19]**	**1998[1]**
Totals*	**4**	**1**	**0.081-7.7**	**0.004-4**	**12**	**NR**	**0.00015-11**	******
Duration of Use								
Leave-On	*3*	*1*	*1.3-7.7*	*0.1-4*	*3*	*NR*	*0.09-11*	**
Rinse-Off	*1*	*NR*	*0.081*	*0.004-0.1*	*9*	*NR*	*0.00015-2.7*	**
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	**
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	**
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	**
Incidental Inhalation-Spray	NR	NR	1.3	NR	3[a]	NR	0.09-3.6; 5.1-11[a]	**
Incidental Inhalation-Powder	NR	NR	7.7[c]	NR	NR	NR	NR	**
Dermal Contact	4	1	0.081-7.7	0.004-4	NR	NR	NR	**
Deodorant (underarm)	NR	NR	4.6 (not spray)	NR	NR	NR	NR	**
Hair - Non-Coloring	NR	NR	NR	NR	4	NR	0.09-11	**
Hair-Coloring	NR	NR	NR	NR	8	NR	0.00015-2.7	**
Nail	NR	NR	NR	NR	NR	NR	NR	**
Mucous Membrane	1	NR	0.081	NR	NR	NR	NR	**
Baby Products	NR	NR	NR	NR	NR	NR	NR	**

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Methyl Methacrylate Crosspolymer				**Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer**			
	2018[25]	**2008[3]**	**2018[23]**	**2009[3]**	**2018[25]**	**2008[3]**	**2018[23]**	**2009[3]**
Totals*	**423**	**144**	**0.0001-13**	**0.1-14**	**38**	**7**	**0.39-1.6**	**0.1-3**
Duration of Use								
Leave-On	*417*	*142*	*0.0001-13*	*0.1-14*	*38*	*7*	*0.39-1.6*	*0.1-3*
Rinse-Off	*6*	*2*	*0.12*	*NR*	*N R*	*NR*	*NR*	*0.1*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	53	15	2-13	0.5-10	2	NR	1.4	NR
Incidental Ingestion	38	15	2	1-10	NR	NR	NR	NR
Incidental Inhalation-Spray	5; 46[a]; 39[b]	1; 24[a]; 16[b]	0.12-0.38; 0.0069[a]	0.1-0.6; 0.8-3[a]; 0.1-3[b]	5[a]; 11[b]	1[a]	NR	0.5[a]; 0.2[b]
Incidental Inhalation-Powder	36; 39[b]	17; 16[b]	7.6-12; 0.5-8[c]	0.8-8; 0.1-3[b]	1; 11[b]	NR	0.65; 1-1.5[c]	3; 0.2[b]
Dermal Contact	370	127	0.0069-13	0.1-14	38	7	0.39-1.6	3
Deodorant (underarm)	1[a]	NR	2 (not spray)	0.9[a]	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	0.1	NR	NR	NR	NR
Hair-Coloring	7	NR	0.12	NR	NR	NR	NR	NR
Nail	2	1	0.0001-4	1	NR	NR	NR	NR
Mucous Membrane	38	15	2	1-10	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Methyl Methacrylate/PEG/PPG-4/3 Methacrylate Crosspolymer				**Poly C10-30 Alkyl Acrylate**			
	2018[25]		**2018[20]**		**2018[25]**		**2018[20]**	
Totals*	**1**		**NR**		**19**		**0.5-3.2**	
Duration of Use								
Leave-On	*1*		*NR*		*19*		*0.5-3.2*	
Rinse-Off	*NR*		*NR*		*NR*		*NR*	
Diluted for (Bath) Use	*NR*		*NR*		*NR*		*NR*	
Exposure Type								
Eye Area	NR		NR		2		3.2	
Incidental Ingestion	NR		NR		3		0.52-1.2	
Incidental Inhalation-Spray	NR		NR		9[a]; 3[b]		NR	
Incidental Inhalation-Powder	NR		NR		3[b]		2[c]	
Dermal Contact	1		NR		15		0.5-2	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	NR		NR		NR		NR	
Hair-Coloring	NR		NR		NR		NR	
Nail	NR		NR		NR		NR	
Mucous Membrane	NR		NR		3		0.5-1.2	
Baby Products	NR		NR		NR		NR	

	Polyacrylate-14				**Polyacrylate-1 Crosspolymer**			
	2018[25]		**2018[20]**		**2018[25]**		**2018[20]**	
Totals*	**3**		**NS**		**14**		**0.2-2**	
Duration of Use								
Leave-On	*2*		*NS*		*4*		*NR*	
Rinse-Off	*1*		*NS*		*10*		*0.2-2*	
Diluted for (Bath) Use	*NR*		*NS*		*NR*		*NR*	
Exposure Type								
Eye Area	NR		NS		NR		NR	
Incidental Ingestion	NR		NS		NR		NR	
Incidental Inhalation-Spray	1[a]		NS		1[a]; 3[b]		NR	
Incidental Inhalation-Powder	NR		NS		NR		NR	
Dermal Contact	NR		NS		11		0.2-2	
Deodorant (underarm)	NR		NS		NR		NR	
Hair - Non-Coloring	3		NS		3		NR	
Hair-Coloring	NR		NS		NR		NR	
Nail	NR		NS		NR		NR	
Mucous Membrane	NR		NS		6		1.5	
Baby Products	NR		NS		NR		NR	

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Polyacrylic Acid				**Polyethylacrylate**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**		**2018[20]**	
Totals*	**111**	**31**	**0.0012-4**	**	**4**		**NR**	
Duration of Use								
Leave-On	*96*	*27*	*0.0012-4*	**	*4*		*NR*	
Rinse-Off	*15*	*7*	*0.0049-0.4*	**	*NR*		*NR*	
Diluted for (Bath) Use	*NR*	*NR*	*0.36*	**	*NR*		*NR*	
Exposure Type								
Eye Area	8	NR	0.5-2.1	**	2		NR	
Incidental Ingestion	2	NR	0.0049-0.048	**	NR		NR	
Incidental Inhalation-Spray	1; 34[a]; 29[b]	3[a]; 14[b]	0.0049-0.62[a]	**	NR		NR	
Incidental Inhalation-Powder	29[b]	14[b]	0.0012; 0.25-4[c]	**	NR		NR	
Dermal Contact	95	28	0.0012-4	**	1		NR	
Deodorant (underarm)	NR	NR	NR	**	NR		NR	
Hair - Non-Coloring	3	1	0.4-1.2	**	NR		NR	
Hair-Coloring	NR	NR	NR	**	NR		NR	
Nail	11	2	NR	**	1		NR	
Mucous Membrane	3	2	0.0049-0.4	**	NR		NR	
Baby Products	NR	NR	0.15	**	NR		NR	
	Polymethyl Acrylate				**Polymethyl Methacrylate**			
	2018[25]		**2018[20]**		**2018[25]**	**2008[3]**	**2018[23]**	**2009[3]**
Totals*	**1**		**0.0014-5.9**		**922**	**892**	**0.0036-44.6**	**0.01-45**
Duration of Use								
Leave-On	*1*		*0.0014-5.9*		*896*	*879*	*0.0036-44.6*	*0.01-45*
Rinse-Off	*NR*		*NR*		*26*	*13*	*0.009-15.6*	*0.3-6*
Diluted for (Bath) Use	*NR*		*NR*		*0*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR		4-5.9		293	304	1-9.8	0.1-45
Incidental Ingestion	NR		2		72	60	0.16-16.1	3-20
Incidental Inhalation-Spray	1[a]		NR		4; 97[a]; 88[b]	6; 74[a]; 79[b]	0.1; 4-14.9[a]	0.5-20; 0.01-15[a]; 0.3-16[b]
Incidental Inhalation-Powder	NR		5		76; 88[b]	93; 79[b]	0.27-44.6; 0.23-8.6[c]	2-30 0.3-16[b]
Dermal Contact	1		0.5-5.9		807	806	0.009-44.6	0.01-45
Deodorant (underarm)	NR		NR		NR	NR	NR	4[a]
Hair - Non-Coloring	NR		NR		4	2	0.1-14.9	0.3-1
Hair-Coloring	NR		NR		9	1	15.6	2
Nail	NR		0.0014-.44		19	14	0.0036-19	0.7-30
Mucous Membrane	NR		2		78	62	0.16-16.1	3-20
Baby Products	NR		NR		NR	NR	NR	NR
	Potassium Acrylates Copolymer				**Potassium Acrylates/C10-30 Alkyl Acrylate Crosspolymer**			
	2018[25]		**2018[20]**		**2018[25]**	**2011[2]**	**2018[21]**	**2011[2]**
Totals*	**16**		**0.00031-1.3**		**2**	**NR**	**0.3**	**NR**
Duration of Use								
Leave-On	*10*		*1.3*		*2*	*NR*	*NR*	*NR*
Rinse-Off	*6*		*0.00031-0.31*		*NR*	*NR*	*0.3*	*NR*
Diluted for (Bath) Use	*NR*		*NR*		*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR		NR		1	NR	NR	NR
Incidental Ingestion	NR		NR		NR	NR	NR	NR
Incidental Inhalation-Spray	NR		NR		1[b]	NR	NR	NR
Incidental Inhalation-Powder	NR		1.3[c]		1[b]	NR	NR	NR
Dermal Contact	14		NR		2	NR	0.3	NR
Deodorant (underarm)	NR		NR		NR	NR	NR	NR
Hair - Non-Coloring	2		0.00031		NR	NR	NR	NR
Hair-Coloring	NR		NR		NR	NR	NR	NR
Nail	NR		NR		NR	NR	NR	NR
Mucous Membrane	1		NR		NR	NR	NR	NR
Baby Products	12		0.00031		NR	NR	NR	NR

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Potassium Carbomer				**Sodium Acrylate/Vinyl Alcohol Copolymer**			
	2018[25]		**2018[20]**		**2018[25]**		**2018[20]**	
Totals*	**73**		**NR**		**NR**		**1.5**	
Duration of Use								
Leave-On	*56*		*NR*		*NR*		*NR*	
Rinse-Off	*13*		*NR*		*NR*		*1.5*	
Diluted for (Bath) Use	*4*		*NR*		*NR*		*NR*	
Exposure Type								
Eye Area	3		NR		NR		NR	
Incidental Ingestion	NR		NR		NR		NR	
Incidental Inhalation-Spray	25[a]; 27[b]		NR		NR		NR	
Incidental Inhalation-Powder	27[b]		NR		NR		NR	
Dermal Contact	73		NR		NR		NR	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	NR		NR		NR		1.5	
Hair-Coloring	NR		NR		NR		NR	
Nail	NR		NR		NR		NR	
Mucous Membrane	6		NR		NR		NR	
Baby Products	NR		NR		NR		NR	
	Sodium Acrylates Copolymer				**Sodium Acrylates Crosspolymer-2**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**	**2011[2]**	**2018[21]**	**2011[2]**
Totals*	**179**	**5**	**0.005-18**	******	**NR**	**NR**	**0.47-1.8**	**0.8**
Duration of Use								
Leave-On	*170*	*NR*	*0.005-18*	**	*NR*	*NR*	*0.47-1.8*	*0.8*
Rinse-Off	*9*	*5*	*NR*	**	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	20	NR	1.5	**	NR	NR	NR	NR
Incidental Ingestion	1	NR	NR	**	NR	NR	NR	NR
Incidental Inhalation-Spray	72[a]; 50[b]	NR	8[a]	**	NR	NR	NR	NR
Incidental Inhalation-Powder	50[b]; 2[c]	NR	0.5-1.2[b]	**	NR	NR	0.47-1.8[c]	NR
Dermal Contact	176	NR	0.005-18	**	NR	NR	0.47-1.8	0.8
Deodorant (underarm)	NR	NR	NR	**	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	**	NR	NR	NR	NR
Hair-Coloring	NR	5	NR	**	NR	NR	NR	NR
Nail	NR	NR	NR	**	NR	NR	NR	NR
Mucous Membrane	2	NR	NR	**	NR	NR	NR	NR
Baby Products	2	NR	NR	**	NR	NR	NR	NR
	Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer				**Sodium Acrylates/Vinyl Isodecanoate Crosspolymer**			
	2018[25]	**2011[2]**	**2018[21]**	**2011[2]**	**2018[25]**	**2011[2]**	**2018[21]**	**2011[2]**
Totals*	**96**	**6**	**0.3**	**NR**	**NR**	**NR**	**0.55**	**NR**
Duration of Use								
Leave-On	*18*	*6*	*NR*	*NR*	*NR*	*NR*	*0.55*	*NR*
Rinse-Off	*78*	*NR*	*0.3*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	2	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	5[a]; 5[b]	1	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	5[b]	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	96	6	0.3	NR	NR	NR	0.55	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 4. Current and historical (where applicable) frequency and concentration of use, according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Sodium Carbomer				**Sodium Polyacrylate**			
	2018[25]		**2018[22]**		**2018[25]**	**1998[1]**	**2018[19]**	**1998[1]**
Totals*	**168**		**0.015-0.65**		**900**	**8**	**0.0001-29.7**	**
Duration of Use								
Leave-On	*146*		*0.015-0.65*		*782*	*5*	*0.0001-29.7*	**
Rinse-Off	*22*		*NR*		*118*	*3*	*0.0002-1.5*	**
Diluted for (Bath) Use	*NR*		*0.16*		*NR*	*NR*	*NR*	**
Exposure Type								
Eye Area	22		0.015		131	NR	0.9-29.7	**
Incidental Ingestion	NR		NR		3	NR	0.0095-0.09	**
Incidental Inhalation-Spray	76[a]; 39[b]		0.65[a]		1; 319[a]; 267[b]	1	0.0001-1.8 0.0005-0.0098[a]; 1.5[b]	**
Incidental Inhalation-Powder	39[b]		0.028-0.13[c]		7; 267[b]	NR	0.05; 1.5[b]; 0.0015-7[c]	**
Dermal Contact	166		0.015-0.16		774	5	0.0005-7	**
Deodorant (underarm)	NR		NR		NR	NR	1.5 (not spray) 2.9 (spray)	**
Hair - Non-Coloring	NR		0.65		83	NR	0.0001-1.8	**
Hair-Coloring	NR		NR		22	3	1.5	**
Nail	1		NR		1	NR	6	**
Mucous Membrane	1		0.16		16	2	0.0098-0.8	**
Baby Products	NR		NR		NR	NR	0.55	**
	Sodium Polymethacrylate				Steareth-10 Allyl Ether/Acrylates Copolymer			
	2018[25]		**2018[20]**		**2018[25]**	**1998[1]**	**2018[19]**	**1998[1]**
Totals*	**62**		**0.063-3.4**		**62**	**6**	**0.025-1.5**	**
Duration of Use								
Leave-On	*62*		*0.063-3.4*		*54*	*NR*	*0.025-1.5*	**
Rinse-Off	*NR*		*NR*		*8*	*6*	*1.5*	**
Diluted for (Bath) Use	*NR*		*NR*		*NR*	*NR*	*NR*	**
Exposure Type								
Eye Area	60		0.063-1.5		NR	NR	NR	**
Incidental Ingestion	NR		NR		NR	NR	NR	**
Incidental Inhalation-Spray	1[a]		NR		53[a]; 1[b]	NR	0.025-1.5[a]	**
Incidental Inhalation-Powder	NR		NR		1[b]	NR	NR	**
Dermal Contact	8		0.5-1.5		3	NR	NR	**
Deodorant (underarm)	NR		NR		NR	NR	NR	**
Hair - Non-Coloring	NR		3.4		53	NR	0.025-1.5	**
Hair-Coloring	NR		NR		6	6	NR	**
Nail	NR		NR		NR	NR	NR	**
Mucous Membrane	NR		NR		1	NR	NR	**
Baby Products	NR		NR		NR	NR	NR	**
	Styrene/Acrylates/Ammonium Methacrylate Copolymer				**VA/Butyl Maleate/Isobornyl Acrylate Copolymer**			
	2018[25]	**1998[1]**	**2018[19]**	**1998[1]**	**2018[25]**	**1998[1]**	**2018[19]**	**1998[1]**
Totals*	**106**	**1**	**1.2-38**	**	**2**	**5**	**1.3-10**	**
Duration of Use								
Leave-On	*102*	*1*	*1.2-38*	**	*2*	*5*	*1.3-10*	**
Rinse-Off	*4*	*NR*	*10*	**	*NR*	*NR*	*NR*	**
Diluted for (Bath) Use	*NR*	*NR*	*NR*	**	*NR*	*NR*	*NR*	**
Exposure Type								
Eye Area	99	1	1.2-22.6	**	NR	NR	NR	**
Incidental Ingestion	NR	NR	NR	**	NR	NR	NR	**
Incidental Inhalation-Spray	1[a]	NR	NR	**	1; 1[a]	NR	1.3-10	**
Incidental Inhalation-Powder	NR	NR	NR	**	NR	NR	NR	**
Dermal Contact	50	1	3.3-22.6	**	NR	NR	1.3-2	**
Deodorant (underarm)	NR	NR	NR	**	NR	NR	NR	**
Hair - Non-Coloring	NR	NR	NR	**	2	5	2.5-10	**
Hair-Coloring	4	NR	10	**	NR	NR	NR	**
Nail	1	NR	21-38	**	NR	NR	NR	**
Mucous Membrane	NR	NR	NR	**	NR	NR	NR	**
Baby Products	NR	NR	NR	**	NR	NR	NR	**

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

** Concentration of use data were not provided at the time of the review.

[#] This ingredient is listed in the VCRP as Carbomer (6175 used under the INCI name) and several tradenames (259 used listed under the tradenames)

[##] At the time of the original assessment, this ingredient was reported under several names. The use frequencies of use were combined for the purposes of this table; this may overestimate the actual 2001 frequency of use

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders

NR – no reported use

NS – not yet surveyed

Table 5. Acrylates copolymers not reported to be used in cosmetics, according to 2018 FDA VCRP[25] and 2018 Council survey[19-24] data

Acrylates Crosspolymer-5	Cyclohexyl Methacrylate/Ethylhexyl Methacrylate Copolymer
Acrylates/Beheneth-25 Methacrylate/Steareth-30 Methacrylate Copolymer	Ethylene/Acrylic Acid/VA Copolymer
Acrylates/C12-13 Alkyl Methacrylates/Methoxyethyl Acrylate Crosspolymer	Ethylene/Calcium Acrylate Copolymer
	Ethylene/Magnesium Acrylate Copolymer
Acrylates/C26-28 Olefin Copolymer	Ethylene/Zinc Acrylate Copolymer
Acrylates/C5-8 Alkyl Acrylate Copolymer	Ethylhexyl Acrylate/Methoxy PEG-23 Methacrylate/Vinyl Acetate Copolymer
Acrylates/Ceteareth-20 Methacrylate Crosspolymer	
Acrylates/Ceteareth-20 Methacrylate Crosspolymer-2	Glycol Dimethacrylate Crosspolymer*
Acrylates/Ceteth-20 Methacrylate Copolymer	Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer
Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer	Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Acrylates/Hydroxyethyl Acrylate/Lauryl Acrylate Copolymer	Lauryl Acrylate/VA Copolymer
Acrylates/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	Lauryl Acrylate/VA Crosspolymer
Acrylates/Laureth-25 Methacrylate Copolymer	Methacrylic Acid/PEG-6 Methacrylate/PEG-6 Dimethacrylate Crosspolymer
Acrylates/Lauryl Methacrylate Copolymer	PEG/PPG-5/2 Methacrylate/Methacrylic Acid Crosspolymer
Acrylates/Lauryl Methacrylate/Tridecyl Methacrylate Crosspolymer	Poly(Methoxy PEG-9 Methacrylate)
Acrylates/Methoxy PEG-4 Methacrylate Copolymer	Polyacrylate-29*
Acrylates/Methoxy PEG-15 Methacrylate Copolymer	Polyacrylate-34*
Acrylates/Methoxy PEG-90 Methacrylate Crosspolymer	Polybutyl Acrylate
Acrylates/PEG-4 Dimethacrylate Crosspolymer	Polybutyl Methacrylate
Acrylates/Steareth-50 Acrylate Copolymer	Polyhydroxyethylmethacrylate
Acrylic Acid/C12-22 Alkyl Acrylate Copolymer	Polyisobutyl Methacrylate
Allyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Polypropyl Methacrylate
Ammonium Acrylates/Ethylhexyl Acrylate Copolymer	Polystearyl Methacrylate
Ammonium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	Potassium Acrylate Crosspolymer
	Potassium Acrylates/Ethylhexyl Acrylate Copolymer
Ammonium VA/Acrylates Copolymer	Potassium Aluminum Polyacrylate
Butyl Acrylate/Cyclohexyl Methacrylate Copolymer	Potassium Polyacrylate
Butyl Acrylate/Ethylhexyl Methacrylate Copolymer	Sodium Acrylate/Acrolein Copolymer
Butyl Acrylate/Hydroxyethyl Methacrylate Copolymer	Sodium Acrylates/Beheneth-25 Methacrylate Crosspolymer
Butyl Methacrylate/Acryoyloxy PG Methacrylate Copolymer	Sodium Acrylates/Ethylhexyl Acrylate Copolymer
C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer	Stearyl/Lauryl Methacrylate Crosspolymer
Calcium Potassium Carbomer	

*not yet surveyed by the Council

Table 6. Acrylates Copolymers Approved for Use as Secondary Direct Food Additives and Indirect Food Additives

Secondary Direct Food Additives

21CFR173.310 - boiler water additives
Sodium Polyacrylate
Sodium Polymethacrylate

21CFR173.340 – defoaming agent
Sodium Polyacrylate

21CFR173.73 - polymer substances and polymer adjuvants for food treatment
Sodium Polyacrylate

Indirect Food Additives

21CFR175.105 – adhesives
Acrylates Copolymer
Ammonium Polyacrylate
Ethylene/Calcium Acrylate Copolymer
Ethylene/Sodium Acrylate Copolymer
Ethylene/Zinc Acrylate Copolymer
Polyacrylic Acid
Polybutyl Acrylate
Polybutyl Methacrylate
Polyethylacrylate
Sodium Polyacrylate
Sodium Polymethacrylate

21CFR175.210 - acrylate ester copolymer coating
Acrylates Copolymer

21CFR175.300 - resinous and polymeric coatings
Acrylates Copolymer
Polyacrylic Acid
Polyethylacrylate

21CFR175.320 - resinous and polymeric coatings for polyolefin films
Acrylates Copolymer
Ethylhexyl Acrylate/Methyl Methacrylate Copolymer
Polyacrylic Acid

21CFR176.170 - components of paper and paperboard in contact with aqueous and fatty foods
Acrylates Copolymer
Ethylene/Acrylic Acid Copolymer
Polyacrylic Acid
Sodium Polyacrylate
Sodium Polymethacrylate

21CFR176.180 - components of paper and paperboard in contact with dry food
Acrylates Copolymer
Acrylates VA Copolymer
Polyacrylic Acid
Polyethylacrylate
Sodium Polyacrylate

21CFR176.200 - defoaming agents used in coatings
Sodium Polyacrylate

21CFR177.1010 acrylic and modified acrylic plastics, semi-rigid and rigid
Ethylhexyl Acrylate/Methyl Methacrylate Copolymer
Polybutyl Acrylate
Polybutyl Methacrylate
Polyethylacrylate

21CFR177.1210 - closures with sealing gaskets for food containers
Sodium Polyacrylate

21CFR177.1310 – ethylene-acrylic acid copolymers
Ethylene/Acrylic Acid Copolymer

21CFR177.1520 - olefin polymers
Polyethylacrylate

21CFR178.3790 - polymer modifiers in semi-rigid and rigid vinyl chloride plastics
Polybutyl Acrylate
Polybutyl Methacrylate
Polymethyl Methacrylate

Table 7. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL						
Acrylates/Beheneth-25 Methacrylate Copolymer	rats	not stated	not stated	details not provided	> 5 g/kg	10
Acrylates Copolymer [as 2-propenoic acid, 2-methyl-, polymer with butyl 2-methyl-2-propenoate, ethyl 2-methyl-2-propenoate and ethyl 2-propenoate]	rats	not stated	not stated	in accord with OECD TG 423; details not provided	> 2 g/kg	13
Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%)	rats	not stated	not stated	in accord with OECD TG 402; details were not provided	>5 g/kg bw	14
VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol	NZW rabbits	3/sex	applied neat	occlusive patch of 2 g/kg of the test material was applied to intact and abraded skin for 24 h	> 2 g/kg	8
ORAL						
Acrylates/Beheneth-25 Methacrylate Copolymer	rats	not stated	not stated	details not provided	> 5 g/kg	10
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	rats (strain not specified)	5/sex	copolymer dispersion was mixed with powdered diet	the copolymer dispersion was mixed with powdered diet to give a content of 20% of dry polymer substance; animals were given the treated feed for 24 h, and then observed for 4 wks	> 25.2 g dry copolymer/kg bw no mortality; no lesions observed at necropsy	15
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	dogs (strain not specified)	2/sex	copolymer dispersion was mixed with powdered diet	the copolymer dispersion was mixed with powdered diet to give a content of 20% of dry polymer substance; fasted animals were fed 60 g formulated diet/kg bw, and then observed for clinical signs	> 7.95 g dry copolymer/kg bw no mortality; no lesions observed at necropsy	15
Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%)	rats	not stated	not stated	in accord with OECD TG 425; details not provided	> 5 g/kg	14
Polyacrylate-1 Crosspolymer	rats	not stated	DMSO	in accord with OECD TG 423; details not provided	> 2 g/kg	12
VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol	Sprague-Dawley rats	5/sex	corn oil	5 g/kg by gavage	> 5 g/kg no mortality	8
INHALATION						
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	Wistar rats	5/sex	the copolymer was dispersed with dry matter	single 4-h exposure (nose-only) to an aerosol of the copolymer dispersion with a dry matter content of 30.2%; the test was performed in accord with OECD TG 403	> 3960 mg/l no mortality; no observations of toxicity	15

Abbreviations: DMSO – dimethyl sulfoxide; NZW – New Zealand White; OECD – Organisation for Economic Co-operation and Development; TG – test guideline

Table 8. Genotoxicity Studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
Acrylates Copolymer [as 2-propenoic acid, 2-methyl-, polymer with butyl 2-methyl-2-propenoate, ethyl 2-methyl-2-propenoate and ethyl 2-propenoate]	not provided	not provided	not provided	Ames test, in accord with OECD TG 471; details not provided	not mutagenic	13
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	312.5 – 5000 µg dry copolymer/plate	acetone	*S. typhimurium* TA98, TA100, and TA1537	Ames test, with and without metabolic activation	not mutagenic	15
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	40% dry substance 3 – 5000 µg dispersion/ plate (corresponds to 1.2 – 2000 µg dry copolymer/ plate	aq. dispersion	S. typhimurium TA98, TA100, TA102, TA1535, and TA1537	Ames test in accord with OECD TG 471, with and without metabolic activation	not mutagenic	15
Acrylates Copolymer (as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid)	157 – 5000 µg dry copolymer/plate	DMSO	S. typhimurium TA98, TA100, TA1535, and TA1537; *E. coli* WP2uvrA	Ames test in accord with OECD TG 471 and 472, with and without metabolic activation	not mutagenic	16
Acrylates Copolymer [as 2-propenoic acid, 2-methyl-, polymer with butyl 2-methyl-2-propenoate, ethyl 2-methyl-2-propenoate and ethyl 2-propenoate]	not provided	not provided	not provided	mouse lymphoma cell assay; in accord with OECD TG 476; details not provided	not mutagenic	13
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	195.3 – 6250 µg dry copolymer /ml	deionized water	mammalian L5178Y cells	mouse lymphoma L5178Y cell mutation assay in accord with OECD TG 476; cells were exposed to the test material for 4 h in the presence and absence of metabolic activation, or for 24 h without metabolic activation	not genotoxic	15
Acrylates Copolymer (as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid)	14.5 - 5000 µg dry copolymer/ml	DMSO	mammalian L5178Y cells	mouse lymphoma L5178Y cell mutation assay in accord with OECD TG 476; cells were exposed to the test material for 4 h in the presence and absence of metabolic activation, or for 24 h without metabolic activation	not genotoxic	16
Acrylates Copolymer (as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid)	≤ 1080 µg dry copolymer/ml (Exp. 1) ≤ 9000 µg dry copolymer/ml (Exp. 2)	DMSO	human lymphocytes	chromosomal aberration assay in accord with OECD TG 473 Exp 1: cells were exposed for 2 h with, and 3 h without, metabolic activation Exp. 2: cells were exposed for 24 h, with and without metabolic activation	not clastogenic	16
Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%)	not provided	not provided	not provided	Ames test, in accord with OECD TG 471; details not provided	not mutagenic	14

Table 8. Genotoxicity Studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VIVO						
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	500, 1000, and 2000 mg dry copolymer/kg bw	sterile water	mice, 5/sex/group	mouse micronucleus test in accord with OECD TG 474; mice were dosed by gavage (10 ml/kg bw) and killed 24 h after dosing; a second high-dose group was killed 48 h after dosing	not genotoxic a minimal increase of MNPCE in male mice killed after 24 h was considered not biologically relevant, and was within historical range	15
Acrylates Copolymer (as a fully polymerized copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid)	500, 1000, and 2000 mg dry copolymer/kg bw	1% aq CMC	mice, 5/sex/group	mouse micronucleus test in accord with OECD TG 474; mice were dosed by gavage (10 ml/kg bw) and killed 24 h after dosing; a second high-dose group was killed 48 h after dosing	not genotoxic	16

Abbreviations: CMC – carboxymethylcellulose; DMSO – dimethyl sulfoxide; MNPCE - micronucleated polychromatic erythrocytes; OECD – Organisation for Economic Co-operation and Development; TG – test guideline

Table 9. Dermal irritation and sensitization

Test Article	Dose/Concentration	Test Population	Procedure	Results	Reference
ANIMAL					
Acrylates/Beheneth-25 Methacrylate Copolymer	not stated	rabbits; # not stated	details not provided	classified as slightly irritating very slight to well-defined erythema and very slight edema were observed; erythema was resolved by day 7 and edema within 48 h	10
Acrylates Copolymer [as 2-propenoic acid, 2-methyl-, polymer with butyl 2-methyl-2-propenoate, ethyl 2-methyl-2-propenoate and ethyl 2-propenoate]	not stated	rabbits; # not stated	skin irritation test conducted in accord with OECD TG404; details not provided	not irritating	13
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	0.5 ml	3 NZW rabbits	4-h semi-occlusive patch was applied to each animal, in accord with OECD TG 404; test sites were observed 1, 24, 48, and 72 h after patch removal	not an irritant	15
Acrylates Copolymer [as 2-propenoic acid, 2-methyl-, polymer with butyl 2-methyl-2-propenoate, ethyl 2-methyl-2-propenoate and ethyl 2-propenoate]	not stated	not stated; assumed to be mice	LLNA, in accord with OECD TG 429	not a sensitizer	13
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	not stated; assumed neat	Dunkin-Hartley albino guinea pigs; 20 test and 10 control animals	Buehler test, performed in accord with OECD TG 406 induction: 6-h occlusive patches were applied 1 x/wk for 3 wks challenge: after a 2-wk non-treatment period, a 6-h occlusive patch was applied to an untreated site	not a sensitizer	15
Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%)	not stated	rabbits; # not stated	skin irritation test conducted in accord with OECD TG404; details not provided	slightly irritating slight erythema observed at 1 and 24 h after patch removal; skin appeared normal after 48 h	14

Table 9. Dermal irritation and sensitization

Test Article	Dose/Concentration	Test Population	Procedure	Results	Reference
VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol	0.5 g	6 NZW rabbits	24 h occlusive patch of the test material moistened with 0.5 ml physiological saline applied to intact and abraded dorsal skin	not an irritant	8
VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol	Neat; 0.5 g	10 Hartley guinea pigs	Buehler test induction: 6-h occlusive patch applied 3x/wk for 3 wks challenge: after a 2-wk non-treatment period, patches were applied to the original test site, and to a previously untested site	not an irritant or a sensitizer	8
			HUMAN		
Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%)	not provided	# subjects not provided	HRIPT; details not provided	not a sensitizer	14
VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol	5 g; slurry in alcohol	25 subjects	48-h patch test	slight erythema observed in 20% of the subjects	8
VA/Butyl Maleate/Isobornyl Acrylate Copolymer	0.2 ml in 10% ethanol	109 subjects	HRIPT induction: 24-h patches 3x/wk for 3 wks challenge: after a 2-wk, non-treatment period, a 24-h patch was applied to a previously untreated site	not likely to be a sensitizer induction: minimal erythema in 3 subjects and hyperpigmentation in 1 subject; in 1 subject, edema and intense erythema with application 8 that did not recur when the patch was moved challenge: minimal erythema in the subject that had a reaction with the 8th induction patch; minimal erythema in 3 subjects that did not react during induction	8

Abbreviations: HRIPT – human repeated insult patch test; NZW – New Zealand White; OECD – Organisation for Economic Co-operation and Development; TG – test guideline

Table 10. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
Acrylates/Beheneth-25 Methacrylate Copolymer	not stated	rabbits; # not stated	details not provided	classified as slightly irritating transient conjunctival effects were observed; eyes were normal within 48 h	[10]
Acrylates Copolymer [as 2-propenoic acid, 2-methyl-, polymer with butyl 2-methyl-2-propenoate, ethyl 2-methyl-2-propenoate and ethyl 2-propenoate]	not stated	NZW rabbits; # not stated	in accord with OECD TG 405; details not provided	slightly irritating	[13]
Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate)	undiluted	3 NZW rabbits	0.1 ml was instilled into the conjunctival sac of one eye of each rabbits, in accord with OECD TG 405; test eyes were observed 1, 24, 48, and 72 h after patch removal	not an ocular irritant	[15]
Acrylates/Hydroxyesters Acrylates Copolymer (product containing < 50%)	not stated	rabbits; # not stated	details not provided	slightly irritating slight conjunctival irritation in treated eyes 1- and 24-h after instillation; irritation resolved within 48 h	[14]
VA/Butyl Maleate/Isobornyl Acrylate Copolymer in ethanol	undiluted	9 NZW rabbits	0.1 g was instilled into the conjunctival sac of one eye of each rabbits; the contralateral eye served as an untreated control. Following instillation, the eyes of 3 rabbits were immediately rinsed; the eyes of the remaining 6 rabbits were not rinsed.	moderate to severe eye irritant Slight corneal opacity, slight to moderate conjunctival redness, slight-to-severe conjunctival chemosis and slight to severe conjunctival discharge observed in the unwashed eyes; some degree of conjunctivitis observed in all unwashed eyes on day 7; within the first 3 days post-exposure, blistering of the conjunctiva was observed in 5 eyes that were not rinsed.	[8]

Abbreviations: NZW – New Zealand White; OECD – Organisation for Economic Co-operation and Development; TG – test guideline

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Concentration of Use by FDA Product Category – Glyceryl Polyacrylate

Product Category	Maximum Concentration of Use
Baby lotions, oils, and creams	0.09%
Other baby products	0.0099%
Eye lotions	0.5%
Other eye makeup preparations	0.25%
Tonics, dressings and other hair grooming aids	0.01%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.008%
Face and neck products Not spray	 0.15-0.99%
Body and hand products Not spray	 0.15%
Moisturizing products Not spray	 0.4%
Paste masks and mud packs	0.4%

Information collected in 2021

Table prepared: December 16, 2021

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 14, 2022

SUBJECT: Glyceryl Acrylate/Acrylic Acid Copolymer

Anonymous. 2022. Toxicology Summary of Glyceryl Acrylate/Acrylic Acid Copolymer.

January 2022

Toxicology Summary of Glyceryl Acrylate/Acrylic Acid Copolymer

Potential Impurities

Acrylic acid, < 5 ppm
Methyl vinyl ether < 0.5 ppm
Maleic acid < 5 ppm

Acute Oral Toxicity

The value of LD50 was greater than 5g/kg for Glyceryl Acrylate/Acrylic Acid Copolymer when evaluated in rats. The rats were fasted for 18 hours and appropriate amounts of the test material were delivered by gavage. Once the material had been ingested completely, feed and water were provided. The rats were individually caged and observed for mortality or other signs of gross toxicity for 14 days. At a dose level of 5.0 g/kg body weight, the test material did not cause any mortality. Glyceryl Acrylate/Acrylic Acid Copolymer may be regarded as NON- TOXIC according to FHSLA, 16 CFR 1500.3 (LD50 > 5g/kg).

Skin Irritation

Glyceryl Acrylate/Acrylic Acid Copolymer was not irritating when evaluated in primary irritation test in rabbits. Primary skin irritation testing was conducted in rabbits according to FHSLA, 16 CFR 1500.41. Six healthy rabbits were each uniquely identified and then prepared by clipping the trunk free of hair. Two 2.5 cm square patches were placed over intact skin and abraded skin on each rabbit; 0.5 ml or 0.5 g of the test material was placed under each patch. The entire trunk of the animal was wrapped with a rubberized elastic cloth to retard evaporation and as an aid in maintaining test patch position. Rabbits were placed in neck collars and returned to their individual cages. Collars were removed after 24 hours. All test s sites were wiped with a cloth to prevent further exposure. Skin lesions were evaluated at 24 and 72 hours and scored in accordance with FHSLA, 16 CFR 1500.41. Glyceryl Acrylate/Acrylic Acid Copolymer was when tested as indicated herein was considered to be non-primary irritant (PII = 0.0).

Eye Irritation

Glyceryl Acrylate/Acrylic Acid Copolymer was not irritating when evaluated in primary eye irritation test in rabbits. Glyceryl Acrylate/Acrylic Acid Copolymer was tested on albino rabbits to determine if it contained any eye irritants. Prior to installation of the test substance, both eyes of each animal were examined and only those animals without eye defects were used. The animal was held firmly, and 0.1 ml of the test substance was placed in one eye of each of six rabbits by gently pulling the lower lid away from the eyeball to form a cup into which the test substance is dropped. The lids were then held together for one second and the animal released. The other eye remaining untreated served as a control. All animal's eyes were examined, and the grade of ocular irritation was recorded at 24, 48 and

72 hours. All six rabbits showed no signs of eye irritation during test period. Glyceryl Acrylate/Acrylic Acid Copolymer was not an eye irritant per 16 CFR 1500.42.

Mucosal Membrane Irritation

Glyceryl Acrylate/Acrylic Acid Copolymer was not irritating when evaluated in mucosal irritation test in rabbits. The vaginal mucosal irritation test was performed by administering the test material into the vaginal orifice of six albino rabbits. The test sample (0.1 ml of liquid or gel) was administered in a 1.0 ml syringe into the vaginal orifice of six rabbits. Six additional rabbits were controls and received only an insertion of the tip of an empty 1.0 ml syringe. Animals are observed for gross signs of edema, erythema and excretion daily (5X) over a seven-day period. There was no evidence of mucosal irritation based upon macroscopic observation of the vagina (Mucosal Irritation Index = 0).

Bacterial Reverse Mutation Assay

Glyceryl Acrylate/Acrylic Acid Copolymer was non-mutagenic in the Salmonella/Mammalian Microsome Reverse Mutation assay. The assay was performed at a concentration of 5,000 microgram/plate both in the absence and presence of an S9 exogenous metabolic activation system. Revertant frequencies in the Glyceryl Acrylate/Acrylic Acid Copolymer treated plates were similar to vehicle control values (Salmonella typhimurium TA 97a, TA 98, TA100, TA 102, and TA1535). All positive control data were within acceptable ranges.

Repeated Insult Patch Test (RIPT)

In an RIPT completed by 55 human panelists, Glyceryl Acrylate/Acrylic Acid Copolymer demonstrated no potential for dermal irritation or allergic contact sensitization. Each of 55 human subjects received 0.2 g of test material on the upper back area (occlusive conditions). Following a 24-hour exposure period, test patches were removed, and sites scored for erythema and edema. A series of nine induction patches was applied three times a week for three weeks. Following a two-week rest period, challenge patches were applied to a virgin site on the back and allowed to remain in skin contact for 24 hours. Challenge sites were scored for erythema and edema at 24 and 72 hours post patching. No significant dermal reactions (non-irritating and non-sensitizing) were exhibited during either the induction phase or challenge phase of the study. Under the study conditions, Glyceryl Acrylate/Acrylic Acid Copolymer was considered non-irritating and non-sensitizing.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 11, 2022

SUBJECT: Glyceryl Polyacrylate

Anonymous. 2022. Summary information Glyceryl Polyacrylate.

January 2022

Summary Information – Glyceryl Polyacrylate

1. Molecular weights and impurities (especially residual monomer levels

Molecular weight: > 500,000 Daltons

Residual Acrylic Acid: < 5 ppm

2. Genotoxicity data

AMES testing has been conducted and no detectible genotoxic activity was found (test material Glyceryl Polyacrylate 1.9%).

3. Skin irritation and sensitization data

Repeated insult patch testing has been conducted and did not indicate potential for dermal irritation or allergic contact sensitization. Glyceryl Polyacrylate was tested at a concentration of 1.9% and 51 subjects completed the test.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: October 28, 2021

SUBJECT: Glyceryl Acrylate Polymers

Anonymous. 2006. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (product contains 7.7% Glyceryl Polymethacrylate).

Anonymous. 2006. Clinical evaluation report: Human patch test (product contains 7.7% Glyceryl Polymethacrylate).

Anonymous. 2015. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (product contains 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer).

Anonymous. 2014. Clinical evaluation report: Human patch test (product contains 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer).

Anonymous. 2014. Repeated insult patch test (product contains 0.5% Glyceryl Polyacrylate).

[redacted]

FINAL REPORT dated March 6, 2006

[redacted] Protocol: [redacted]

Sample: Facial Treatment coded [redacted]

[redacted]

[redacted]

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

product contains 7.7% Glyceryl Polymethacrylate

Sponsor: [redacted]

Principal Investigator: [redacted] (Board Certified Dermatologist)

Testing Facility: [redacted]

Protocol: [redacted] Protocol [redacted]

Final Report Date: March 6, 2006

[redacted]

[redacted], M.D.
Principal Investigator

March 6, 2006
Date

[redacted]

F I N A L R E P O R T

[redacted] PROTOCOL:

[redacted] Protocol [redacted]

SPONSOR:

[redacted]

[redacted]

SPONSOR STUDY:

Authorization Letter Dated: January 11, 2006

STUDY TITLE:

Evaluation of the contact-sensitizing potential of a coded topically-applied test agent.

STUDY OBJECTIVE:

The objective of this study is to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

TEST MATERIAL:

The test sample, supplied by the sponsor, was a product labeled Facial Treatment coded [redacted] and tested as supplied.

TEST PRODUCT ACCOUNTABILITY:

All test samples and materials were received in good condition by our Quality Assurance Department. The test materials and quantities were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). All test materials were stored under ambient conditions in an inaccessible location under the supervision of the investigator.

PRINCIPAL INVESTIGATOR:

[redacted], M.D. (Board Certified Dermatologist)

Medical Director, [redacted]

[redacted]

[redacted]

KGL ADMINISTRATIVE STRUCTURE:

[redacted] (Screening, Patch Applications/Removals, Recognize AE's)

[redacted] (Expert Grader)

[redacted] (Panel Recruitment)

TESTING FACILITY:

[redacted]

[redacted]

[redacted]

CONDUCTION DATES:

This study was conducted from January 16, 2006 through February 17, 2006

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics. The criteria for exclusion were:

1 - History of sun hypersensitivity and photosensitive dermatoses

2 - History of drug hypersensitivity or recurrent dermatological diseases

3 - Pregnancy or mothers who are breastfeeding

4 – History of recurrent urticaria or hives

5 - Scars, moles or other blemishes over the test site which can interfere with the study

6 - Subjects receiving systemic or topical drugs or medications, including potential sensitizers within the previous 4 weeks

7 - Other medical conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

INFORMED CONSENT:

After the protocol, reasons for the study, possible associated risks and potential benefits or risks of the treatment had been completely explained, signed, informed subject consent was obtained from each volunteer prior to the start of the study. Copies of all consent forms are on file at [redacted].

METHOD:

Patches were applied to the upper outer arm, volar forearm or the back of each subject. The entire test was composed of two distinct phases: (1) an Induction phase and (2) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material coded [redacted] (Facial Treatment) was applied to the same site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Challenge Phase**:

After a ten day rest period which follows the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded 15-30 minutes later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

[redacted] Protocol: [redacted] **Facial Treatment coded [redacted]**

SENSITIZATION RATES:	**GRADES:**	**CLASSIFICATION:**
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

RESULTS:

A total of twenty-seven (27) healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 22 females and 5 males. Their ages ranged from 19 to 62 years. All 27 subjects completed this investigation as outlined in the standard protocol.

The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Facial Treatment and coded [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	[redacted]	59	F	C
02		62	F	C
03		56	F	C
04		42	F	C
05		51	M	C
06		47	F	C
07		60	F	C
08		40	F	C
09		58	F	C
10		48	F	C
11		55	F	C
12		44	F	C
13		43	F	C
14		47	F	C
15		45	F	C
16		49	F	C
17		43	F	C
18		52	F	C
19		57	M	C
20		48	F	C
21		19	M	C
22		44	M	C
23		24	M	C
24		19	F	C
25		56	F	C
26		50	F	C
27		52	F	C

C = Caucasian

[redacted] Protocol: [redacted] Facial Treatment coded [redacted]

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Facial Treatment coded [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26	0	0
27	0	0

Challenge Readings:

48-Hour Reading – February 16, 2006
72-Hour Reading – February 17, 2006

[redacted]

RESEARCH AND DEVELOPMENT
CLINICAL EVALUATION DEPARTMENT

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1

TO: [redacted]

PRODUCT PROFILE NO: [redacted] DATE: August 2, 2006 LAB REF.: [redacted]6

1. TEST MATERIAL: [redacted] Esthetic Treatment [redacted] contains 7.7% Glyceryl Polymethacrylate

2. CONTROL MATERIAL: [redacted] Replenishing Cleanser (in-line) [redacted]

3. TEST PROCEDURE:

Single-Insult (24hr.)__X__ Occlusive (Blenderm) Patch__X__Semi-Occlusive Patch_____.

4. CONCENTRATION:

Full-Strength__X__ Aqueous _____Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

_____Volatiles were allowed to evaporate on the patch. _____.Patch was hydrated just prior to application to skin.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	±	1	1+	2	2+	3	3+	4	PII
[redacted] Esthetic Treatment [redacted]	19	18	0	1	0	0	0	0	0	0	0.05
[redacted] Replenishing Cleanser (in-line) [redacted]	19	19	0	0	0	0	0	0	0	0	0.00

___ Skin staining noted. Erythematous response were read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). __X__.

B. _____.

Study Conducted By: [redacted] Approved By: [redacted].

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

CC: [redacted]

[redacted]

FINAL REPORT

[redacted] Protocol: [redacted]

Sample: Face Serum coded [redacted]

[redacted]

[redacted]

Title: An Evaluation of the Contact-Sensitizing Potential of a Topically-Coded Product in Human Skin by means of the Human Maximization Assay

Sponsor: [redacted] product contains 0.586% Glyceryl Acrylate/Acrylic Acid Copolymer

ASF Date: [redacted] Submission Form dated 01/07/15

Principal Investigator: [redacted]

Senior Consultant:

Testing Facility: [redacted]

[redacted] 3.2.15

Principal Investigator Date

[redacted]

[redacted]

FINAL REPORT

STUDY TITLE:

An assessment of the contact-sensitizing potential of a coded topically-applied test agent using a Human Maximization Assay.

PROTOCOL:

Protocol

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) 21 CFR 50, 56, 312 ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register and in accordance with Standard Operating Procedures (SOPs).

STUDY OBJECTIVE:

The objective of this study was to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

DESIGN RATIONALE:

A repeat insult patch test wherein the test product was applied under an occlusive dressing to an SLS (sodium lauryl sulfate) pre-treated site on the arm or back repeatedly to the same designated area for five 48-hour induction periods followed 10 days later by a single challenge to a naïve skin site on the opposite arm or the opposite side of the back.

CONDUCTION DATES:

This study was conducted from January 12, 2015 through February 12, 2015.

PRINCIPAL INVESTIGATOR:

SENIOR CONSULTANT:

[redacted]

STUDY SPONSOR:

[redacted]

SPONSOR CONTACT:

[redacted]

SPONSOR STUDY:

[redacted] Submission Form dated January 7, 2015

TESTING FACILITY:

[redacted]

[redacted] **ADMINISTRATIVE STRUCTURE**:

[redacted] (Technician/Panel Recruitment/Screening/Patch Applications /Removals/ Recognize/Report AE's)

[redacted] (Technician/Screening, Patch Applications/Removals/ Recognize/Report AE's)

[redacted] (Medical Review)

[redacted] (Evaluator/Expert Grader)

[redacted] (Quality Control)

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to read and sign the consent form prior to enrollment. Original consent forms are on file at [redacted].

TEST MATERIAL:

The test product, supplied by the sponsor, was labeled Face Serum coded [redacted]. One (1) jar of the test product was supplied. The test product was tested neat under occlusive patching.

TEST PRODUCT ACCOUNTABILITY:

The test product was received in good condition. The product was checked for (1) amount (2) test product number or code (3) product container etc. The product was individually listed on the Test Product Inventory form and signed by the receiver. The test products were stored in a secure environmentally-controlled product storage room and kept at room temperature under the supervision of the Investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test product(s) will be disposed of in accordance with applicable governmental regulations and in accordance with [redacted] SOPs following completion of the study and submission of the final written report to the Sponsor.

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. Panelists had no blemishes, excess hair or other marks on their volar forearms, upper outer arms or back that would obscure grading of the test site. Both male and female panelists were eligible. None of the subjects had a medical or dermatological illness and none were sensitive to

sunscreens or to topical preparations and/or cosmetics. A completed panelist was a panelist who satisfied the inclusion/exclusion criteria and who completed the scheduled study procedures.

Inclusion Criteria:

1. Healthy adult male and female panelists between the ages of 18 and 70 years.
2. All panelists who were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. Panelists with any significant internal diseases e.g., cardiac, pulmonary, renal, hepatic, etc.
2. History of allergy or hypersensitivity to fragrances, cosmetics, tapes, toiletries or other dermatological products
3. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria
4. Pregnancy or mothers breastfeeding or planning a pregnancy
5. Scars, moles or other blemishes over the arms or back which could interfere with the study
6. Subjects receiving systemic or topical drugs or medications which could interfere with delayed immunologic responses e.g., corticosteroids, retinoids, immunosuppressants
7. Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each panelist accepted into the study were recorded as they were enrolled.

RECORDING OF DATA:

The case report forms (CRFs) for this study were provided by the Investigator. All case report forms were completed in actual time, during each panelist's visit. Original CRFs will be retained by the Investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS:

All study related documents, case report forms (CRFs), original informed consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

STUDY PROCEDURES:

Method and Procedures[1,2]

Patches were applied to the arm or back of each panelist. The entire test was composed of three distinct phases: (1) an Induction phase and (2) a Rest Phase and (3) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape (Blenderm, 3M and Scanpor) for a period of 24 hours. After 24 hours, the SLS patch was removed. A Webril pad loaded with the product (0.05ml) was then applied to the same site and again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test product to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test product application was continued for a total of 5 induction exposures. If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test product was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Rest Phase**:

No exposure to the test material was made during this rest period, which lasted for 11 days after the last induction patch.

(3) **Challenge Phase**:

After a 10 day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm or opposite side of the back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 1.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and 0.05ml of the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded, and again 24 hours later for any reactions.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	**GRADES:**	**CLASSIFICATION**:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

ADVERSE EVENTS:

There were no adverse events or serious adverse events during the course of this study.

PROTOCOL DEVIATION:

In anticipation of a major snowstorm on Monday evening, January 26, 2015, a decision was made to close [redacted] on Tuesday, January 27, 2015. As a result, during the third week of induction, the patching schedule was modified as follows to ensure the sequence of patching without interruption.

- Monday, January 26, 2015 – no SLS patch was applied
- Monday, January 26, 2015 – test product patches applied for 48-hours
- Wednesday, January 28, 2015 – test product patches removed and test sites graded and rest period began.

RESULTS:

A total of 29 subjects who satisfied the inclusion/exclusion criteria were enrolled into the study. There were 13 females and 16 males. Their ages ranged from 19 to 52 years. One subject, #19 voluntarily withdrew from the study. Three subjects (#08, #09 and #26) were dropped from the study for lack of compliance. The remaining 25 subjects completed this investigation as outlined in the standard study protocol. The demographic data are shown in Table 1. No unexpected reactions were seen in any of the subjects during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample – Face Serum coded [redacted] – does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials	Age:	Gender:	Race:
01	[redacted]	28	M	C
02	[redacted]	22	M	C
03	[redacted]	24	F	A
04	[redacted]	33	F	B
05	[redacted]	20	M	C
06	[redacted]	31	F	C
07	[redacted]	23	M	C
08	[redacted]	19	M	C
09	[redacted]	22	M	C
10	[redacted]	22	F	A
11	[redacted]	30	F	C
12	[redacted]	20	M	C
13	[redacted]	52	F	C
14	[redacted]	21	F	C
15	[redacted]	22	M	B
16	[redacted]	19	M	C
17	[redacted]	19	F	C
18	[redacted]	26	F	A
19	[redacted]	22	F	A
20	[redacted]	50	M	B
21	[redacted]	22	F	A
22	[redacted]	20	M	C
23	[redacted]	21	M	C
24	[redacted]	21	M	B
25	[redacted]	20	M	C
26	[redacted]	23	F	A
27	[redacted]	26	F	B
28	[redacted]	21	M	A
29	[redacted]	22	M	C

C = Caucasian
A = Asian
B = Black

TABLE 2

RESULTS OF THE MAXIMIZATION SCHEDULED CHALLENGE

Sample: Face Serum coded [redacted] (tested as supplied)

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08*	-	-
09*	-	-
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19*	-	-
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26*	-	-
27	0	0
28	0	0
29	0	0

Challenge Evaluations:

48-Hour Evaluation: February 11, 2015
72-Hour Evaluation: February 12, 2015

*indicates subject dropped from study

[redacted]

RESEARCH AND DEVELOPMENT
CLINICAL EVALUATION DEPARTMENT

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT. 1

TO: [redacted]

PRODUCT PROFILE NO: [redacted]

DATE: 10/11/2014

LAB REF: [redacted]

1. TEST MATERIAL: [redacted] Smoothing Line Serum [redacted]

product contains 0.586% Glyceryl Acrylate/ Acrylic Acid Copolymer

2. CONTROL MATERIAL: [redacted] Vanishing Cream [redacted]

3. TEST PROCEDURE: Single Insult 24hr, Occlusive AllerEAZE Patch

4. CONCENTRATION: 100% Full strength.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS (n)*	*IRRITATION SCORE**									
		0	±	1	1+	2	2+	3	3+	4	PII
[redacted] Smoothing Line Serum [redacted]	23	20	0	0	0	0	0	0	0	0	0.00
[redacted] Vanishing Cream [redacted]	23	20	0	0	0	0	0	0	0	0	0.00

_____Skin staining noted. Erythematous response was read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material(s) and the Reference Control(s). _____

B. _____

Study Conducted By: [redacted] _____

Approved by: [redacted]

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) =minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2(Moderate) = Pink-red erythema visibly uniform in entire contact area.
3(Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. – Primary Irritation Index – a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

[redacted]

REPEATED INSULT PATCH STUDY

product contains 0.5 % Glyceryl Polyacrylate

[redacted] **STUDY NO.** [redacted]

CONDUCTED FOR:

[redacted]

DATE OF REISSUE:

November 7, 2014

[redacted]

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and [redacted] Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

[redacted]

[redacted]
Dermatologist
Principal Investigator

November 7, 2014
Date

[redacted]

[redacted], CCRP
Vice President, Clinical Operations

November 7, 2014
Date

[redacted]

Manager, Dermatologic Safety Testing

November 7, 2014
Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIAL

Gel, [redacted]

DATE STUDY INITIATED

August 11, 2014

DATE STUDY COMPLETED

September 26, 2014

DATE OF REISSUE

November 7, 2014

INVESTIGATIVE PERSONNEL

[redacted] - Dermatologist
Principal Investigator

[redacted], CCRP
Vice President, Clinical Operations

[redacted]
Manager, Dermatologic Safety Testing

CLINICAL SITE

[redacted]

SUMMARY

One product, [redacted], was evaluated as supplied to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. One hundred (100) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to product, [redacted].

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of [redacted] These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 100 completed subjects. In the absence of any sensitization reactions in this sample size (100 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 3.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 years of age or older, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. Patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2]

Following the 9th evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last Induction Visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading). Subjects who missed the 9th evaluation (N9G) but have had 9 patch applications were considered to have completed the Induction Phase.

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Following a negative Induction, a 48/72-hour sequence of "-/+," "?/+," or "+/+"

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

resulted in an additional reading being performed at the 96-hour interval. Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1[3]	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

1-6	Same as Week 2

WEEK 4

1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU induction patches
3	Staff graded MU induction sites at MU visit
2-7	Rest Period

WEEK 5

1-7	Rest Period

WEEK 6

1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

[3] Study flow starting with Week 1, Day 1, will be altered when enrollment occurs other than on Monday. Study flow could be altered when a holiday occurs during the study.

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

- = No reaction
? = Minimal or doubtful response, slightly different from surrounding normal skin
+ = Definite erythema, no edema
++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema
S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p = Papular response > 50%
pv = Papulovesicular response > 50%
D = Damage to epidermis: oozing, crusting and/or superficial erosions
I = Itching
X = Subject absent
PD = Patch dislodged
NA = Not applied
NP = Not patched (due to reaction achieved)
N9G = No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting [redacted] strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : Gel, [redacted]
Amount Applied : 0.2 mL

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by [redacted]. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for

a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm. Unless otherwise directed by the Sponsor, the study material was discarded upon completion of the study.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. [redacted] preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under

both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a [redacted] facility in a secured room accessible only to [redacted] employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of [redacted].

7.0 RESULTS AND DISCUSSION

One hundred twenty three (123) subjects between the ages of 19 and 73 were enrolled and 100 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition:

Number enrolled:		123
Number discontinued:		22
Lost to follow-up:	11	
Voluntary withdrawal:	10	
Adverse events:	1	
Patch not applied:		1
Number completed:		100

Source: Table 1, Appendix I

There was one non-product related adverse event (AE) reported during the study. Please see Data Listing 4, Appendix II for more details.

Subject No. 123 experienced definite erythema, definite edema (++) at the fifth induction evaluation. Due to the reaction achieved, the subject requested not to be patch with this product for the remainder of the study therefore, patching for this subject was discontinued for the remainder of the study. This is a deviation from the protocol-specified requirement of switching patch conditions to a new site under semi-occlusive conditions after experiencing a reaction greater than definite erythema, no edema (+) during the Induction Phase.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to product, [redacted].

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

Draize JH, Woodward G, Calvary HO. Methods for the study of irritation and toxicology of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 82: 377-390.

Lanman BM, Elvers WB, Howard CS. The role of human patch testing in a product development program. Joint Conf Cosmet Sci Toilet Goods Assoc 1968; 135-145.

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Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	123
Subjects completed induction phase	104 (84.6)
Subjects completed all phases	100 (81.3)
Total subjects discontinued	23 (18.6)
Lost to follow-up	11 (8.9)
Voluntary withdrawal	11 (8.9)
Adverse events	1 (0.8)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	47 (38.2)
N (%) 45 to 65	59 (48.0)
N (%) 66 and up	17 (13.8)
Mean (SD)	48.7 (13.9)
Median	48.7
Range	19.7 to 73.8
Gender	
N (%) Male	31 (25.2)
N (%) Female	92 (74.8)
Race	
Asian	2 (1.6)
Black	36 (29.3)
Caucasian	51 (41.5)
Hispanic	32 (26.0)
Other	2 (1.6)

See data listing 2 for further detail.

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Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = [redacted]

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	104	98	103	96	102	98	98	96	93	10	101	100	
?	5	4	4	2	4	4	2	3	4	0	0	0	
+	0	1	2	1	0	0	1	3	2	0	0	0	
++	0	0	0	0	0	1	0	0	0	0	0	0	
Total evaluable	109	103	109	99	106	103	101	102	99	10	101	100	
Number absent	6	12	4	11	1	3	4	2	4		0	0	
Number discontinued	8	8	10	13	16	17	18	19	20		22	23	
Patch not applied	0	0	0	0	0	0	0	0	0				

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=104)

Response	n(%) Subjects
-	90 (86.5%)
?	10 (9.6%)
+	3 (2.9%)
++	1 (1.0%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	08/11/14	08/11/14	--	08/29/14	I7	L	19
002	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
003	08/11/14	08/11/14	--	08/22/14	I4	S	12
004	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
005	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
006	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
007	08/11/14	08/11/14	--	08/15/14	I0	S	5
008	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
009	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
010	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
011	08/11/14	08/11/14	--	08/15/14	I0	L	5
012	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
013	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
014	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
015	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
016	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
017	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
018	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
019	08/11/14	08/11/14	--	08/15/14	I0	L	5
020	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
021	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
022	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
023	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
024	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
025	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
026	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
027	08/11/14	08/11/14	09/16/14	09/19/14	C	C	40
028	08/15/14	08/15/14	--	08/25/14	I3	L	11
029	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
030	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
031	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	08/15/14	08/15/14	--	08/22/14	I3	S	8
033	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
034	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
035	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
036	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
037	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
038	08/15/14	08/15/14	--	08/25/14	I2	L	11
039	08/15/14	08/15/14	--	09/03/14	I8	AE	20
040	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
041	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
042	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
043	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
044	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
045	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
046	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
047	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
048	08/15/14	08/15/14	--	08/20/14	I0	L	6
049	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
050	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
051	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
052	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
053	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
054	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
055	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
056	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
057	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
058	08/15/14	08/15/14	--	08/22/14	I2	S	8
059	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
060	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
061	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
062	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
064	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
065	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
066	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
067	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
068	08/15/14	08/15/14	--	08/27/14	I4	S	13
069	08/15/14	08/15/14	--	08/15/14	I0	S	1
070	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
071	08/15/14	08/15/14	--	08/18/14	I0	S	4
072	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
073	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
074	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
075	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
076	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
077	08/15/14	08/15/14	--	08/20/14	I0	S	6
078	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
079	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
080	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
081	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
082	08/15/14	08/15/14	--	09/02/14	I5	L	19
083	08/15/14	08/15/14	09/16/14	09/19/14	C1	L	36
084	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
085	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
086	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
087	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
088	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
089	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
090	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
091	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
092	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
093	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
095	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
096	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
097	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
098	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
099	08/15/14	08/15/14	--	08/20/14	I0	L	6
100	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
101	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
102	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
103	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
104	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
105	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
106	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
107	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
108	08/15/14	08/15/14	09/16/14	09/19/14	C	C	36
109	08/18/14	08/18/14	--	08/29/14	I4	L	12
110	08/18/14	08/18/14	09/23/14	09/26/14	C	C	40
111	08/18/14	08/18/14	09/23/14	09/26/14	C	C	40
112	08/18/14	08/18/14	09/23/14	09/26/14	C	C	40
113	08/18/14	08/18/14	09/23/14	09/26/14	C	C	40
114	08/18/14	08/18/14	--	09/23/14	I9	L	37
115	08/18/14	08/18/14	09/23/14	09/26/14	C	C	40
116	08/20/14	08/20/14	09/23/14	09/26/14	C	C	38
117	08/20/14	08/20/14	09/23/14	09/26/14	C	C	38
118	08/20/14	08/20/14	09/23/14	09/26/14	C	C	38
119	08/20/14	08/20/14	09/23/14	09/26/14	C	C	38
120	08/20/14	08/20/14	--	09/22/14	I9	S	34
121	08/20/14	08/20/14	09/23/14	09/26/14	C	C	38
122	08/20/14	08/20/14	--	08/27/14	I3	S	8
123	08/20/14	08/20/14	--	09/03/14	C	S	15

*Subject 123 Discontinued per the subjects request due to reactions achieved at Reading 7 on 9/3/14.
Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
001	33.4	Female	Hispanic
002	45.5	Female	Hispanic
003	48.5	Female	Black
004	47.5	Female	Hispanic
005	53.7	Female	Caucasian
006	63.8	Female	Black
007	36.5	Female	Black
008	59.8	Female	Caucasian
009	56.7	Male	Black
010	72.8	Male	Caucasian
011	38.1	Male	Black
012	73.8	Male	Caucasian
013	37.9	Female	BLACK/WHITE
014	56.1	Male	Caucasian
015	57.9	Female	Hispanic
016	35.2	Female	Caucasian
017	28.9	Male	Hispanic
018	39.8	Female	Black
019	58.8	Female	Caucasian
020	69.7	Male	Black
021	71.4	Female	Caucasian
022	54.1	Female	Caucasian
023	54.4	Female	Caucasian
024	25.5	Female	Hispanic
025	34.6	Female	Hispanic
026	38.6	Male	Hispanic
027	62.8	Female	Asian
028	28.1	Female	Caucasian
029	62.8	Female	Caucasian
030	52.5	Female	Black
031	55.4	Female	Caucasian
032	51.8	Female	Caucasian
033	57.2	Female	Caucasian
034	44.6	Female	Hispanic
035	58.7	Male	Caucasian
036	66.5	Male	Caucasian
037	50.3	Female	Caucasian

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
038	57.6	Male	Black
039	47.3	Female	Caucasian
040	58.3	Female	Caucasian
041	61.9	Male	Caucasian
042	39.8	Female	Hispanic
043	50.2	Female	Caucasian
044	67.3	Female	Caucasian
045	59.8	Female	Caucasian
046	56.4	Female	Caucasian
047	67.6	Female	Caucasian
048	43.6	Male	Hispanic
049	58.8	Female	Caucasian
050	70.1	Female	Hispanic
051	42.5	Male	Hispanic
052	43.8	Female	Hispanic
053	47.8	Male	Caucasian
054	22.2	Male	Black
055	54.7	Male	Black
056	36.7	Female	Caucasian
057	28.8	Female	Black
058	41.0	Female	Caucasian
059	42.8	Female	Hispanic
060	46.3	Female	Caucasian
061	25.9	Female	Black
062	48.5	Female	Black
063	48.7	Female	Black
064	40.7	Female	Caucasian
065	45.2	Male	Hispanic
066	50.4	Female	Caucasian
067	49.9	Female	Caucasian
068	45.1	Female	Black
069	59.8	Female	Caucasian
070	57.6	Male	Black
071	34.3	Female	Caucasian
072	59.8	Female	Caucasian
073	42.3	Female	Black
074	44.0	Female	Caucasian

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[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
075	30.0	Female	Black
076	43.5	Female	Hispanic
077	35.9	Female	Black
078	51.6	Female	Hispanic
079	26.7	Male	Caucasian
080	65.7	Female	Caucasian
081	47.0	Female	Hispanic
082	37.2	Female	Black
083	32.1	Female	Hispanic
084	44.6	Female	Caucasian
085	41.0	Female	Black
086	54.3	Female	Caucasian
087	48.0	Male	Black
088	20.3	Male	Hispanic
089	64.9	Female	Caucasian
090	33.6	Female	Hispanic
091	33.3	Male	Black
092	27.9	Female	Hispanic
093	60.3	Female	Hispanic
094	22.9	Female	Black
095	66.4	Female	Black
096	36.7	Female	Hispanic
097	60.0	Female	Caucasian
098	69.3	Female	Caucasian
099	28.6	Female	Black
100	46.8	Female	Caucasian
101	26.6	Female	Black
102	28.1	Female	Hispanic
103	28.5	Male	Hispanic
104	50.0	Female	Asian
105	27.0	Female	HISPANIC/WHITE
106	48.4	Male	Black
107	59.3	Male	Black
108	53.0	Female	Hispanic
109	70.0	Female	Black
110	66.7	Male	Black
111	51.1	Female	Hispanic
112	19.7	Male	Hispanic
113	65.5	Female	Black
114	64.3	Female	Black
115	45.3	Female	Black
116	67.3	Female	Caucasian
117	67.6	Male	Caucasian
118	71.5	Female	Hispanic
119	50.3	Male	Black
120	29.5	Female	Caucasian
121	71.1	Male	Caucasian
122	56.4	Female	Caucasian
123	67.6	Female	Hispanic

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	X	-	-	X	X		X	X	
002	-	-	X	-	-	-	-	-	-	-	-	-	
003	-	-	X	-	X	X	X	X	X		X	X	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	X	-	-	-	-	-	-	-	-	
006	-	X	-	-	-	-	-	-	-	-	-	-	
007	X	X	X	X	X	X	X	X	X		X	X	
008	?	?	-	-	-	-	-	-	-		-	-	
009	-	-	-	-	-	-	-	-	-		-	-	
010	-	-	-	-	-	-	-	-	-		-	-	
011	X	X	X	X	X	X	X	X	X		X	X	
012	-	-	-	-	-	-	-	-	-		-	-	
013	-	-	-	-	-	-	-	-	-		-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	N9G		-	-	
016	-	-	-	-	-	-	-	-	-		-	-	
017	-	-	-	-	-	-	-	-	-		-	-	
018	-	-	-	-	-	-	X	-	-	-	-	-	
019	X	X	X	X	X	X	X	X	X		X	X	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	X	-	-	-	-	-	-	-	N9G	-	-	
022	-	-	-	X	-	-	-	-	-	-	-	-	
023	?	?	?	+	?	?	?	+	+		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required
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[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	-	X	-	-	-	-	-	-	-	-	-	
027	-	-	X	-	-	-	-	-	-	-	-	-	
028	-	X	-	X	X	X	X	X	X		X	X	
029	-	-	-	-	-	-	X	-	-	N9G	-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	?	+	+	X	X	X	X	X	X		X	X	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	X	-	-	-	-	-	-	-	N9G	-	-	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	X	X	X	X	X	X	X		X	X	
039	-	-	-	-	-	-	-	-	X		X	X	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	X	-	-	-	N9G	-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 10/01/14:14:58 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	-	?	+	+	?		-	-	
048	X	X	X	X	X	X	X	X	X		X	X	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	-	-	-	-	-	?	-		-	-	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	-	-	-	-	-	-	-	-	-		-	-	
056	-	-	-	X	-	-	-	-	-	N9G	-	-	
057	-	-	-	X	-	-	-	-	N9G		-	-	
058	-	-	X	X	X	X	X	X	X		X	X	
059	X	-	-	-	-	-	-	-	-	N9G	-	-	
060	-	X	-	-	-	-	-	-	-	N9G	-	-	
061	X	-	-	-	-	-	-	-	-	N9G	-	-	
062	-	-	-	-	-	X	-	-	-	N9G	-	-	
063	-	-	-	-	-	-	-	-	-		-	-	
064	-	-	-	X	-	-	-	-	-	N9G	-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	X	-	-	-	-	-	N9G	-	-	
067	-	-	-	-	-	-	-	-	-		-	-	
068	-	-	-	-	X	X	X	X	X		X	X	
069	X	X	X	X	X	X	X	X	X		X	X	

(*) When required
Generated on 10/01/14:14:58 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	-	-	-	-	-	-		-	-	
071	X	X	X	X	X	X	X	X	X		X	X	
072	-	-	?	?	-	-	X	-	-	N9G	-	-	
073	-	-	-	-	-	-	-	X	-	N9G	-	-	
074	?	?	+	X	?	?	?	+	+	N9G	-	-	
075	-	-	-	-	-	-	-	-	-		-	-	
076	-	-	-	-	-	-	-	-	-		-	-	
077	X	X	X	X	X	X	X	X	X		X	X	
078	X	-	-	-	-	-	-	-	-	N9G	-	-	
079	-	-	-	-	-	-	-	-	N9G		-	-	
080	-	-	-	-	-	-	-	-	-		-	-	
081	-	-	-	-	-	-	-	-	-		-	-	
082	-	-	-	-	-	X	X	X	X		X	X	
083	-	-	-	X	-	-	-	-	-	N9G	-	X	
084	-	-	-	-	-	-	-	-	-		-	-	
085	-	-	-	-	-	-	-	-	-		-	-	
086	-	-	-	-	-	-	-	-	-		-	-	
087	-	-	-	-	-	-	-	-	-		-	-	
088	-	-	-	X	-	-	-	-	-	N9G	-	-	
089	-	-	-	-	-	-	-	-	-		-	-	
090	-	-	-	-	-	-	-	?	-		-	-	
091	-	-	-	-	-	-	-	-	-		-	-	
092	-	-	-	-	-	-	-	-	?		-	-	

(*) When required
Generated on 10/01/14:14:58 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	-	-		-	-	
094	-	-	-	-	-	-	-	-	-		-	-	
095	-	?	?	-	?	?	-	-	-		-	-	
096	-	-	-	-	-	-	-	-	-		-	-	
097	-	-	-	-	-	-	-	-	-		-	-	
098	X	-	-	-	-	-	-	-	?	N9G	-	-	
099	X	X	X	X	X	X	X	X	X		X	X	
100	-	-	-	-	-	-	X	-	-	N9G	-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	-	-	-	-	-		-	-	
103	X	-	-	-	-	-	-	-	-	N9G	-	-	
104	-	-	-	X	-	-	-	-	-	N9G	-	-	
105	?	X	-	-	-	-	-	-	-	N9G	-	-	
106	-	X	-	-	-	-	-	-	-	N9G	-	-	
107	-	X	-	-	-	-	-	-	?	N9G	-	-	
108	-	X	-	-	-	-	-	-	-	N9G	-	-	
109	-	X	-	-	X	X	X	X	X		X	X	
110	-	-	-	-	-	-	-	-	N9G		-	-	
111	X	-	-	-	-	-	-	?	-	-	-	-	
112	-	-	-	X	-	-	-	-	-	-	-	-	
113	-	X	-	-	-	-	-	-	-	N9G	-	-	
114	-	-	-	-	-	-	-	-	-		X	X	
115	-	-	-	-	-	-	-	X	-	-	-	-	
116	-	-	-	-	-	-	-	-	-		-	-	
117	-	-	-	-	-	-	-	-	-		-	-	
118	-	-	-	-	-	-	-	-	-		-	-	
119	-	-	-	-	-	-	-	-	-		-	-	
120	-	-	-	-	-	-	-	-	-		X	X	
121	-	-	-	-	-	X	-	-	-	N9G	-	-	
122	-	-	-	X	X	X	X	X	X		X	X	
123	-	X	?	?	?	++	NP	NP	NP	NP	NP	NP	

(*) When required
Generated on 10/01/14:14:58 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 4: Adverse Events

Subject No. 039

Adverse Event: ECZEMATOUS DERMATITIS - THIGHS, LEGS ABDOMEN, BACK	Date of Onset: 08/27/14	Date of Resolution: 09/09/14
Severity: Moderate		Outcome: Recovered
Relation to Study Product: Not Related	Duration: N/A	Action Taken/Study Product: Discontinued
Serious? NO		Action Taken/Treatment?: YES

Comment: CALLED FOR 1ST TIME TODAY TO SEE SUBJECT THAT DEVELOPED RASH ON HER ANT THIGHS ON 8/27/14, HAS SPREAD TO POST THIGHS, POPLITEAL FOSSA, ANTECUBITAL FOSSA, ABDOMEN & TO HER BACK LAST NIGHT. TREATED TWICE WITH 1% HYDROCORTISONE CREAM. THINKS MIGHT HAVE POISON IVY. SUBJECT DISCONTINUED FROM THE STUDY ADVISED TO SEE HER PRIMARY CARE DOCTOR
FOR TREATMENT. TEMP 98.2. 9/9/14 SUBJECT WAS SEEN AND RASH RESOLVED.

Generated on 10/01/14:14:58 by AE.SAS / Uses: AE, COMMENTS

2022 VCRP data - Glyceryl Acrylates

Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer – 0 uses

Glyceryl Acrylate/Acrylic Acid Copolymer	01B	Baby Lotions, Oils, Powders, and Creams	1	**295**
Glyceryl Acrylate/Acrylic Acid Copolymer	03A	Eyebrow Pencil	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	03D	Eye Lotion	16	
Glyceryl Acrylate/Acrylic Acid Copolymer	03G	Other Eye Makeup Preparations	7	
Glyceryl Acrylate/Acrylic Acid Copolymer	05G	Tonics, Dressings, and Other Hair Grooming Aids	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	07C	Foundations	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	07E	Lipstick	12	
Glyceryl Acrylate/Acrylic Acid Copolymer	07F	Makeup Bases	2	
Glyceryl Acrylate/Acrylic Acid Copolymer	07I	Other Makeup Preparations	3	
Glyceryl Acrylate/Acrylic Acid Copolymer	08E	Nail Polish and Enamel	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	08G	Other Manicuring Preparations	3	
Glyceryl Acrylate/Acrylic Acid Copolymer	10E	Other Personal Cleanliness Products	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	11A	Aftershave Lotion	4	
Glyceryl Acrylate/Acrylic Acid Copolymer	11E	Shaving Cream	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	11G	Other Shaving Preparation Products	2	
Glyceryl Acrylate/Acrylic Acid Copolymer	12A	Cleansing	2	
Glyceryl Acrylate/Acrylic Acid Copolymer	12C	Face and Neck (exc shave)	117	
Glyceyl Acrylate/Acrylic Acid Copolymer	12C	Face and Neck (exc shave)	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	12D	Body and Hand (exc shave)	13	
Glyceryl Acrylate/Acrylic Acid Copolymer	12F	Moisturizing	81	
Glyceryl Acrylate/Acrylic Acid Copolymer	12G	Night	4	
Glyceryl Acrylate/Acrylic Acid Copolymer	12H	Paste Masks (mud packs)	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	12I	Skin Fresheners	1	
Glyceryl Acrylate/Acrylic Acid Copolymer	12J	Other Skin Care Preps	18	
Glyceryl Acrylate/Acrylic Acid Copolymer	13A	Suntan Gels, Creams, and Liquids	1	

Glyceryl Polyacrylate	03D	Eye Lotion	9	**119**
Glyceryl Polyacrylate	03G	Other Eye Makeup Preparations	6	
Glyceryl Polyacrylate	05I	Other Hair Preparations	1	
Glyceryl Polyacrylate	10E	Other Personal Cleanliness Products	1	
Glyceryl Polyacrylate	11A	Aftershave Lotion	1	
Glyceryl Polyacrylate	11G	Other Shaving Preparation Products	5	
Glyceryl Polyacrylate	12A	Cleansing	2	
Glyceryl Polyacrylate	12C	Face and Neck (exc shave)	17	
Glyceryl Polyacrylate	12D	Body and Hand (exc shave)	2	
Glyceryl Polyacrylate	12F	Moisturizing	43	
Glyceryl Polyacrylate	12G	Night	2	
Glyceryl Polyacrylate	12H	Paste Masks (mud packs)	1	
Glyceryl Polyacrylate	12J	Other Skin Care Preps	27	
Glyceryl Polyacrylate	13A	Suntan Gels, Creams, and Liquids	2	

Glyceryl Polymethacrylate	03D	Eye Lotion	5	**142**
Glyceryl Polymethacrylate	03G	Other Eye Makeup Preparations	4	
Glyceryl Polymethacrylate	07A	Blushers (all types)	1	
Glyceryl Polymethacrylate	07B	Face Powders	1	
Glyceryl Polymethacrylate	07C	Foundations	2	
Glyceryl Polymethacrylate	07F	Makeup Bases	1	
Glyceryl Polymethacrylate	07I	Other Makeup Preparations	6	
Glyceryl Polymethacrylate	10E	Other Personal Cleanliness Products	1	
Glyceryl Polymethacrylate	12A	Cleansing	3	
Glyceryl Polymethacrylate	12C	Face and Neck (exc shave)	42	
Glyceryl Polymethacrylate	12D	Body and Hand (exc shave)	7	
Glyceryl Polymethacrylate	12F	Moisturizing	44	
Glyceryl Polymethacrylate	12G	Night	6	
Glyceryl Polymethacrylate	12I	Skin Fresheners	3	
Glyceryl Polymethacrylate	12J	Other Skin Care Preps	15	
Glyceryl Polymethacrylate	13C	Other Suntan Preparations	1	