Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	November 10, 2021
Panel Meeting Date:	December 6-7, 2021

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.; Lisa, A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst/Writer.

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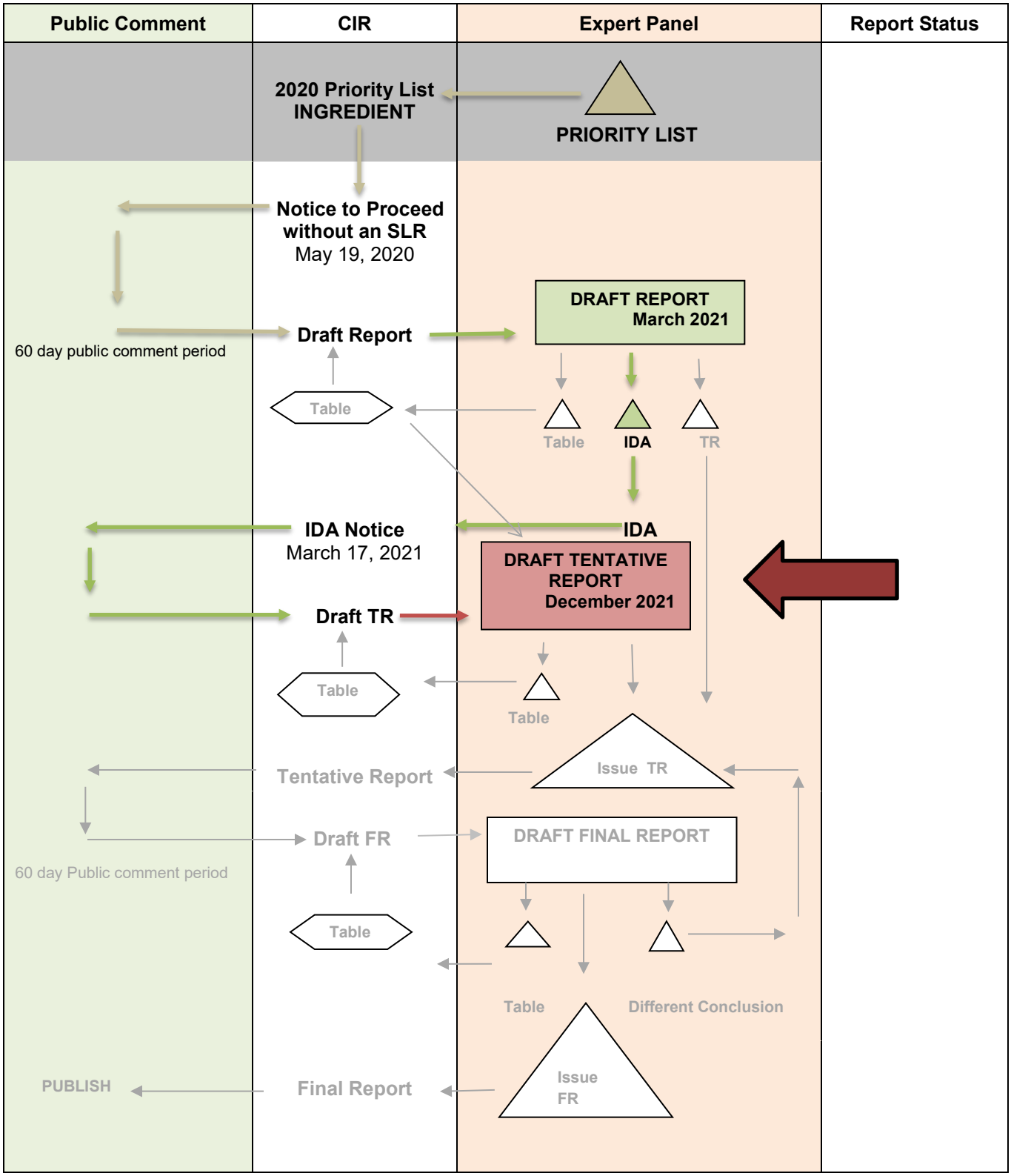
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Acryloyloxyethyl Phosphorylcholine Polymers

MEETING December 2021



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst/Writer, CIR

Date: November 10, 2021

Subject: Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics

Enclosed is a draft Tentative Report of the Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics (*report_AcryloyloxyethylPhosphorylcholinePolymers_122021*).

At the March 2021 Panel meeting, an insufficient data announcement (IDA) with the following data requests was issued:

- Composition/impurities data on all ingredients
- Molecular weight data (e.g., average, distribution) on all ingredients
- Skin sensitization data on Polyquaternium-51 at the maximum use concentration
- Structures for Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer and Polyquaternium-10/ Phosphorylcholine Glycol Acrylate Copolymer

The following data (highlighted in the report and enclosed) were received from the Council in response to the IDA:

(1) Method of manufacture and impurities data on Phosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61 (NOF Corporation, 2021) (*data1_AcryloyloxyethylPhosphorylcholinePolymers_122021*)

(2) Molecular weight averages and distribution data on Phosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61 (NOF Corporation, 2021) (*data1_AcryloyloxyethylPhosphorylcholinePolymers_122021*)

(3) Negative guinea pig maximization test on Polyquatermium-51 (challenge concentrations up to 100%) (Hatano Research Institute, 2003) (*data1_AcryloyloxyethylPhosphorylcholinePolymers_122021*)

(4) Negative guinea pig adjuvant and patch test on Polyquaternium-61 (challenge concentration of 25%) (Consumer Product Testing Company, 2005) (*data1_AcryloyloxyethylPhosphorylcholinePolymers_122021*)

(5) Negative human repeated insult patch test on an undiluted serum containing 0.12% Polyquaternium-51 (Anonymous, 2012) (*data2_AcryloyloxyethylPhosphorylcholinePolymers_122021*)

The structures for Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer and Polyquaternium-10/ Phosphorylcholine Glycol Acrylate Copolymer were not provided.

In consideration of the data received, a draft discussion (highlighted in text) has been developed for the Panel's review.

Also included in this package for your review are the:

- report history (*history_AcryloyloxyethylPhosphorylcholinePolymers_122021*),
- flow chart (*flowchart_AcryloyloxyethylPhosphorylcholinePolymers_122021*),
- literature search strategy (*search_AcryloyloxyethylPhosphorylcholinePolymers_122021*),
- ingredient data profile (*dataprofile_AcryloyloxyethylPhosphorylcholinePolymers_122021*),
- 2021 FDA VCRP data (*VCRP_AcryloyloxyethylPhosphorylcholinePolymers_122021*).
- transcripts from the March 2021 Panel meeting (*transcripts_ AcryloyloxyethylPhosphorylcholinePolymers_122021)*

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data remain insufficient, the Panel should issue a Tentative Report with an insufficient data conclusion, specifying the data needs in the report Discussion.

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CIR History of:

Acryloyloxyethyl Phosphorylcholine Polymers

A Scientific Literature Review (SLR) Notice to Proceed (NTP) on Polyquaternium-6 was issued on May 19, 2020.

Draft Report, Teams/Panel: March 11-12, 2021

The draft report also contains 2020 use concentration data and in vitro skin and ocular irritation data that were received from the Council. Report comments, from the Council, were received prior to the Panel meeting.

An insufficient data announcement (IDA) with the following data requests was issued:

- Composition/impurities data on all ingredients
- Molecular weight data (e.g., average, distribution) on all ingredients
- Skin sensitization data on Polyquaternium-51 at the maximum use concentration
- Structures for Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer and Polyquaternium10/Phosphorylcholine Glycol Acrylate Copolymer

Draft Tentative Report, Teams/Panel: December 6-7, 2021

The following data (included in the report) were received from the Council in response to the IDA:

(1) Method of manufacture and impurities data on Phosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61

(2) Weight average molecular weight data on Phosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61

(3) Negative guinea pig maximization test on Polyquatermium-51 (challenge concentrations up to 100%) (Hatano Research Institute, 2003)(*acrylo122021data 2)*

(4) Negative guinea pig adjuvant and patch test on Polyquaternium-61 (challenge concentration of 25%) (Consumer Product Testing Company, 2005) (*acrylo122021data 2)*

(5) Negative human repeated insult patch test on an undiluted serum containing 0.12% Polyquaternium-51 (Anonymous, 2012)(*acrylo122021data 3)*

However, the structures for Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer and Polyquaternium10/Phosphorylcholine Glycol Acrylate Copolymer were not provided.

Acryloyloxyethyl Phosphorylcholine Polymers Data Profile* – December 6-7, 2021 – Wilbur Johnson, Jr.																														
						Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents	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	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer			X																											
C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer			X																											
Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer			X																											
Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer			X																											
Polyphosphorylcholine Glycol Acrylate	12		X	X	X																									
Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer			X																											
Polyquaternium-51	275		X	X	X															X		X		X	X		X			
Polyquaternium-61	2		X	X	X				X							X				X		X		X				X		

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

[Acryloyloxyethyl Phosphorylcholine Polymers – 4/3/20; 1/11/21; 10/19/21]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Polyquaternium-51	125275-25-4	Yes		41/11		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Polyquaternium-61		Yes		0/		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Polyphosphorylcholine Glycol Acrylate	67881-99-6	Yes		0/		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer		Yes		0/		No	No	No	No	No	No	No	No	No	No	No	No	Yes
C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer		Yes		0/		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Hydroxyethylcellulose/Phosphorylcho-line Glycol Acrylate Copolymer		Yes		0/		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer		Yes		0/		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer		Yes		0/		No	No	No	No	No	No	No	No	No	No	No	No	Yes

Search Strategy

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

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

LINKS

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

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS, 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);
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (drugs@FDA)
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/

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

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/

MARCH 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – March 11, 2021

DR. BELSITO: Okay, is everyone back?

DR. KLAASSEN: I'm here.

DR. LIEBLER: Hi, this is Dan, I'm back.

DR. SNYDER: Yup, I'm here.

DR. KLAASSEN: We're all here.

DR. BELSITO: Okay, great. So, we're going to the Phosphorylcholine Polymers, and, this is the first time we're looking at these eight acryloyloxyethyl phosphorylcholine polymers. So, I guess we got a lot of data, and we should just look at it rather than my reading this whole big long list.

So one of the things we always ask for is method of manufacture, and on PDF Page 9, we've got some information. And, my question to you all is do you feel that this is sufficient, or do we need more?

DR. LIEBLER: Yeah, this is Dan. I think that this is probably sufficient. I mean, it's a little sketchy, the chemical properties were sketchy but we can tell that all of these are very large molecules, polymers. The way that they're produce indicates they're polymers. The way that they're purified -- I've highlighted a couple things in the method of manufacture indicating that these are, you know, polymers, large molecules.

The only other thing I think we could ask for, perhaps -- I don't need to insist on this -- but whether or not we need to ask for like residual monomer, under impurities. But other than that, I think the descriptive information we have is satisfactory to proceed.

DR. BELSITO: Okay. And then, the next question is, despite not knowing whether these manufacturing practices are for cosmetic grade, do we have any concerns about residual reagents -- impurities?

DR. LIEBLER: Yeah, that's the only thing -- I think some of these are, you know, methacrylates. I'm not really concerned because the description of the preparation includes essentially dialysis or rinsing of precipitated polymer that would remove residual monomers pretty easily.

So, I mean, if the other team wanted a residual monomer, I certainly wouldn't object. But I'm not going to insist myself. How would that sound?

DR. BELSITO: Okay. So, we could put in the discussion that the dialysis washing would remove residual monomers?

DR. LIEBLER: Right.

DR. BELSITO: We'll see how the other team responds to that.

DR. LIEBLER: Right. I mean, the acrylate and methacrylate monomers are actually quite volatile also. So, they would be, you know, they would be lost on store- -- these are all powders. And, so, again, that's another reason for my lack of concern about residual monomer. But if they want to see if they can get a specification, that's often available, then we can ask for it.

DR. BELSITO: Okay. And then on the toxicokinetic studies, the dermal penetration, is that adequate to show that it's not absorbed, so we don't need systemic tox endpoints? This is PDF Page 11.

DR. LIEBLER: Right.

DR. KLAASSEN: I mean, there's very little data there, but, you know, with the 30,000 molecular weight and (inaudible), et cetera, you know, absorption, basically can't occur.

DR. LIEBLER: I mean, I thought it was actually a nifty study, you know, the dye labeling approach. And, you see exactly what you'd expect to see, which is the dye is found just on the skin surface.

DR. SNYDER: So the other question, Dan, I had is that in these reports have we always, well, put the subheading, here Polyquaternium-51? It's actually a read-across molecule, it's actually not Polyquaternium-51; it's a read-across molecule. And, so, haven't we -- I thought we always put the actual chemical up above and then we can -- we say someplace where we're using that as a read-across. Because this -- the same thing with the one tox study we have, it's under Polyquaternium-51, but it's not really that, it's the read-across molecule, the methacrylate.

DR. LIEBLER: So, Paul, I was a little confused because the Polyquaternium-51 is in the list, in the introduction, of the ingredients we're reviewing.

DR. SNYDER: Yes.

DR. HELDRETH: So, in the past we have commonly used the actual ingredient name for the heading, and then explained in the summary paragraph that it was a read-across source for that ingredient. We can change that, but that's what we've done most often with these. And, Polyquaternium-51, and this read-across source differ by one methacrolein in each repeat unit.

So, propyl, in the case of Polyquaternium-51, versus butyl, in this read-across source. And that's mentioned in the intro, PDF Page 9, right before you jump into the chemistry section, that's explained there.

DR. LIEBLER: Okay.

DR. KLAASSEN: Yeah.

DR. SNYDER: I just had a query today, and is this okay? I mean, because it's not --

DR. BELSITO: Yes.

DR. LIEBLER: I think, listing it as Polyquaternium-51, and then having in the text that actually it was this poly methacryloyloxyethyl, blah, blah, as a read-across analogue of Polyquaternium-51. I don't think that's the right way to do it. I would say -- I would put the name of the read-across molecule, the heading, and then parentheses read-across analogue. As opposed to source, read-across analogue for Polyquaternium-51. Is that okay with you, Paul?

DR. SNYDER: Yeah, that's why I just -- I thought that was different then the way we've done it before. Because at first I thought, oh we got Polyquaternium-51 data, but no, it's read-across data, so.

DR. LIEBLER: Yeah.

DR. SNYDER: Okay.

DR. LIEBLER: But I think it's a good read-across.

DR. SNYDER: Yeah.

DR. BELSITO: So where are we putting that?

DR. LIEBLER: Where it is under Dermal Penetration, PDF Page 11.

DR. HELDRETH: So any subheading where it said Polyquaternium-51, but we were actually describing data on the read-across source, we'll change that subheading as Dr. Liebler mentioned.

DR. LIEBLER: Is that clear, Don?

DR. BELSITO: Yeah, so the subheading should be poly --

DR. LIEBLER: The name of the chemical.

DR. BELSITO: Right, the actual name of the chemical. And do you want it to say, read-across for Polyquaternium-51, or not?

DR. LIEBLER: Yes. Yes.

DR. BELSITO: In the subtitle, or in the text?

DR. LIEBLER: In the subtitle, where it has italicized Polyquaternium-51, underlined.

DR. BELSITO: Right.

DR. LIEBLER: At the front of that put the name of the chemical, and then parenthesis read-across analogue for Polyquaternium-51 close parenthesis.

DR. BELSITO: Okay, so, as it is already in the sentence below.

DR. LIEBLER: Right.

DR. BELSITO: There's a five percent fluorescent...

DR. LIEBLER: Yes.

DR. BELSITO: So you want it twice.

DR. LIEBLER: Yeah, in the subheading, so that it's clear that these are data on a read-across analog of Polyquaternium-51, not on Polyquaternium-51 itself.

DR. SNYDER: I think what Don is saying is you could delete that second parentheses there, as a read-across source since you're already putting that up in the heading, right?

DR. BELSITO: Yeah, that's what I'm wondering. Do you want it both in the heading and in the text?

DR. LIEBLER: Oh, I see. Gosh, you know, either is fine with me; I don't really care. You could delete it.

DR. BELSITO: So, this just, we're going to put the name of the chemical up and then we'll get rid of that parenthesis as a read-across source for Polyquaternium-51. Okay?

DR. LIEBLER: Just in the text.

DR. BELSITO: Right. Okay, good. Okay, so, we have no genotox studies, is this going to be problematic? Because even though it's not absorbed, I mean, it presumably could cause issues with skin, or not? It's just going to sit on the stratum corneum, so we're not concerned?

DR. LIEBLER: Right.

DR. KLAASSEN: Correct.

DR. LIEBLER: I mean there are no structure alerts for genotox. And, it's too big; it's not going to penetrate the stratum corneum.

DR. KLAASSEN: Yeah, we actually have nothing for DART, and we have nothing for mutagen, and nothing for carcinogenicity.

DR. BELSITO: Right.

DR. KLAASSEN: But I don't think any of those are a concern because it's not going to be absorbed.

DR. SNYDER: Or even when they bypass absorption and did an intraperitoneal, up to 200 mg there was nothing.

DR. BELSITO: Right.

DR. LIEBLER: Right.

DR. BELSITO: But, I mean, we could also put that in -- do we put that in the toxicokinetic studies with dermal penetration? Or do we say that -- do we leave that for later? Because I had sort of added, in the dermal penetration, is that these data indicate that the material is of large molecular weight and would not be absorbed; therefore, mitigating the need for systemic endpoints.

DR. SNYDER: I think it goes where we just discussed, Don, in the previous report where we say in the discussion that the panel considered the data to be adequate for determining safety. The panel noted an absence of -- and then put our justification just like we did in the other ones. That we don't (audio skip).

DR. BELSITO: So, don't put it under dermal penetration?

DR. SNYDER: No, don't.

DR. BELSITO: And don't say anything other than we don't have DART data and all that, and then put that sentence, the large molecular weight, not absorbed, mitigates need for systemic endpoints, at the end.

DR. SNYDER: Right. Correct.

DR. KLAASSEN: Yes, at the end.

DR. SNYDER: Well, and we have an IP study where there was nothing, so it's -- yeah. So, it's okay.

DR. BELSITO: That would go in the discussion.

DR. SNYDER: Yes.

DR. LIEBLER: When we have ingredients that are like food, for example, and we state that, you know, because these are widely consumed as foods that mitigate concerns about systemic toxicity. Don't we usually put that in the introduction somewhere?

DR. HELDRETH: Yes.

DR. LIEBLER: Because then I'm thinking we could use the same approach here. Is that these are large molecular weight molecules, you know, that apparently would not be absorbed, and this mitigated concerns about systemic toxicity. I don't know how you feel about putting that further up front and not just putting it in the, you know, in the dermal absorption, dermal penetration, toxicokinetic section.

Otherwise, just remain silent about the, you know, high molecular weight affecting absorption. You'd basically say, no sub-chronic, no chronic, no DART, no genotox, no carcinogenicity, and then you get to the discussion and you explain why that's not of a concern.

DR. BELSITO: Yeah, I think that's the way we've normally done, no?

DR. LIEBLER: I'm okay with that, I just --

DR. SNYDER: Yeah, I think it's -- we can't really do it that way -- or the way you propose -- because we haven't presented the data yet.

DR. LIEBLER: Right, okay, that's fine. That's fine. So, right up front in the discussion then, I think that's a key point to raise that mostly governs our approach to the entire report.

MR. JOHNSON: Dr. Belsito?

DR. BELSITO: Yes.

MR. JOHNSON: Yes, I'd like to call the panel's attention to the cosmetic use section on PDF Page 10. And this change relates to the highest maximum use concentration. The Acrylic Acid, Phosphorylcholine Glycol Acrylate Crosspolymer has the highest use concentration of 0.18 percent. And, the product type is a foundation. So the text will be revised to indicate that highest maximum use concentration.

DR. BELSITO: Okay, Wilbur, I'm sorry. I was trying to add something here to the discussion. So what page you're on again, I'm sorry.

MR. JOHNSON: PDF Page 10.

DR. SNYDER: Don, we got new data, use data that bumped it up from .14 to .18, based upon a foundation.

DR. LIEBLER: Second paragraph.

DR. BELSITO: Um-hmm.

DR. SNYDER: And we have sensitization data at .08125 with only 25 subjects. So my question to you on Wave 2, was that adequate for sensitization, 25 at .08125 percent?

DR. BELSITO: Okay, Paul, where are you there?

DR. SNYDER: On Wave 2, Page 34 to 46. We got a HRIPT of Polyquaternium-51 at .08125 percent with 25 subjects that was negative, but we have the highest concentration used is .18.

DR. BELSITO: Yeah, I mean, I think if you have something that's not going to penetrate the stratum corneum, then you're really not concerned about irritation or sensitization.

DR. SNYDER: Okay.

DR. BELSITO: Right?

DR. KLAASSEN: Makes sense.

DR. BELSITO: So, I mean, we can mention that -- where are you, Paul, on the PDF, because I'm just seeing under dermal irritation and sensitization, Polyquaternium-51?

DR. LIEBLER: It was the Wave 2, Don, the Wave 2.

DR. BELSITO: Oh, Wave 2, okay.

DR. SNYDER: Wave 2, Page 34.

DR. BELSITO: Yeah, for some reason I didn't mark -- yeah, Wave 2. I see it. So, .0 -- yeah, I did have a comment, .08125, Polyquaternium-51, human max, highest leave-on .18.

Yeah, I mean, I was not concerned about that because, again, it's not going to be absorbed. So, it's not going to get to the epidermal antigen-presenting cells. It's not going to get to the keratinocytes to cause irritation. It's just going to sit on the stratum corneum. And, we also have irritation at 1.4 Polyquaternium-51, as well, so we really need to just focus on the lack of concern about sensitization given the molecular weight.

I mean, I almost don't know if it needs to be a point of discuss. We could put it in the discussion as well. The panel noted that the sensitization data was at a lower concentration than maximum use data. This data was negative, and as well, given the large molecular size it wouldn't penetrate the stratum corneum, and therefore, would not induce an (inaudible) type of sensitivity reaction -- or something like that.

DR. SNYDER: And also supported by the 1.4 percent nonirritating, so. Okay.

DR. BELSITO: Okay. Yeah, so, the next question that I had, under the dermal irritation and sensitization, that in vitro study? There are -- you know, it's not been accepted by authorities, this Irrectection assay. There are no OECD guidelines for it, so do we usually put in studies like that where it have not been scientifically -- or have not been accepted by scientific authorities?

DR. KLAASSEN: Oh, I think we have.

DR. SNYDER: Correct.

DR. KLAASSEN: We, you know, we might want to make a -- might make a statement after if it's necessary, but --

DR. BELSITO: No, I'm not -- I don't even know that we need to make a statement. I mean, I just, you know, my only question was, you know, because it hasn't been accepted by ICCVAM and there are no OECD guidelines, should we use that data. And, I guess what I'm hearing, Curt, is you say, yeah, we probably have before so you're not concerned.

DR. KLAASSEN: Yeah, I'm fine. I'm not concerned unless, well, you know, it's making a major determination in our conclusion.

DR. BELSITO: Well, we brought in the fact that 1.4 percent wasn't irritating, and it's based on this study.

DR. LIEBLER: But I agree with Curt that if we -- we typically have cited kind of a more experimental, not highly validated, test systems in our data if it's the only data that we have to make -- draw a crucial conclusion, then I'm reluctant to lean on that. But in this case, you know, the lack of penetration to the stratum corneum kind of makes all these endpoints, you know, of little concern.

So, I don't -- but, I'm going to defer to you and Paul -- Don and Paul on that as to whether or not you're, you know, unwilling to cite those data. I think if we have them available, we should mention that and then in the discussion we can, you know, perhaps, comment on the fact that this assay isn't highly validated. We considered it along with the fact that these molecules will not penetrate the stratum corneum. Are you comfortable with something like that?

DR. BELSITO: Sure.

DR. SNYDER: Yeah, I think if we do like what you initially said, if we put it in the context of a negative HRIPT at .08125, and the absence of irritation, you know, I think that's -- if we just had those and we were going to go out on a limb and say we weren't worried about sensitization, but we do have, albeit, a small study of 25 individuals, I think it -- I'm comfortable with it.

DR. BELSITO: Okay.

DR. SNYDER: And, it won't penetrate, so, like you said. So, again, I think the discussion has to be that the panel found the data to be adequate. The panel noted the absence of absorption data, however. And then the chemical physical properties, et cetera.

And then also, you know, with the genotox, no structure alerts, it's not absorbed -- that kind of stuff. So, the systemic tox was not an issue because there was an IP study, so. And we have to have the heavy metal boilerplate in this one.

MR. JOHNSON: But the irritation data should not be mentioned in the discussion because the study has not been validated -- the methodology (audio skip).

DR. BELSITO: Now, we can -- no, no, no. It can be mentioned.

MR. JOHNSON: okay.

DR. BELSITO: I mean, I think that what -- correct me if I'm wrong, and I've been typing the wrong thing. But, large molecular weights so absorption wouldn't occur, and the negative parenteral study mitigate the need for systemic endpoints. And that we have sensitization only at 0.018. Is that right?

DR. SNYDER: .08.

DR. BELSITO: .08, yeah, that's what I said I think. And it's used up to .18.

DR. SNYDER: Yeah.

DR. BELSITO: So that's a little funny, .018 is where we have sensitization and it's used up to .18?

DR. SNYDER: No, we have .08, not .018.

DR. BELSITO: Oh, .08.

DR. SNYDER: Yeah.

DR. BELSITO: We're not concerned, again, because of size, and we have irritation data that was clean at 1.4 (audio skip). I mean, do we even want to put that the methodology has not yet been accepted by authorities or just leave it at that?

DR. SNYDER: I would just leave it at that. Like I said, since it's not the sole basis for us not being concerned about sensitization.

DR. BELSITO: Okay.

DR. KLAASSEN: Yes, I agree.

DR. BELSITO: Okay. So then, based on all that, safe as used?

DR. LIEBLER: Yup.

DR. BELSITO: Anything else that needs to go into the discussion?

DR. SNYDER: Did you catch that heavy metal boilerplate, Don?

DR. BELSITO: Yup. Okay. Anything else on these? No? Okay. So it looks like you're off the hook, Wilbur. Is Christina with us?

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DR. COHEN: I see you, Ron. Present and accounted for. Okay. Let's move on to acryloyloxyethyl phosphorylcholine polymers. Wilbur, this is a draft report, and it's the first time we're reviewing this.

MR. JOHNSON: Yes.

DR. COHEN: And sorry, Wilbur, did you say something?

MR. JOHNSON: Oh, no. I just said yes. You had called my name, so I --

DR. COHEN: Oh, yeah. No. I just, yeah. You're on this one. So --

MR. JOHNSON: Okay. Thanks.

DR. COHEN: So we have eight ingredients to review. These are used as film formers in hair and skin conditioning agents. Polyquaternium-51 has the highest use of all of them with a max use of 0.14 on a leave-on product. Polyquaternium-61 has a max use in a rinse-off hair conditioner of 0.01. So just starting out, can we read-across with the polyquaternium-51, -61 for the rest for these?

MR. JOHNSON: Dr. Cohen --

DR. COHEN: Yes.

MR. JOHNSON: I have to just make a correction --

DR. COHEN: Of course.

MR. JOHNSON: -- on the use section on PDF page 10, actually the highest reported use concentration is for acrylic acid phosphorylcholine glycol acrylate cross-polymer, and that is in concentrations up to 0.18 percent in a foundation. And that correction will be made in the next round.

DR. COHEN: Okay. And that was for --

MR. JOHNSON: The acrylic acid phosphorylcholine glycol acrylate cross-polymer.

DR. COHEN: Got it.

MR. JOHNSON: Yeah.

DR. COHEN: Thank you.

MR. JOHNSON: You're welcome.

DR. COHEN: Okay. So Lisa, is it -- are we okay reading across on these?

DR. SHANK: Can we do polyquaternium-51 and -61 to read-across?

DR. SLAGA: Yeah. I had the same question.

DR. COHEN: Yeah.

DR. SHANK: That'll help if we can.

DR. COHEN: That's the question out to Lisa now.

DR. PETERSON: Well, I was going to ask you guys the same thing. I mean, structurally they're very similar in their polymers. You know, there is a confusion about the polyquaternium-61. I'm not -- actually, I was confused about the read-across from -- I didn't think it was actually the -61 that had all the information on it but rather a structurally related to -51. But maybe Wilbur -- and I think it was raised in the memo that came through yesterday. Yeah.

MR. JOHNSON: Dr. Peterson, I know that Bart had said that the isothiocyanate labeled poly-2 with acryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate could be used as a read-across for polyquaternium-51.

DR. PETERSON: Right. Right. And I agree with that because it's just a difference of a butyl versus propyl. And that is -- is that in the table?

MR. JOHNSON: Well, actually, in the dermal penetration section on PDF page 11 that is stated in that section. And I think that it's in the introduction also.

DR. SHANK: What's the difference between saying it was found on the surface of the skin, but it was also -- and another time it was found associated with the corneocytes? Corneocytes are --

DR. BERGFELD: Skin.

DR. SHANK: -- the surface of the skin, aren't they?

DR. BERGFELD: Right.

DR. SHANK: So same thing.

DR. BERGFELD: You can always put skin in parentheses or --

DR. SHANK: Okay.

DR. COHEN: Yeah. You know what? I think maybe it's just mentioned, like, in the context of the confocal microscopy. Like, they're using it that context, which is a surface microscope that looks just at the very top layer, and it's an in vivo technique.

DR. SHANK: Okay.

DR. COHEN: Yeah.

DR. SHANK: Well --

DR. BERGFELD: Stratum --

DR. SHANK: -- sounds basically like they're both the same.

DR. COHEN: Yeah.

DR. BERGFELD: Well, stratum corneum of the epidermis. Yeah.

DR. PETERSON: Yeah. So, I mean, I think -- going back to the initial question, could you read-across for all of them? And I think there's a lot of similarities. More similarities than there's differences. And I don't know polymer chemistry very much and how polymers vary -- different from one another based on the chemical structure, but I would think that it's the positive charge of the acetyl choline portion of the molecule that's going to be driving the big differences between this polymer and other polymers.

So it seems reasonably safe to say that you could read-across. I had a question getting back to what was said earlier today. Since we don't have the method of manufacturing for the cosmetic ingredients, do we need to ask for that? And then I had a concern about the impurities because I think it would be important to demonstrate that the monomers were not present in the polymer.

And one might expect based on how they do the purification that they're probably not, but there would be -- and then again, you know, the toxicity would tell you if it was a sensitizer. For example, one might blame an impurity as opposed to the polymer. So that's my comment about that. But, you know, I am not -- yeah. Those are my comments.

DR. BERGFELD: We've always worried about the monomer in these polymers.

DR. COHEN: Particularly these acrylate monomers, right? So that was a very reassuring comment. I see we have impurities only on -51.

DR. PETERSON: But they don't address the monomers. You know, they talk about the -- they say that it's 94 percent -- greater than or equal to 94 percent pure, and then it says that, you know, the arsenic and heavy metals is low. But they don't make a comment, specifically on the monomers. So, you know, are they part of the 6 percent that -- or is that 6 percent water? You know? You don't know.

So I just think getting some clarification of whether they tested for the presence of the monomers or not is really where the concern would lie. And again, you know, if they test safe and aren't irritating and sensitizing, then it's less of a concern. I mean, that is what drives the concern about the absence of information.

MR. JOHNSON: Dr. -- sorry.

DR. COHEN: No. Go ahead, Wilbur.

MR. JOHNSON: I'm sorry. Yes. I know in the other team, focusing on the method of manufacture, it was mentioned that because dialysis and rinsing of the precipitate is mentioned -- and that would, you know, likely mean that the monomer would be easily removed. And it was also stated that the acrylate monomers are rather volatile, so concern about monomer content was not, you know, expressed based up that.

DR. PETERSON: Okay. And I would support that. I think that was my also initial reaction to reading through this thing. And so my only comment would be this morning, because we had method of manufacturing for non-cosmetic ingredients and we were asking for the method of manufacturing for the ingredients used in -- you know, it's maybe possible that they buy this ingredient from somebody who makes it this way, but, you know -- so I'm not -- I'm -- I don't have a huge concern, but I'm only, you know, saying what I'm saying because of the conversation we had this morning.

DR. COHEN: Okay.

DR. PETERSON: And I understand that that was a botanical versus this is a chemical reagent that presumably that -- you know, I don't know how the cosmetic companies are getting it so this may be totally appropriate for this particular ingredient.

DR. COHEN: We have some late-breaking sensitization data on --

DR. BERGFELD: David, can't hear you.

DR. SLAGA: Yeah. You disappeared.

DR. COHEN: Oh. I don't know why. It looked like it auto-muted me.

DR. SLAGA: We don't read lips very well.

DR. COHEN: No. And sometimes I talk too fast. It looked like we received late-breaking sensitization data for -51 at 0.08125 in 25 people. It looked okay, but it was about 40 percent lower than the max use for the leave-on for -51. So I think interesting initial data. And so, why don't we just start articulating what we want because it looks like it's going to be an IDA for this.

DR. BERGFELD: Can I ask Ron a question? Ron, what about the penetration of this polymer? Usually, they're too large to penetrate. So is there any reason to think it would penetrate?

DR. SHANK: Yes. I think polyquaternium-51 we have data that it doesn't penetrate. If we can use that to read-across to the others, then that eliminates the need for systemic toxicity data. We can just say they don't cross the epidermis.

DR. BERGFELD: Do we have any idea --

DR. SHANK: For skin sensitization- --

DR. BERGFELD: -- about molecular weight?

DR. SHANK: Pardon me?

DR. BERGFELD: Is there molecular weight with this one? I didn't see it anywhere.

DR. PETERSON: No. There's no information about molecular weight.

DR. SHANK: No. I didn't see that.

DR. BERGFELD: Sorry to interrupt.

DR. SHANK: For sensitization, we have some sensitization as Dr. Cohen said on polyquaternium-51. About half the concentration, that's from the maximum concentration used in cosmetics. I don't know. Is it worth asking for more sensitization data at the higher concentration?

DR. BERGFELD: You have some ocular of -51, which was mildly irritating in fairly high doses it looks like.

DR. SHANK: Uh-huh. So if we can read-across from -- with polyquaternium-51, then I don't think we have any needs other than possible impurities. I did have a question. In the beginning of the report, it says there's not enough information to determine the structures of two of these ingredients. If that's the case, I would think they should be taken out of the report. If we don't know what the structure is, I think we're dead in the water with those two. Do you want me to name them?

DR. COHEN: Please do.

DR. SHANK: It's hydroxyethyl cellulose phosphorylcholine glycol acrylate copolymer, and the other one is polyquaternium-10 phosphorylcholine methacryloxyloxyethyl --

DR. COHEN: Got it. I got it. I'm using the table. It's easier.

DR. SHANK: Okay. Those two. And if we don't know -- if the chemists can't see what the structures are, I think they should be taken out of the report. If they're left in the report for some reason, then they are totally insufficient.

DR. BERGFELD: Can I ask a question? Doesn't a cosmetic dictionary mandate they have a chemistry with it? Monice?

DR. SHANK: You're on mute.

MS. FIUME: I know. My mouse wasn't wanting to go to the mute button. A lot of times the definitions do not have the associated structures, or they're just very minimal. So that's why often in the table CIR staff is referenced because Bart will create the structures. So what is in the table, the definition was in the dictionary. The part in italics I'm assuming is what Bart added to the table -- that he couldn't create a structure.

DR. COHEN: So isn't that salient to Ron's point?

DR. SHANK: So if we can't figure out what the structure is --

DR. PETERSON: Well, I think, you know, some of these --

DR. SHANK: -- I don't see how we can proceed --

DR. PETERSON: Yeah. Some of the issues --

DR. SHANK: -- with those two.

DR. PETERSON: -- is that hydroxyethyl cellulose is, like, a polymer itself.

DR. BERGFELD: Have we covered that before, Monice? We did a lot of polymers.

MS. FIUME: Let me check.

DR. SHANK: Well, you would need methods of manufacturing. You would need impurities. You need penetration data, chemical properties.

DR. SLAGA: And genotox.

DR. SHANK: If there's no -- if there's penetration, then you need 28-day dermal, genotox, DART. If you take those two out, then I think we've got a pretty nice document, and the only need would be impurities.

MS. FIUME: Hydroxyethyl cellulose was last reviewed in 2008 with the cellulose and related polymers. And I'm trying to get to the conclusion. They were safe as used.

DR. BERGFELD: So we could use some of that data. Does it have a structure?

DR. SHANK: That's just hydroxyethyl cellulose.

DR. SLAGA: Yeah. That's not --

DR. SHANK: That's only part of this ingredient.

DR. COHEN: And since we don't know molecular weights, we don't know how much of it is -- what part of it is -- right?

DR. SHANK: Right.

DR. BERGFELD: Do we need molecular weight on all of them?

DR. COHEN: Wouldn't it help us in being more comforted that they're not getting through? All of them aren't getting through, even though we just have it on -51.

DR. SHANK: Yes. I like that.

MR. JOHNSON: Dr. Cohen?

DR. COHEN: Yes.

MR. JOHNSON: Yes. We received in the way of a comment from Carol over at the Council. She provided a website that has information on the molecular weight of polyquaternium-51, and it is 600K. And it also indicates that polyquaternium-51 is sold at a concentration of 5 percent in water. And that's for one of the trade name material, Lipidure.

DR. COHEN: So it's sold to manufacturers at five percent in water, right? That's a change?

MR. JOHNSON: Yes. And the molecular weight is 600K.

DR. COHEN: It's big.

MR. JOHNSON: Mm-hmm.

DR. COHEN: Okay. So one other thing, Wilbur, quick question. On the profile, the chart with all the data together, I saw it looked like human dermal irritation was checked off on polyquaternium-61. Did that come in later, or did I miss it?

MR. JOHNSON: Let me see. No. Not to my knowledge. That must have been a mistake.

DR. COHEN: All right. I just wanted to -- I was trying to find it, and I didn't see it. So it's probably just meant for the -51 column.

MR. JOHNSON: Yeah. Mm-hmm.

DR. COHEN: Row, I'm sorry.

MR. JOHNSON: Yeah. Just the irritation data on the -51. Yeah. No sensitization data.

DR. COHEN: So just to summarize, are we going to have an IDA because this is a --

DR. BERGFELD: Draft.

DR. COHEN: -- draft report? Am I getting that right?

DR. BERGFELD: Yeah.

DR. COHEN: And we want impurities, particularly for monomers -- the presence of monomers. And do we ask for all of them for that? Yeah.

DR. SHANK: I would say yes. More than just monomers. You would want more than just the monomer content.

DR. COHEN: Right. Well, all impurities, but we want --

DR. SHANK: Yes.

DR. COHEN: -- to see monomers mentioned in there --

DR. SHANK: Yes.

DR. COHEN: -- right?

DR. SHANK: Yes.

DR. COHEN: We want all impurities including monomer.

DR. SHANK: Right.

DR. COHEN: We'd like the molecular weights. And I guess we can bring up tomorrow whether we want those other two entities in this report since we don't have their structure.

DR. SHANK: Right.

DR. BERGFELD: If you did, you'd need the penetration, blah, blah, blah, after that on those.

DR. SHANK: Everything. Yes. What about the skin sensitization data we got on -51?

DR. COHEN: I think it's way below max use. It's like, really much below max use, right?

DR. SHANK: It's about half of maximum use -- a little more than half.

DR. COHEN: I'm --

DR. SHANK: Close enough, or no?

DR. COHEN: Well, I'm just throwing it out there. I'm highlighting that issue a little bit more because it's our only sensitization data we have for the entire group.

DR. SHANK: Yes.

DR. COHEN: And we're dragging it across the whole table, and we only have half. I mean, I felt -- I would feel better if we had at least a max use in one that we could pull across, but we don't have any other data on sensitization.

DR. SHANK: That's right. Okay. Then that would be an insufficient data need is skin sensitization --

DR. SLAGA: For -51.

DR. SHANK: -- for -51 at the maximum leave-on concentration of 0.014 percent.

MR. JOHNSON: But should --

DR. SLAGA: Also, we would need a genotox for -51. We don't have that.

DR. BERGFELD: But does it -- if it doesn't --

DR. SLAGA: We have it for -61.

DR. SHANK: But if it doesn't penetrate, we don't need genotox do we?

DR. SLAGA: Huh?

DR. SHANK: If it doesn't penetrate the epidermis, we don't need genotox.

DR. SLAGA: Well, if it would cause skin cancer, you would need it. Right?

DR. BERGFELD: Well, we'd have to have --

DR. SHANK: Well, the poly- --

DR. BERGFELD: -- to be a carcinogen or photoactivated.

DR. SLAGA: Well, it -- the -51 to read-across I would prefer to have genotox with it because there is genotox with -61, unless we use both -51 and -61 as read-across.

DR. SHANK: We know -51 sticks to the surface of the skin, so it doesn't get to any viable cells.

DR. SLAGA: Okay. We don't need genotox then. I thought it (audio skip) skin.

DR. BERGFELD: No.

DR. SHANK: But if you think -61 might be different -- if you think polyquaternium-61 might get into the viable cells of the epidermis, then, yes, you would want genotox.

DR. SLAGA: All right. Skip it.

DR. COHEN: Yeah. I thought the whole presumption of the read-across is to at least generalize some of that information.

DR. SHANK: Yes. Right.

DR. COHEN: Okay. So I have the IDA for impurities, molecular weight, sensitization at max use, and maybe those other two coming out because we don't have structure. And that might be a --

DR. SHANK: Correct.

DR. COHEN: -- source of discussion tomorrow where we could be persuaded otherwise. We'll see if they have other insights. Does that sound right to the team?

DR. SHANK: Yeah. You're good.

DR. BERGFELD: Are you doing -51 and -61 or just -51?

DR. COHEN: Which one? What are you asking?

DR. BERGFELD: Are you doing -51 polymer -- the -51 or the -61 or both? You said you were asking for sensitization. Is it on both or single or --

DR. COHEN: I think we were going to ask for -51 since we had some data already on it. But, you know, I suppose if we -- what's the max? The -61 only has two uses, and -51 has 275 uses. I think we would want -51 at that point.

DR. SLAGA: Yeah.

DR. SHANK: I agree. I agree.

MR. JOHNSON: Dr. Cohen, you mentioned impurities. Would we need method of manufacture also or just impurities?

DR. COHEN: Lisa, what do you think?

DR. PETERSON: Well, you know, you have a method of manufacturing in here. I'm just referring back to the conversation we had earlier today, which said that you wanted to have method of manufacturing for the cosmetic ingredient. So my only -- in that was we were talking about sage, I believe, or tree --

DR. COHEN: Yeah. Sage, we had the issue with the cosmetic ingredient.

DR. PETERSON: It's just a different beast on a chemical, you know, so that -- and I think -- so I'm fine with what's there if that's acceptable.

MR. JOHNSON: Okay. Thank you.

DR. SHANK: Could we have the structure of polyquaternium-51 added to the report? The only structure given is -61.

DR. COHEN: Okay. Any other --

DR. PETERSON: -51 is in the report in the Table 1.

DR. COHEN: Yes, it's on Table 1.

MR. JOHNSON: Yeah. -51 and -61 are there.

DR. SHANK: Okay.

DR. PETERSON: So are you meaning the --

DR. SHANK: Well, at the very beginning of the report under chemistry definition we have structure for -61 but not -51.

DR. PETERSON: Oh, I see what you're saying.

DR. SHANK: So why don't we have it -- -51 there was well since we're talking mostly about -51?

DR. SLAGA: That would be good.

DR. COHEN: Yeah. That's a good point.

DR. SHANK: Just a suggestion.

DR. BERGFELD: It's a good one.

DR. SHANK: Yeah.

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DR. COHEN: Okay, so this is the first time that we are review this, the Acryloyloxyethyl Phosphorylcholine Polymers. These are used as film formers and hair and skin conditioning agent. There are eight derived ingredients under consideration. In our discussions we are coming out with an IDA, insufficient data announcement. We have a number of comments.

We're concerned about the inclusion of two items, which we do not have enough information such as their structure, particularly for Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer and Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer. So, consequently we don't know if they're sufficiently similar to the other two to do a read across.

We felt there wasn't certitude from the chemist on what these look like, was it reasonable to include them here. We'd like composition and impurities for all of them and for that to also call out the presence or absence of monomer. We felt they were unlikely to penetrate the skin.

And we have information on Polyquaternium-51, in that vein, we'd like the molecular weights for all of the products, to help us corroborate whether the likelihood of penetration. And that would help dictate that we might not need genotox. We have sensitization on 51 at use .14, but the (audio skip) is on 0.08. So I think we might want higher max use information. Either on that or -- yeah, I think I'll stop there.

DR. BERGFELD: And that's a motion?

DR. COHEN: Yes.

DR. BERGFELD: To go IDA? May I ask, Monice, particularly, do we go IDA in our first draft, or we just ask the request?

MS. FIUME: For the first draft it would be an insufficient data announcement or IDA.

DR. BERGFELD: Okay. Thank you. Don, you have anything?

DR. BELSITO: Our team concluded that these products were safe as used, so I'll let Dan address one of the issues which was the read-across.

DR. LIEBLER: Well, there are a couple issues. One is the composition and impurities, which is really minimal. We didn't have anything on residual monomer. A couple of the descriptions of manufacturing indicated the wash steps or precipitation steps would clean up the monomers (audio distorted) which would be a concern. (Audio distorted).

DR. BERGFELD: We're not hearing you well, Dan.

DR. BELSITO: I think those not speaking should mute their mic.

DR. LIEBLER: So I have no problem with the request for additional information -- are you hearing me now?

DR. BERGFELD: Yes.

DR. LIEBLER: Okay. And, I think that I would just say with respect to which ingredients to include, from the descriptions I can see there may be some differences. On polymers like this, I developed a wide tolerance for ingredient inclusion based on my experience on the panel. But, again, I have no objection to looking at more information on the structures of these in case there's something that I'm overlooking at that looks like it won't fit.

So, I think these are all big molecules that won't penetrate the skin, but I don't have any problem with any of the IDA requests at this point in the report.

DR. BERGFELD: Anyone else have a comment on this? Curt, Paul? Lisa? No? Okay.

DR. PETERSON: I just want to second what Dan said. The concern about the chemistry kind of came from the others, and because I'm not a polymer chemist I decided to defer to their concerns. So, just wanted to let people know I was on the same page.

DR. BERGFELD: Okay, so, we've had a motion to go IDA, but we haven't had a second. Don, will you second it? Don? You're muted.

DR. BELSITO: Yeah, I'm muted. For the first time in my life I've been muted. Yes, I seconded it.

DR. BERGFELD: Second it. Anything needs to be discussed regarding this motion then, and the needs that are being requested?

DR. COHEN: Wilma, can I ask Don a quick question?

DR. BERGFELD: Yeah.

DR. COHEN: Don, so the sensitization data for 51 was plus/minus 40 percent lower than the max used for 51. And it's the only sensitization data we have in the group. So, did you have any specific comment regarding that being the sole sensitization information we have?

DR. BELSITO: Yeah, so, Dan looked at this and obviously the one concern would be residual monomers, because otherwise these are still large, they're not going to get past the stratum corneum. And, on Page PDF -- I'm not sure where it occurs, but anyway they're manufactured and then they go through dialysis and washing, which Dan felt would remove residual monomers and acrylates and methacrylate monomers. Plus, as you know those are very volatile, so they'll volatilize off as well. So, we really weren't concerned about levels of residual monomers that would sensitize and felt that this would just sit on the skin.

DR. SNYDER: Don, we also considered the negative irritation, at 1.4 percent, considering these are used at maximum concentration .18 percent.

DR. BELSITO: That's right.

DR. BERGFELD: I'm not sure of the writer on this one, but if we could capture what has just been said for the discussion so we can look at that again.

DR. BELSITO: It's Wilbur, he's here.

DR. BERGFELD: Wilbur? Okay. Thank you. All right, so we've had a motion and it's been seconded. I'm going to call for the vote then. All those opposed for an IDA on this with a list of needs that have been stated? Opposing? Abstaining? It passes, it's approved. Thank you. Okay, and any discussion that's needed again for the needs? Wilbur, you need anything? Are you okay?

MR. JOHNSON: Yes, I am Dr. Bergfeld.

DR. BERGFELD: Okay, thank you.

MR. JOHNSON: You're welcome.

Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics

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ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 8 acryloyloxyethyl phosphorylcholine polymers in cosmetic products; most of these ingredients are reported to function as film formers and hair/skin conditioning agents in in cosmetics. The Panel reviewed data relevant to the safety of these ingredients in cosmetic formulations, and concluded [TBD]

INTRODUCTION

The safety of the following 8 acryloyloxyethyl phosphorylcholine polymers as used in cosmetics is reviewed in this safety assessment.

Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer
C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer
Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer
Phosphorylcholine Glycol Methacrylate/PEG-10 dimethacrylate Crosspolymer
Polyphosphorylcholine Glycol Acrylate
Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer
Polyquaternium-51
Polyquaternium-61

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), most acryloyloxyethyl phosphorylcholine polymers are reported to function as film formers and hair/skin conditioning agents in cosmetic products (See Table 1).[1] Two other functions associated with ingredients in this group include humectant and viscosity increasing agent. These ingredients are all vinyl-type polymers and share in common certain phosphorylcholine acrylate monomers.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. The published data in this document were identified by conducting an exhaustive search of the world's literature. A list of the search engines and websites that are used, and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is available 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 may be provided by the cosmetics industry, as well as by other interested parties. These searches yielded limited toxicity data relating to the 8 acryloyloxyethyl phosphorylcholine polymer ingredients listed above. Of these ingredients, only safety test data on Polyquaternium-61 were identified. Additionally, data (toxicity and other relevant data) on poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate), which is very similar structurally to Polyquaternium-51 (which is poly(2-methacryloyloxyethyl phosphorylcholine-co-n-***propyl*** methacrylate)) are included in this safety assessment.

CHEMISTRY

Definition

Acryloyloxyethyl phosphorylcholine polymers have been defined as amphiphilic block copolymers comprising, at least in part, 2-acryloyloxyethyl phosphorylcholine monomers.[2] The ingredients are constructed as vinyl-type polymers and share in common these phosphorylcholine substituted acrylate monomers. For example, Polyquaternium-61 (no CAS No.) comprises the two monomers shown in Figure 1. The definitions, idealized structures, and CAS Nos. of the acryloyloxyethyl phosphorylcholine polymers included in this safety assessment are presented in Table 1.[1] The only ingredients with reported CAS Nos. in this safety assessment are Polyphosphorylcholine Glycol Acrylate (CAS No. 67881-99-6) and Polyquaternium-51 (125275-25-4).

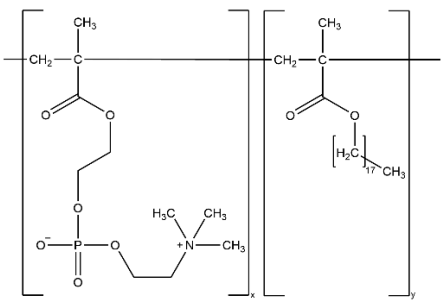


Figure 1. Polyquaternium-61

Chemical Properties

Some of the weight-averaged molecular weights that have been reported for acryloyloxyethyl phosphorylcholine polymers include: 338,820 Da (Polyquaternium-51), 20,182 Da (Polyquaternium-61), and 62,393 Da (Polyphosphorylcholine Glycol Acrylate).[3] These and other properties data on acryloyloxyethyl phosphorylcholine polymers are presented in Table 2.

Method of Manufacture

No ingredient-specific methods of manufacture were found in the literature or submitted as unpublished data. However, some general methodologies were found in the literature, and a sample is provided below.

Amphiphilic block copolymers based on poly(2-acryloyloxyethyl phosphorylcholine) have been prepared via RAFT polymerization.[2] The block copolymers were prepared by dissolving 1 g (0.111mmol) macroRAFT agent (M_n = 9000 Da) and 2 mg (0.0121 mmol) 2,2′- azoisobutyronitril (AIBN) in 15 ml *N*-methylpyrrolidone (NMP). 2-Acryloyloxyethyl phosphorylcholine (APC, 7.3 g [0.026 mol]) was dissolved in 25 ml methanol and added to the solution of RAFT agent and initiator in NMP. The sample was sealed and degassed by purging nitrogen through the solution, and the sample was heated in an oil bath (60 °C) with vigorous stirring. Samples were taken with a gastight syringe at preset reaction times. The conversion was determined using nuclear magnetic resonance spectroscopy (solvent: deuterated methanol/ chloroform 2:1). The polymers were purified by dissolving the final product in methanol and dialyzing for several days against water using cellulose tubular membranes (molecular weight cut-off: 10 kDa).

The synthesis of the polymer, poly(methyl methacrylate-co-methyl acrylate-co-2-acryloyloxyethyl phosphorylcholine) has also been described.[4] Radical copolymerization of methyl methacrylate (146 mg, 1.46 mmol), methyl acrylate (300 mg, 3.75 mmol), and 2-acryloyloxyethyl phosphorylcholine, initiated with α,α'-azoisobutyronitril (8 mg, 1.5 wt %) was performed in methanol (15 ml) at a concentration of 0.035 g/ml. The stirred solution was degassed with argon, the tubes were sealed, and the temperature of the solution was increased and maintained at 55 ºC. Next, the reaction was stopped by cooling at room temperature, and the tubes were stored at -18 ºC to allow precipitation of more of the polymer. The polymer was rinsed in methanol, centrifuged, and dried over phosphorus pentoxide.

Composition/Impurities

Polyphosphorylcholine Glycol Acrylate

Data on the composition of a Polyphosphorylcholine Glycol Acrylate (tradename mixture) that were received from a supplier indicate that it consists of the following: Phosphorylcholine Glycol Acrylate (40%), water (54.85%), 1,3-butylene glycol (5%), and methyl (0.15%).[5] Specifications for this material state 20 ppm (max) heavy metals and 2 ppm (max) arsenic.[6]

Polyquaternium-51

According to one source, the purity of Polyquaternium-51 is ≥ 94%.[7] In addition, the same source indicates that the heavy metals content of Polyquaternium-51 is ≤ 10 ppm, and the arsenic content is ≤ 2 ppm. Data on the composition of a Polyquaternium-51 (tradename mixture) that were received from a supplier indicate that it contains Polyquaternium-51 (5%) and water (95%).[5] Additionally, the specifications for Polyquaternium-51 (tradename mixture,) provided include: heavy metals (20 ppm max), /arsenic (2 ppm max), 2-methacryloyloxyethyl phosphorylcholine (100 ppm max), and butyl methacrylate (100 ppm max).[6]

Polyquaternium-61

Data on the composition of Polyquaternium-61 that were received from a supplier indicate that it consists of 100% Poyquaternium-61.[5] Additional composition data on Polyquaternium-61 (that were received includeheavy metals (20 ppm max) and arsenic (2 ppm max).[6]

USE

Cosmetic

The safety of acryloyloxyethyl phosphorylcholine polymers 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 2021 VCRP data, Polyquaternium-51 is reported to be used in 275 cosmetic products (245 leave-on products and 30 rinse-off products; Table 3).[8] Of the acryloyloxyethyl phosphorylcholine polymers that are being reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey completed in 2019 - 2020 and provided by the Council in 2020 indicate that Acrylic Acid/Phosphorylcholine Glycol Acrylate

Crosspolymer is being used at maximum use concentrations up to 0.18% in leave-on products (foundations); Table 3).[9] This is the highest maximum cosmetic use concentration that is being reported for the acryloyloxyethyl phosphorylcholine polymers that are being reviewed in this safety assessment. Polyquaternium-61 is being used at the highest concentration in rinse-off products, at maximum use concentrations up to 0.01% (hair conditioners).

According to VCRP and Council survey data, 4 of the 8 acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment are not currently in use in cosmetic products.[8,9] These ingredients are presented in Table 4.

Cosmetic products containing acryloyloxyethyl phosphorylcholine polymers may be applied to the skin/hair or, incidentally, may come in contact with the eyes (e.g., 0.05% Polyquaternium-51 in eye makeup preparations).[9] Acryloyloxyethyl phosphorylcholine polymers are being used in cosmetic products that come in contact with mucous membranes (e.g., Polyquaternium-51 in bath soaps and detergents and personal cleanliness products [concentrations not reported]). Products containing acryloyloxyethyl phosphorylcholine polymers may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Polyquaternium-61 is reported to be used in aerosol hair sprays at maximum use concentrations up to 0.000006%.[9] 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.[10-13] 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.[10,11] Polyquaternium-61 is reported to be used in face powders at maximum use concentrations up to 0.0069%. 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.

The acryloyloxyethyl phosphorylcholine polymers are not restricted from use in any way under the rules governing cosmetic products in the European Union.[14]

Non-Cosmetic

No non-cosmetic uses were found.

TOXICOKINETIC STUDIES

Dermal Penetration

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read across source for Polyquaternium-51)

Excised abdominal skin from male hairless rats (WBM/ILA-Ht strain) was positioned in a Franz-type diffusion cell (effective diffusion area = 3.14 cm^2).[15] A 5% fluorescent isothiocyanate-labeled poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) solution (2 ml) or free fluorescent isothiocyanate was applied on the stratum corneum. Phosphate buffered saline (~ 17 ml, receptor fluid) was on the dermal side. The skin surface was washed with distilled water at the end of the 6-h permeation experiment, and fluorescence (from the skin surface to 0 µm thickness) was observed using confocal laser scanning microscopy. At 6 h after application of 5% fluorescent isothiocyanate-labeled poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) solution, the fluorescent dye was found evenly on the skin surface. However, when free fluorescent isothiocyanate was applied, it was distributed mainly to the corneocytes (confocal laser scanning microscopy image not available).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Data on the acute toxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

Short-Term Toxicity Studies

Oral

The safety of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) of different formula weights (FW; 30,000 and 100,000 Da) was evaluated using groups (3 per group) of specific pathogen-free male Wistar rats.[16] Each copolymer was administered orally as a 10% solution in distilled water (dose volume = 10 ml/kg/d), once daily for 14 successive days. The control group was dosed with distilled water. The animals were killed 24 h after the last dose, and the following organs were removed and examined microscopically: kidneys, liver, small intestine, and large intestine. There was no evidence of lesions in these organs. Furthermore, there were no statistically significant differences in the following biomarkers of toxicity between test and control groups: serum creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.

Subchronic Toxicity Studies

Data on the subchronic toxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

Chronic Toxicity Studies

Data on the chronic toxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

Data on the genotoxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

ANTI-CARCINOGENICITY STUDIES

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

The anti-tumor activity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) was evaluated using groups of 4 female BALB/cA nude mice.[17] Two MX-1 tumor tissue fragments (human breast tumor, 3 mm x 3 mm x 3 mm) were inoculated into the subcutaneous tissue of the bilateral dorsum of each animal. Treatment with the test substance was initiated when the tumor weight reached 200 to 300 mg. The test substance was administered i.p. (in weekly cycles) at doses of 50 mg/kg and 200 mg/kg over a 2-wk period. Relative mean tumor weight (T) of the treated group and the relative mean tumor weight of the control group (C) at any given time were determined. Antitumor efficacy was evaluated based on the lowest T/C value (%) during the experiment. Anti-tumor activity was not observed at either dose of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate). None of the animals died.

OTHER RELEVANT STUDIES

Cytotoxicity

The cytotoxicity studies below may be useful in terms of evaluating a potentially anti-carcinogenic effect of Polyquaternium-51 using in vitro methodology.

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

The cytotoxicity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) was evaluated in the in vitro lactase dehydrogenase (LDH) assay using the MBT-2 cell line (mouse bladder cancer cell line).[18] This assay is used to examine damage to the cell membrane, and is based on the leakage of LDH from cytosol. Cytotoxicity was not observed at test substance concentrations up to 5%.

In another cytotoxicity evaluation of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate), the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used.[17] Testing involved the following cell types (breast cancer cells): MCF-7, SK-BR-3, and MX-1 cells. The test substance (concentration not stated) did not cause growth inhibition in any of the cell types.

Hemolytic Activity

This in vitro experiment relating to hemolytic activity is included below because the red blood cell hemolytic assay has been found to be a useful and rapid test for use as a screening method to assess the ocular irritation potential of cosmetic products.[19]

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

A hydrogel containing a 2-methacryloyloxyethyl phosphorylcholine moiety was formed from aqueous solution with a water-soluble 2-methacryloyloxyethyl phosphorylcholine polymer with carboxylic acid and alkyl groups because of hydrogen bonding formation.[20] The alkyl 2-methacryloyloxyethyl phosphorylcholine polymer was poly(2-methacryloyloxy-ethyl phosphorylcholine-co-n-butyl methacrylate). The biocompatibility of the spontaneously formed 2-methacryloyloxy-ethyl phosphorylcholine polymer hydrogel was investigated using a hemolysis test involving human whole blood.

Absorbance at 405 nm of the supernatant (of the erythrocyte suspension) was measured after addition of the polymer at final concentrations of 0.1, 0.5, and 2 wt %. The absorbance corresponded to the number of hemolyzed erythrocytes. Results for the polymer were compared to those for the erythrocyte suspension in Hank's balanced salt solution (HBSS). The relative absorbance was as low as HBSS, even at the highest concentration of 2 wt %, indicating low hemolytic activity.

Inhibition of Skin Penetration

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

The inhibitory effect of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) on the in vitro skin permeation of methylparaben and *n*-butylparaben was evaluated.[15] Excised abdominal skin from male hairless rats (WBM/ILA-Ht strain) was positioned in a Franz-type diffusion cell (effective diffusion area = 3.14 cm^2). Methylparaben (10 mM) and n-butylparaben (1 mM) aqueous solution with or without 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) were used as the donor solution. Phosphate buffered saline (receptor fluid, ~17 ml) was on the dermis side. The addition of 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) decreased the skin penetration of methylparaben and *n*-butylparaben. Using the cumulative amount permeated over 8 h, the skin permeation of methylparaben and n-butylparaben was decreased by 54.8% and 85.6%, respectively, by the addition of 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate). These results suggest that the inhibitory effect of 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) on the skin penetration of parabens was more marked for a more lipophilic compound.

Tissue Regeneration

The toxicogenomics field aims to understand and predict toxicity using omics data in order to study systems-level responses to compound treatments. Thus, the following study, indicating an effect on gene expression by a read-across source chemical for Polyquaternium,-51, may be of some relevance in a safety evaluation.

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

A study was performed to promote the understanding of initial host body reactions toward successful tissue regeneration.[21] Three-dimensional porous polyethylene scaffolds with collagen (bioactive) and poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) were used, and the genetic level of host body reactions was analyzed. Scaffolds were implanted subcutaneously (s.c.) into male Wistar rats and male C57BL/6 mice. One mouse was used for comprehensive genetic analysis and 3 rats were used for immunohistochemistry. The scaffolds were resected with surrounding tissue at 7 d after operation, and, after immunostaining of tissues for CD68 on macrophages, the early foreign body reaction to the scaffolds was assessed. Host body reactions at scaffolds were studied using a DNA microarray assay. Local ribonucleic acids (RNAs) in infiltrating cells into the porous scaffolds were extracted using a laser microdissection technique. The relationships between the expression levels of important genes for tissue regeneration on the collagen and poly(2-methacryloyloxyethyl phosphorylcholine) surface scaffold were discussed in combination with histological results. A significant number of monocytes/macrophages surrounded the scaffold. The DNA microarray assay showed that a number of genes may be involved in actively neglecting the poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)-coated scaffold. The authors noted that these results suggest that macrophages may also play a significant role in host body suppressing reactions. The poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)-coated scaffold slightly up-regulated genes that are related to suppression of inflammation and wound healing.

DERMAL IRRITATION AND SENSITZATION STUDIES

The dermal irritation and sensitization studies summarized below are presented in Table 5.

The skin irritation potential of a trade name mixture containing 1.4% Polyquaternium-51 was evaluated in the Irrectection® assay at doses of 25, 50, 75, 100, and 125 µl.[22] The mixture was classified as a non-irritant over the range of doses tested.

In the maximization test using groups of 10 Hartley guinea pigs (Std:Hartley), the skin sensitization potential of Polyquaternium-51 (tradename mixture) was evaluated.[23] Polyquaternium-51, at concentrations up to 100%, exhibited no skin sensitization potency in this study. The skin sensitization potential of 25% Polyquaternium-61 in petrolatum was evaluated in the guinea pig adjuvant and patch test, using 5 (3 males, 2 females) albino guinea pigs (Aai: (HA) outbred, viral and antibody free).[24] . Polyquaternium-61 was not a sensitizer in guinea pigs. A maximization test involving 25 subjects (13 women, 12 men) was performed to evaluate the sensitization potential of a foundation containing 0.08125% Polyquaternium-51. The foundation did not possess a contact-sensitizing potential. A human repeated insult patch test (occlusive patches) on a serum containing 0.12% Polyquaternium-51 was performed using 212 male and female subjects.[25] The product (tested neat) did not demonstrate a potential for eliciting dermal irritation or sensitization.

OCULAR IRRITATION STUDIES

In Vitro

Polyquaternium-51

The ocular irritation potential of a trade name mixture containing 1.4% Polyquaternium-51 was evaluated in the Irrectection® assay at doses of 25, 50, 75, 100, and 125 µl.[22] The mixture was classified as a slight ocular irritant over the range of doses tested.

SUMMARY

The safety of 8 acryloyloxyethyl phosphorylcholine polymers as used in cosmetics is reviewed in this safety assessment. Most of the polymers reviewed in this safety assessment are reported to function as film formers and hair/skin conditioning agents in cosmetic products. These ingredients are all vinyl-type polymers and share in common certain phosphorylcholine acrylate monomers.

Data on the composition of a Polyphosphorylcholine Glycol Acrylate (tradename mixture) that were received from a supplier indicate that it consists of the following: Polyphosphorylcholine Glycol Acrylate (40%), water (54.85%), 1,3-butylene glycol (5%), and methyl *p*-hydroxybenzoate (0.15%). According to one source, the purity of Polyquaternium-51 is ≥ 94%. Data on the composition of Polyquaternium-51 (tradename mixture), received from a supplier, indicate that it contains Polyquaternium-51 (5%) and water (95%). Composition data on Polyquaternium-61 (same source) that were received indicate that it 100% Polyquaternium-61.

According to 2021 VCRP data, Polyquaternium-51 is reported to be used in 275 cosmetic products (245 leave-on products and 30 rinse-off products). Of the acryloyloxyethyl phosphorylcholine polymers that are being reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey completed in 2019 - 2020, and provided by the Council in 2020, indicate that Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymeris being used at maximum use concentrations up to 0.18% in leave-on products (foundations). Additionally, according to both VCRP and Council survey data, the following 4 acryloyloxyethyl phosphorylcholine polymers are not being used in cosmetic products: C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer, Hydroxyethylcellulose/ Phosphorylcholine Glycol Acrylate Copolymer, Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer, and Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer.

A skin penetration experiment was performed using excised abdominal skin from male hairless rats (WBM/ILA-Ht strain). The test substance was a 5% fluorescent isothiocyanate-labeled poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) solution. At 6 h post-application, the fluorescent dye was found evenly on the skin surface. However, when free fluorescent isothiocyanate was applied, it was distributed mainly to the corneocytes.

The safety of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) of different FW (30,000 and 100,000 Da) was evaluated using groups (3 per group) of specific pathogen-free male Wistar rats. Each polymer was administered orally as a 10% solution in distilled water (dose volume = 10 ml/kg/d), once daily for 14 successive days. There was no evidence of organ lesions at microscopic examination. Additionally, there were no statistically significant differences in the following toxicity biomarkers between test and control groups: serum creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.

In a study involving groups of 4 female BALB/cA nude mice previously injected with human breast tumor fragments, poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) was administered i.p. at doses of 50 mg/kg and 200 mg/kg) over a 2 wk period. Mortalities were not observed in either of the 2 dose groups. The antitumor activity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) was evaluated using groups of 4 female BALB/cA nude mice. Tumor tissue fragments (MX-1, human breast tumor, 3 mm x 3 mm x 3 mm) were injected subcutaneously, and the test substance was administered i.p. (in weekly cycles) at doses of 50 mg/kg and 200 mg/kg) over a 2-wk period. Anti-tumor activity was not observed at either dose of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate).

The cytotoxicity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) was evaluated in the in vitro LDH assay using the MBT-2 cell line (mouse bladder cancer cell line). Cytotoxicity as not observed at test substance concentrations up to 5%. Another assay, the MTT assay, was used to evaluate the cytotoxicity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51; concentration not stated) in the following breast cancer cells: MCF-7, SK-BR-3, and MX-1 cells. There was no evidence of growth inhibition.

The inhibitory effect of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) on the in vitro skin permeation of methylparaben (10 mM aqueous solution) and n-butylparaben (1 mM aqueous solution) was evaluated using excised abdominal skin (male hairless rats) in a Franz-type

diffusion cell. The addition of 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) decreased the skin penetration of methylparaben (by 54.8%) and n-butylparaben (by 85.6%).

A study was performed to promote the understanding of initial host body reactions toward successful tissue regeneration. Three-dimensional porous polyethylene scaffolds with collagen (bioactive) and poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) were implanted s.c. into male 3 Wistar rats and 1 male C57BL/6 mouse. Host body reactions at scaffolds were studied using a DNA microarray assay. This assay showed that a number of genes may be involved in actively neglecting the poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)-coated scaffold. The poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)-coated scaffold slightly up-regulated genes that are related to suppression of inflammation and wound healing.

The skin irritation potential of a trade name mixture containing 1.4% Polyquaternium-51 was evaluated in the in vitro Irrectection® assay. The mixture was classified as a non-irritant over the range of doses tested (25, 50, 75, 100, and 125 µl).

In the maximization test, the skin sensitization potential of Polyquaternium-51 (tradename mixture) was evaluated using 10 Hartley guinea pigs (Std:Hartley). The test substance was injected (100% v/v, in Freund's adjuvant) and applied topically (100% v/v) during the induction phase. On d 22 (challenge phase), the following concentrations (in water) were applied under a 48-h occlusive patch: 6.25 v/v%, 12.5 v/v%, 25 v/v%, 50 v/v%, and 100 v/v%. Polyquaternium-51 exhibited no skin sensitization potency in this study. The skin sensitization potential of Polyquaternium-61 was evaluated in the guinea pig adjuvant and patch test, using 5 (3 males, 2 females) albino guinea pigs (Aai: (HA) outbred, viral and antibody free). During induction, the test substance (25% in petrolatum) was injected (in adjuvant/water emulsion) and applied topically (25% in petrolatum). Challenge applications of Polyquaternium-61 (24 h, 25% in petrolatum, 0.1 ml) were made to new sites on the flank (open patch, 5 cm^2 area) of test animals. Polyquaternium-61 was not a sensitizer in guinea pigs.

A maximization test involving 25 subjects (13 women, 12 men) was performed to evaluate the sensitization potential of a foundation containing 0.08125% Polyquaternium-51. Repeated occlusive patch applications of the product (after SLS pretreatment) were made during induction. A single 48-h occlusive challenge patch application of the undiluted foundation (0.1 ml) was made to a new site on the opposite arm, forearm, or side of the back. The foundation did not possess a contact-sensitizing potential. A human repeated insult patch test on a serum containing 0.12% Polyquaternium-51 was performed using 212 male and female subjects. The undiluted product was applied repeatedly, under an occlusive patch, to the upper back (between the scapulae and waist, lateral to the midline) during induction. A challenge patch was applied to the original site on the back and to a new site. The product did not demonstrate a potential for eliciting dermal irritation or sensitization.

The ocular irritation potential of a trade name mixture containing 1.4% Polyquaternium-51 was evaluated in the in vitro Irrectection® assay. The mixture was classified as a slight ocular irritant over the range of doses tested (25, 50, 75, 100, and 125 µl).

DRAFT DISCUSSION

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

This assessment reviews the safety of 8 acryloyloxyethyl phosphorylcholine polymers, as used in cosmetic formulations. The Panel concluded [TBD].

The Panel considered the available data to be adequate for determining safety. It was noted that the data provided indicate that Phosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61 are high molecular weight polymers. In the absence of molecular weight data on the remaining 5 acryloyloxyethyl phosphorylcholine polymers in this safety assessment, the expectation is that their molecular weights are comparable. The only skin penetration data in this report are on poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate), which is considered by the Panel to be a sufficient read-across source chemical for Polyquaternium-51. These data indicate the absence of skin penetration, and the Panel agrees that the data are relevant to all of the acryloyloxyethyl phosphorylcholine polymers that are being reviewed. Furthermore, the Panel agrees that these skin penetration data essentially eliminate the need for systemic toxicity data (i.e., subchronic/chronic toxicity, carcinogenicity, and reproductive/developmental toxicity data) on the acryloyloxyethyl phosphorylcholine polymers.

Also taken into consideration were the absence of structural alerts for genotoxicity in the polymers reviewed, obviating the need for genotoxicity data, and the absence of toxicity when the read-across source chemical was administered to animals in a 2-wk anti-tumor activity study, using a method (i.p.) that by-passed the dermal absorption pathway. The Panel agreed that these findings also support the lack of concern over the systemic toxicity of acryloyloxyethyl phosphorylcholine polymers.

The Panel noted that the chemical characterization data provided include information on the residual monomer content of Polyquaternium-51 (100 ppm max, for butyl methacrylate), and that butyl methacrylate is a sensitizer. However, because the method of manufacture of amphiphilic block copolymers based on poly(2-acryloyloxyethyl phosphorylcholine) involves purification (dialysis and rinsing) of the final product, the Panel agrees that residual monomer content is not a major

concern. Additionally, the volatility of acrylate and methacrylate monomers was considered, and supports the lack of concern over monomer content. In addition to the issue of monomer-induced sensitization potential, the issue of skin sensitization potential of acryloyloxyethyl phosphorylcholine polymers was also addressed. The Panel noted that the absence of skin penetration mitigates concern over the skin irritation/sensitization potential of these polymers. However, a determination relating to skin sensitization potential (non-sensitizer) was made using data on 2 polymers (Polyquaternium-51 and Polyquaternium-61) that were received. Polyquaternium-51 (most frequently used acryloyloxyethyl phosphorylcholine polymer) is being used in cosmetics at maximum use concentrations up to 0.14% (in face and neck products [not spray]), compared to the highest maximum cosmetic use concentration of 0.18% (in foundations) reported for Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer. Polyquaternium-61 is being used in cosmetics at maximum concentrations up to 0.01% (in hair conditioners). The negative human repeated insult patch test on a serum containing 0.12% Polyquaternium-51 involved an ingredient concentration that is lower than the maximum reported use concentration (0.14%) for this ingredient in cosmetics and the highest reported maximum cosmetic use concentration (0.18%) for acryloyloxyethyl phosphorylcholine polymers. However, the Panel determined that this lower test concentration is not of concern, given the negative guinea pig maximization test on Polyquaternium-51at challenge concentrations up to 100% and negative guinea pig adjuvant and patch test results on Polyquaternium-61 at a challenge concentration of 25%.

Concern about the presence of heavy metals in acryloyloxyethyl phosphorylcholine polymers was expressed by the Panel. It was stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities in these ingredients before blending into cosmetic formulation.

The Panel discussed the issue of incidental inhalation exposure that could result from use of some of these ingredients; for example, Polyquaternium-61 is reported to be used in aerosol hair sprays (at maximum use concentrations up to 0.000006%) and in face powders (at maximum use concentrations up to 0.0069%). 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 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

To be determined…

TABLES

Table 1. Definitions, Functions, and Idealized Structures of the Ingredients in this Safety Assessment.[CIR Staff;1)]

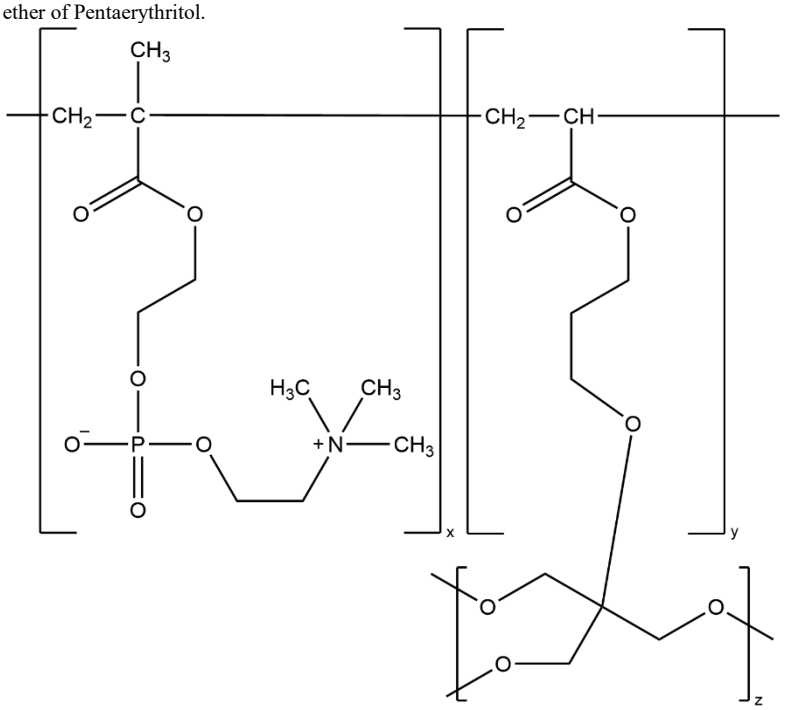
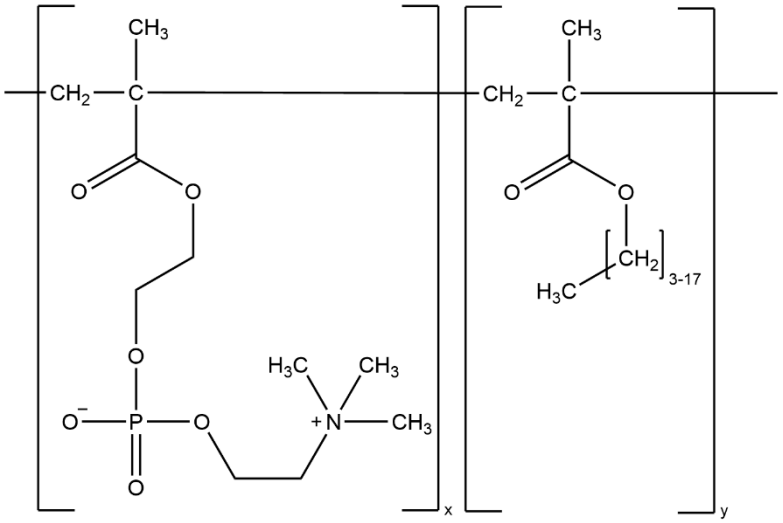
Ingredient/CAS No.	Definition & Structures	Function(s)
Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer	Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer is a copolymer formed from Acrylic Acid and phosphorylcholine glycol methacrylate, crosslinked with an allyl ether of Pentaerythritol. 	Viscosity Increasing Agents – Aqueous.[1]
C4-18 Alkyl Methacrylate/ Methacryloyloxyethyl Phosphorylcholine Copolymer	C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer is a copolymer of Methacryloyloxyethyl Phosphorylcholine and C4-18 alkyl methacrylate. 	Humectants
Hydroxyethylcellulose/ Phosphorylcholine Glycol Acrylate Copolymer	Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer is the copolymer formed from Hydroxyethylcellulose and phosphorylcholine glycol methacrylate. *Not enough information available about connectivity to provide a structure.*	Film Formers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Miscellaneous

Table 1. Definitions, Functions, and Idealized Structures of the Ingredients in this Safety Assessment.[CIR Staff;1]

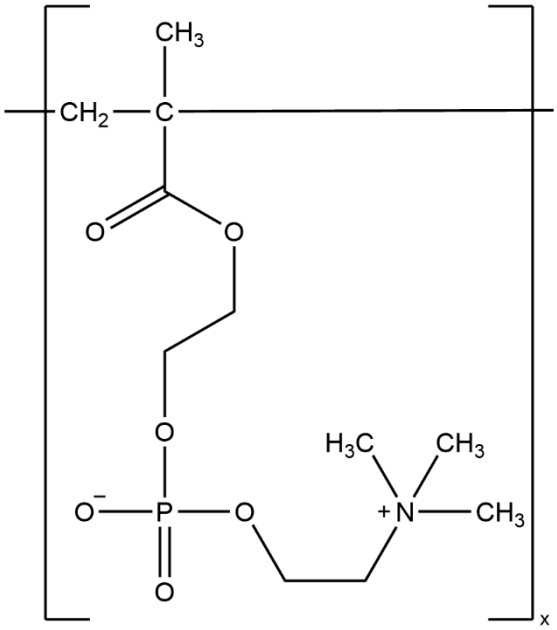
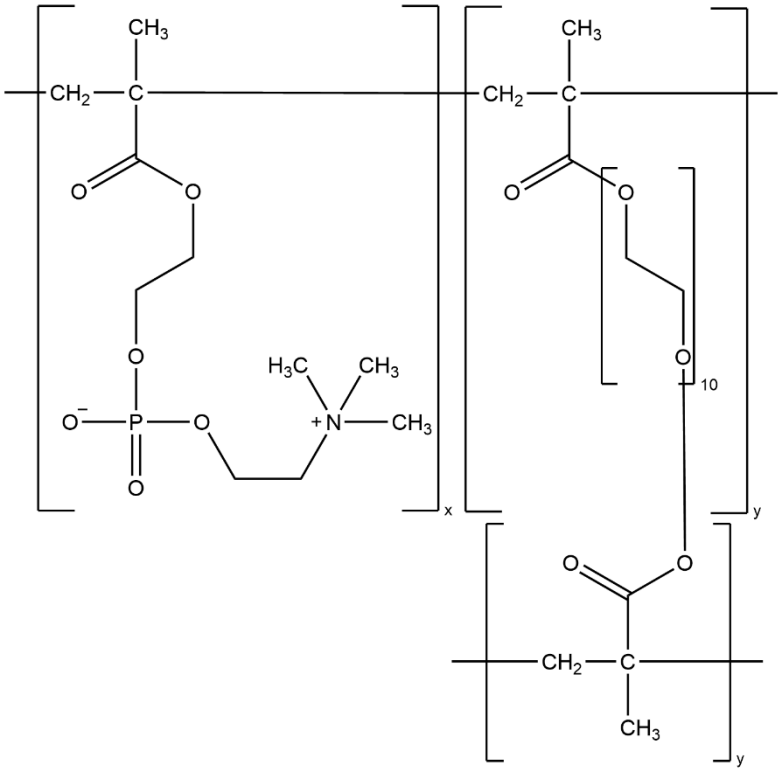
Ingredient/CAS No.	Definition & Structures	Function(s)
Polyphosphorylcholine Glycol Acrylate	Polyphosphorylcholine Glycol Acrylate is the polymer that conforms generally to the formula: 	Film Formers; Skin-Conditioning Agents - Miscellaneous
Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer	Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer is the crosslinked polymer formed from phosphorylcholine glycol methacrylate and PEG-10 dimethacrylate monomers. 	Film Formers; Skin-Conditioning Agents - Humectant
Polyquaternium-10/ Phosphorylcholine Glycol Acrylate Copolymer	Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer is a copolymer of Polyquaternium-10 and phosphorylcholine glycol methacrylate. *Polyquaternium-10 is a polymeric quaternary ammonium salt of hydroxyethyl cellulose reacted with 2,3-epoxypropyltrimonium Chloride. Not enough information available about connectivity to provide a structure.*	Film Formers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient

Table 1. Definitions, Functions, and Idealized Structures of the Ingredients in this Safety Assessment.[CIR Staff;1)]

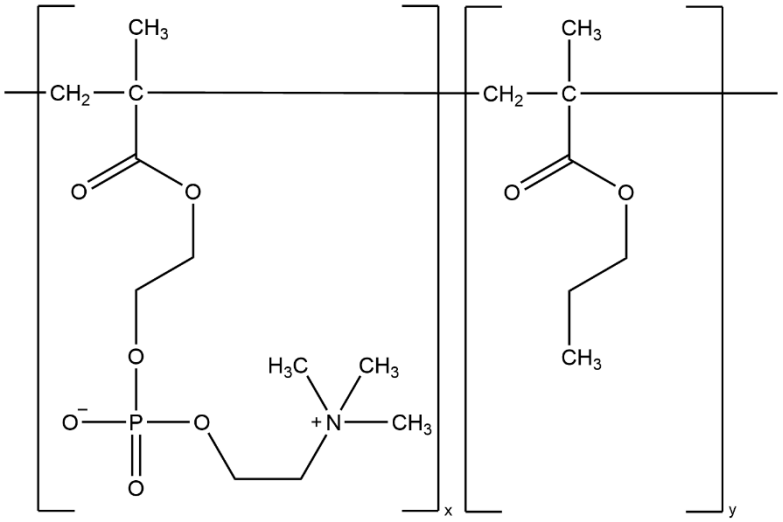
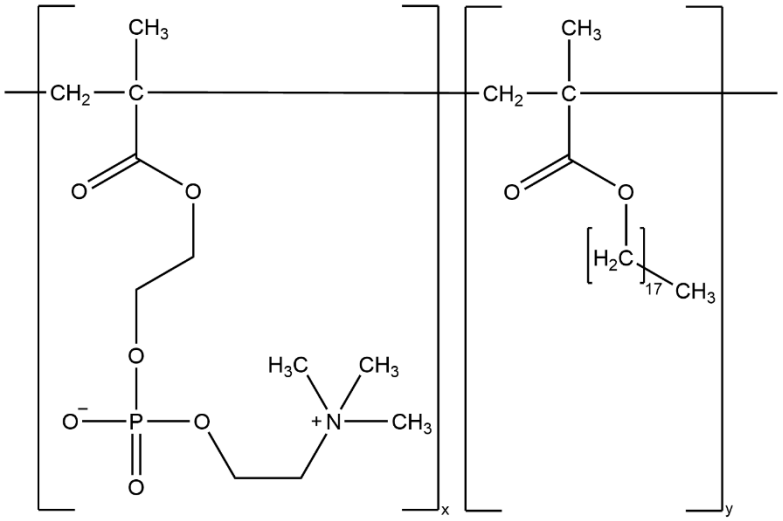
Ingredient/CAS No.	Definition & Structures	Function(s)
Polyquaternium-51 125275-25-4	Polyquaternium-51 is the polymeric quaternary ammonium salt that conforms generally to the formula: 	Film Formers; Skin-Conditioning Agents - Humectant
Polyquaternium-61	Polyquaternium-61 is the polymeric quaternary ammonium salt that conforms generally to the formula: 	Film Formers; Skin-Conditioning Agents - Humectant

Table 2. Chemical properties

Property	Value/Results	Reference
Polyquaternium-51 (tradename mixture)		
Form	Transparent liquid	[6]
M_w (3 different lots)	329,666; 338,513; 338,820	[3]
M_n (3 different lots)	87,071; 83,179; 86,294	[3]
M_w/M_n (3 different lots)	3.79; 4.07; 3.93	[3]
Viscosity (cSt, @ 40ºC)	6 - 60	[6]
Residue on drying (%)	4 - 6	[6]
Polyquaternium-61		
Form	White or pale yellow powder	[6]
M_w (3 different lots)	20,027; 20,182; 19,951	[3]
M_n (3 different lots)	8028; 8298; 7981	[3]
M_w/M_n (3 different lots)	2.50; 2.43; 2.50	[3]
Loss on drying (% max)	5; 1.8	[6]
Polyphosphorylcholine Glycol Acrylate (tradename mixture)		
Form	Transparent liquid	[6]
M_w (3 different lots)	61,179; 61,665; 62,393	[3]
M_n (3 different lots)	40,313; 40,671; 40,762	[3]
M_w/M_n (3 different lots)	1.52; 1.52; 1.53	[3]
Viscosity (cSt, 20ºC)	500 - 3000	[6]
Residue on drying (%)	43 - 48	[6]

Table 3. Frequency (2021) and Concentration of Use (2020) According to Duration and Type of Exposure.[8,9]

	Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer		Phosphorylcholine Glycol Acrylate		Polyquaternium-51	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals*	**NR**	**0.13-0.18**	**12**	**0.0005-0.075**	**275**	**0.000005-0.14**
Duration of Use						
Leave-On	*NR*	*0.13-0.18*	*11*	*0.0005-0.075*	*245*	*0.002-0.14*
Rinse off	*NR*	*NR*	*1*	*NR*	*30*	*0.000005-0.025*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	1	NR	23	0.021-0.05
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation - Sprays	NR	NR	8[a];2[b]	0.0005[b]	79[a];88[b]	0.01[a]
Incidental Inhalation - Powders	NR	NR	2[b]	0.0005[b]	3;88[b]	0.008-0.14[c]
Dermal Contact	NR	0.13-0.18	6	0.0005-0.075	269	0.000005-0.14
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	6	NR	6	0.0005-0.025
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	0.1
Mucous Membrane	NR	NR	NR	NR	6	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Polyquaternium-61	
	# of Uses	Conc. (%)
Totals/Conc. Range	**2**	**0.000006-0.01**
Duration of Use		
Leave-On	*2*	*0.000006-0.0069*
Rinse off	*NR*	*0.01*
Diluted for (bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	NR	0.005
Incidental Ingestion	NR	NR
Incidental Inhalation - Sprays	1[a];1[b]	0.000006
Incidental Inhalation - Powders	1[b]	0.0069
Dermal Contact	2	0.001-0.0069
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	0.000006-0.01
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR

***** Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays
[b]Not specified that 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. Acryloyloxyethyl Phosphorylcholine Polymers With No Reported Uses.[8,9]

C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer
Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer
Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer
Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IN VITRO STUDIES					
Tradename mixture containing 1.4% Polyquaternium-51	Doses of 25, 50, 75, 100, and 125 µl		Skin irritation evaluated in Irrectection® assay. In vitro system involves use of proprietary solution comprised of both proteins and macromolecules in well covered by membrane. Doses applied to membrane diffused into well. According to protocol, proteins and macromolecules undergo conformational changes based on irritancy of diffused material. Conformational changes cause solution to become turbid, and there is direct correlation between irritancy level of material and solution's turbidity. Irritancy measured quantitatively using a spectrophotometer. Samples were left at room temperature for 24 h prior to spectrophotometry.	Mixture classified as a non-irritant over the range of doses tested	[22]
ANIMAL					
Polyquaternium-51 (tradename mixture; 5% aqueous)	Challenge concentrations of 6.25 v/v%, 12.5 v/v%, 25 v/v%, 50 v/v%, and 100 v/v% [For preparation of test solutions, Polyquaternium-51(5 wt % aqueous solution) was defined as 100% v/v% original solution. Thus, the highest test concentration was 100 v/v% solution.]	20 Hartley guinea pigs (Std:Hartley). The test group comprised 10 animals, and negative control (water) and positive control (1-choloro-2,4-dinitrobenzene [DCNB])groups contained 5 animals each.	Sensitization potential evaluated in maximization test. For first induction (on day 1), test substance (100 v/v%) injected intradermally (with water/Freund's complete adjuvant emulsion) in cranial part of scapular region. Prior to second induction (on day 9), skin pretreated with sodium lauryl sulfate (SLS) (10 w/w%). Second induction involved topical 48-h application of Polyquaternium-51 (100 v/v%, under occlusive patch). On day 22 (challenge phase), the following concentrations (in water) were applied under a 48-h occlusive patch: 6.25 v/v%, 12.5 v/v%, 25 v/v%, 50 v/v%, and 100 v/v%. Challenge sites evaluated for reactions at 24 h and 48 h after patch removal.	No skin reactions (erythema or edema) observed at any observation time during study. Polyquaternium-51 exhibited no skin sensitization potency.	[23]

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Polyquaternium-61	25% in petrolatum	5 (3 males, 2 females) albino guinea pigs (Aai: (HA) outbred, viral and antibody free).	Skin sensitization potential evaluated in guinea pig adjuvant and patch test. Additional groups included negative control group (petrolatum; only applied during challenge phase) of 5 and positive control (DNCB) group of 5. Prior to induction phase of sensitization test, topical screens were run using 4 guinea pigs (2 males, 2 females), to determine highest non-irritating concentration for topical application (under open patch conditions). On the same day, test sites treated with decreasing concentrations of test substance (suspended or dissolved in petrolatum). Test substance (0.1 ml) applied for 24 h. Reactions scored at 24 h and 48 h post-application. Because skin irritation not observed, challenge concentration for sensitization test set at maximum concentration of 25%. During first induction, each test animal received intradermal injections (2 cm x 4 cm section of shoulder area) of adjuvant/water emulsion (0.1 ml), followed by 3 topical 24-h applications (occlusive patches, in 25 mm chamber) of test substance (25% in petrolatum, 0.5 ml) on 3 consecutive days (1 application per day). Second week of induction involved pretreatment of patch application sites with SLS. Test substance (25% in petrolatum, 0.4 ml) applied topically (occlusive patches, in 25 mm chamber) for 48 h to induction site of each test animal. Challenge phase initiated 2 wk after topical induction applications. Challenge applications of Polyquaternium-61 (24 h, 25% in petrolatum, 0.1 ml) made to new site on flank (open patch, 5 cm x 5 cm area) of test animals. Negative control (petrolatum) also applied to the flank (5 cm x 5 cm area) of each animal in negative control group. 1,2-dichloro-4-nitrobenzene (DNCB) (up to 1%) similarly applied to 5 positive control animals. Observations relating to erythema, edema, recorded at 24 h and 48 h after challenge applications.	Polyquaternium-61 was not a sensitizer in guinea pigs. DNCB induced sensitization.	[24]
HUMAN					
Foundation containing 0.08125% Polyquaternium-51.	tested neat.	25 subjects (13 women, 12 men)	Skin sensitization evaluated in maximization test. During induction, 48-h occlusive patch (15 mm cotton disc) applications of the undiluted foundation (0.1 ml) made to upper outer arm, volar forearm, or back. Induction site pretreated with 0.25% SLS (0.1 ml; under occlusive patch) for 24 h prior to test substance application. When induction patch placed over weekend, it remained in place for 72 h. SLS patch plus induction patch application sequence repeated for total of 5 induction exposures. After 10-d non-treatment period, challenge phase initiated. Single 48-h occlusive challenge patch application of undiluted foundation (0.1 ml) made to new site on opposite arm, forearm, or side of back. Challenge site pretreated for 1 h with SLS (5% aqueous). Reactions scored at 1 h post-removal and 24 h later.	No adverse or unexpected reactions observed during induction, and there no instances of contact allergy during challenge phase. Foundation did not possess contact-sensitizing potential and not likely to cause contact sensitivity reactions under normal use conditions	[26]

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Serum containing 0.12% Polyquaternium-51	tested neat	212 male and female subjects	Skin sensitization evaluated in human repeated insult patch test. Undiluted product applied, under an occlusive patch, to upper back (between scapulae and waist, lateral to midline). Induction applications made 3 times per week for total of 9 exposures. Reactions scored at 48 h after Monday and Wednesday applications, and 24 h after Sunday removals. After 2-wk non-treatment period, challenge patch applied to original site on back and to new site. Reactions evaluated at time of patch removal and at 72 h and 96 h.	Product did not demonstrate potential for eliciting dermal irritation or sensitization	[25]

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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: June 11, 2021

SUBJECT: Polyquaternium-51 (Lipidure-PMB), Polyquaternium-61 (Lipidure-S) and Phosphorylcholine Glycol Acrylate (Lipidure-HM)

NOF Corporation. 2021. Certificates of analysis Polyquaternium-51 (Lipidure-PMB), Polyquaternium-61 (Lipidure-S) and Phosphorylcholine Glycol Acrylate (Lipidure-HM).

NOF Corporation. 2021. Chemical composition Polyquaternium-51 (Lipidure-PMB), Polyquaternium-61 (Lipidure-S) and Phosphorylcholine Glycol Acrylate (Lipidure-HM).

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To whom it may concern,

Tokyo , Apr , 7 , 2021

CERTIFICATE OF ANALYSIS

We hereby certify that the undermentioned commodity was manufactured by us and the analysis is as follows.

1. Commodity : Lipidure-PMB
2. Quantity : 0.5 KG (0.1 KG net × 5 polyethylene)
3. Destination :
4. Appearance : Transparent Liquid

5. Analysis :

	Lot No :	390411	390613
Identification/IR Spectrum	Adaptation	Adaptation	Adaptation
Identification/Choline	Adaptation	Adaptation	Adaptation
Identification/Phosphate	Adaptation	Adaptation	Adaptation
PH (1 %)	4.0 ～ 6.0	4.7	4.8
Purity/Heavymetals(ppm)	20 MAX	20 MAX	20 MAX
Purity/Arsenic(ppm)	2 MAX	2 MAX	2 MAX
Residue on drying (%)	4.0 ～ 6.0	5.7	5.6
Viscosity (40°C) (cSt)	6.0 ～ 60.0	13.7	14.2
Purity/MPC(ppm)	100 MAX	50 MAX	50 MAX
Purity/BMA(ppm)	100 MAX	10 MAX	10 MAX

Very truly yours,

NOF CORPORATION
OLEO&SPECIALITY CHEMICALS DIVISION
INTERNATIONAL BUSINESS GROUP
+81-3-5424-6704

MANAGER

Quantity (kgs) : 0.2 0.3

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NOF CORPORATION

YEBISU GARDEN PLACE TOWER
20-3 EBISU 4-CHOME, SHIBUYA-KU, TOKYO 150-6019 JAPAN
TEL. +81-3-5424-6600 FAX. +81-3-5424-6800

To whom it may concern,

Tokyo , Apr . 7 . 2021

CERTIFICATE OF ANALYSIS

We hereby certify that the undermentioned commodity was manufactured by us and the analysis is as follows.

1. Commodity : Lipidure-S
2. Quantity : 0.3 KG (0.1 KG net × 3 polyethylene)
3. Destination :
4. Appearance : White or pale yellow powder, odorless or a faint characteristic odor

5. Analysis :

	Lot No :	200422
Identification/IR Spectrum	Adaptation	Adaptation
Loss on Drying (%)	5.0 MAX	1.8
Purity/Heavymetals(ppm)	20 MAX	20 MAX
Purity/Arsenic(ppm)	2 MAX	2 MAX

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MANAGER

Quantity (kgs) : 0.3

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20-3 EBISU 4-CHOME, SHIBUYA-KU, TOKYO 150-6019 JAPAN
TEL. +81-3-5424-6600 FAX. +81-3-5424-6800

To whom it may concern,

Tokyo , Apr . 7 , 2021

CERTIFICATE OF ANALYSIS

We hereby certify that the undermentioned commodity was manufactured by us and the analysis is as follows.

1. Commodity : Lipidure-HM
2. Quantity : 0.5 KG (0.1 KG net × 5 polyethylene)
3. Destination :
4. Appearance :
5. Analysis :

	Lot No :	591101
Description (Transparent Liquid)	Adaptation	Adaptation
Description (Faint, Characteristic Odor)	Adaptation	Adaptation
Description (Colorless)	Adaptation	Adaptation
Identification/IR Spectrum	Adaptation	Adaptation
Identification/Choline	Adaptation	Adaptation
Identification/Phosphate	Adaptation	Adaptation
PH(2.5%aq)	4.0 ～ 6.0	4.5
Viscosity 20°C (cPs)	500 ～ 3000	1280
Purity/Heavymetals(ppm)	20 MAX	20 MAX
Purity/Arsenic(ppm)	2 MAX	2 MAX
Residue on drying (%)	43.0 ～ 48.0	44.5

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NOF CORPORATION
OLEO&SPECIALITY CHEMICALS DIVISION
INTERNATIONAL BUSINESS GROUP
+81-3-5424-6704

MANAGER

Quantity (kgs) : 0.5

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CHEMICAL COMPOSITION

Material name	INCI Name	Chemical Name	
		CAS No.	Content
Lipidure-PMB	POLYQUATERNIUM-51	2-(Methacryloyloxy)ethyl 2-(trimethylammonio)ethyl phosphate-n-butylmethacrylate copolymer	
		125275-25-4	5%
	WATER	Water	
		7732-18-5	95%
Lipidure-S	POLYQUATERNIUM-61	2-(Methacryloyloxy)ethyl 2-(trimethylammonio)ethyl phosphate-stearylmethacrylate copolymer	
		144514-08-9	100%
Lipidure-HM	POLYPHOSPHORYLCHOLINE GLYCOL ACRYLATE	Poly (2-(Methacryloyloxy)ethyl 2-(trimethylammonio)ethyl phosphate)	
		67881-99-6	40%
	WATER	Water	
		7732-18-5	54.85%
	BUTYLENE GLYCOL	1,3-Butylene glycol	
		107-88-0	5%
	METHYLPARABEN	Methyl p-hydroxybenzoate	
		99-76-3	0.15%

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NOF Corporation
2021

Product name	Lot. No.	Mn	Mw	Mw/Mn
Lipidure-PMB	310113	87,071	329,666	3.79
	310311	83,179	338,513	4.07
	310411	86,294	338,820	3.93
Lipidure-HM	590701	40,313	61,179	1.52
	591101	40,671	61,665	1.52
	501101	40,762	62,393	1.53
Lipidure-S	201121	8,028	20,027	2.50
	210221	8,298	20,182	2.43
	210222	7,981	19,951	2.50

※Average value analyzed with n = 3 for each lot

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Copy of the original document
Y. Hara
November 1, 2011

03-K-060
October 31, 2003

Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)

(Translated from the Report in Japanese)

For

NOF CORPORATION

Hatano Research Institute,
Food and Drug Safety Center

Distributed for Comment Only -- Do Not Cite or Quote

Title	Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)
Contract No.	03-K-060 (July 7, 2003)
Sponsor	NOF CORPORATION
Project No.	I-03-041
Test Article	Lipidure-PMB
Test Item	Skin sensitization test
Test Method	Maximization test
Start of Study	July 7, 2003
End of Study	October 31, 2003
Storage of Documents	The archives of Hatano Research Institute
Retention Term	Ten years from the completion of the test The storage period after that is determined through consultations with the sponsor.
Testing Facility	Hatano Research Institute, Food and Drug Safety Center (729-5 Ochiai, Hadano, Kanagawa 257-8523, Japan)
Management	Hiroshi Ono, M.D. (sealed) October 31, 2003 Director-General Hatano Research Institute, Food and Drug Safety Center

Distributed for Comment Only -- Do Not Cite or Quote

Title	Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)
Study Director	Chiaki Matsuoka (Laboratory of Safety Testing)
Project Leader	Yukiko Kanazawa
Project Members (*person responsible)	
Treatment and Observation	Kazuhiro Shimozawa*, Chiaki Matsuoka, Yukiko Kanazawa, Tomomi Sekino, Kazuichi Shukunobe, Aki Matsumoto, Yukio Kamiya, Yutaka Takaoka, Hajime Yamaguchi, Hiroshi Hidaka
Preparation of Test Solutions	Hiroko Inada*, Hiroko Komeya, Yukiko Kanazawa
Animal Husbandry (including quarantine)	Shinji Horiuchi*, Chiaki Matsuoka, Yukiko Kanazawa, Kazuhiro Shimozawa, Tomomi Sekino, Kazuichi Shukunobe, Aki Matsumoto, Yukio Kamiya, Yutaka Takaoka, Hajime Yamaguchi, Hiroshi Hidaka
Control of Test Article	Katsuhiko Saegusa*, Hatsumi Kato

This study was conducted in accordance with "Guidelines for Toxicity Studies of Drugs" (Pharmaceutical Affairs Bureau, Japanese Ministry of Health and Welfare, Notification Yakusin No. 1-24, September 11, 1989), and in compliance with "Good Laboratory Practice Standard Ordinance for Nonclinical Laboratory Studies on Safety of Drugs" (Japanese Ministry of Health and Welfare, Ordinance No. 21, March 26, 1997) and "Implementation of Ordinance on Standard of Conduct of Nonclinical Laboratory Studies of Drug Safety" (Pharmaceutical Affairs Bureau, Japanese Ministry of Health and Welfare, Notification Yakuhatsu No. 424, March 27, 1997).

October 31, 2003

Chiaki Matsuoka (signed and sealed)
Study Director

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CONFIDENTIAL

Quality Assurance Certificate

Title: Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)

Project No.: I-03-041

The state of inspections by the Quality Assurance Unit on this study was as follows:

Item of inspection	Date of inspection	Date of report to management and study director
Protocol	July 7, 2003	July 7, 2003
Amendment to the protocol		
I-03-041-No. 1	July 25, 2003	July 25, 2003
I-03-041-No. 2	July 25, 2003	July 28, 2003
I-03-041-No. 3	September 26, 2003	September 26, 2003
Acceptance and quarantine of animals	July 10, 2003	July 10, 2003
Preparation of test solutions and intradermal injection for sensitization	July 29, 2003	July 29, 2003
Challenge treatment	August 19, 2003	August 19, 2003
Reading of skin reactions	August 21, 2003	August 22, 2003
Draft report (I) and raw data	September 5, 2003	September 8, 2003
Draft report (II)	October 31, 2003	October 31, 2003
Final report	October 31, 2003	October 31, 2003

This study was conducted in accordance with "Good Laboratory Practice Standard Ordinance for Nonclinical Laboratory Studies on Safety of Drugs" (Japanese Ministry of Health and Welfare, Ordinance No. 21, March 26, 1997) and "Implementation of Ordinance on Standard of Conduct of Nonclinical Laboratory Studies of Drug Safety" (Pharmaceutical Affairs Bureau, Japanese Ministry of Health and Welfare, Notification Yakuhatsu No. 424, March 27, 1997). This report accurately describes the methods and procedures used in the study, and the reported results accurately reflect the raw data of the study.

October 31, 2003

Kazuki Yamaguchi (sealed)

Quality Assurance Manager

Hatano Research Institute, Food and Drug Safety Center

[Contents]

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[Summary]

To evaluate the contact sensitizing potency of Lipidure-PMB (L-PMB), a skin sensitizing test in guinea pigs (Maximization test) was carried out.

For the first induction (intradermal induction, Day 1 of the experiment), 100 v/v% L-PMB was injected intradermally with Freund's complete adjuvant to the cranial part of the scapular region in guinea pigs. Prior to the second induction, the skin in the area including the first induction treatment was pretreated with 10w/w% sodium lauryl sulfate by topical application without covering. On the following day (Day 9 of the experiment), the second induction (topical induction) was performed by topical application of 100 v/v% L-PMB to the pretreated area using a patch with an occlusive dressing for 48 hours. On Day 22 of the experiment, 100, 50, 25 12.5 and 6.25 v/v% L-PMB aqueous solution and water for injection were topically applied for 24 hours using patches with occlusive dressings for the challenge treatment. The challenged sites were observed 24 and 48 hours after removal of the patches and dressings. Then, their appearances were evaluated using the classification system by the Draize method.

As a result, animals in the L-PMB treated group showed no skin reactions, including erythema or edema, at any time point of observation at any concentration of the compound.

From these results, L-PMB caused no positive reaction in this study. Thus, it was concluded that Lipidure-PMB exhibited no skin sensitizing potency in guinea pigs under the condition of this study.

[Purpose of the Study]

As a part of safety evaluation of Lipidure-PMB, a skin sensitization test in guinea pigs (Maximization test) was carried out in accordance with "Guidelines for Toxicity Studies of Drugs" (Pharmaceutical Affairs Bureau, Japanese Ministry of Health and Welfare, Notification Yakusin No. 1-24, September 11, 1989), and in compliance with "Good Laboratory Practice Standard Ordinance for Nonclinical Laboratory Studies on Safety of Drugs" (Japanese Ministry of Health and Welfare, Ordinance No. 21, March 26, 1997) and "Implementation of Ordinance on Standard of Conduct of Nonclinical Laboratory Studies of Drug Safety" (Pharmaceutical Affairs Bureau, Japanese Ministry of Health and Welfare, Notification Yakuhatsu No. 424, March 27, 1997).

[Test Methods]

1. Test Article

Test article, Lipidure-PMB [abbreviation: L-PMB; chemical name: 2-methacryloyloxyethyl

phosphorylcholine-butyl methacrylate copolymer (5 wt% aqueous solution); CAS no. 12527-25-4; molecular weight: approximately 500,000; lot no. 330311] was colorless liquid consisting of 2-methacryloyloxyethyl phosphorylcholine/*n*-butyl methacrylate copolymer (4 to 6 wt%) and water (94 to 96 wt%). The test article was supplied by NOF CORPORATION on June 25, 2003 and stored at room temperature (24 to 27°C) until use. A list of reagents and equipments used in this study are shown below.

Name (abbreviation)	Lot No.	Manufacturer
Reagents		
Olive oil	HI-30*	Kozakai Pharmaceutical
Ethanol	ASP7564	Wako Pure Chemical Industries
Water for injection JP (water for injection)	A207TT*	Hikari Pharmaceutical
White Vaseline For SLS (Vaseline)	SEF7514	Wako Pure Chemical Industries
Equipments		
Bytac VF-81 (VF-81)	—	Saint-Gobain Norton
Filter paper No. 131 (filter paper) [approximately 2×4 cm, lined with VF-81]	—	Toyo Roshi Kaisha
Elastic adhesive bandage	—	Alcare
Lint patch [approximately 1.5×1.5 cm, lined with VF-81]	—	Yabane Jirushi Honpo

*, Production number

For preparation of test solutions, L-PMB (5 wt% aqueous solution) was defined as 100 v/v% original solution. L-PMB was serially diluted with water for injection in the preliminary test and the challenge phase. A new bottle of L-PMB was opened at each use.

Concentrations of L-PMB in the main test were decided based on the preliminary test stated below. The highest concentration was set at 100 v/v% original solution in the preliminary test. Test solutions were prepared at each use for every application. Based on the Material Safety Data Sheet (MSDS) and other document supplied by the sponsor indicating that the test article is stable at room temperature, it was judged that the test article had remained stable during the experimental period of this test. It was confirmed by the sponsor (non-GLP) that the test article was stable in the solvent at the concentrations of 2.5 v/v% and 0.05 v/v% for 4 hours under room temperature.

2. Positive Control Substance

As a positive control, 1-chloro-2,4-dinitrobenzene (hereafter referred to as DNCB; CAS no. 97-00-7) was selected. DNCB, used in this study, was manufactured by Wako Pure Chemical Industries (lot no. ELF1735, appearance and property: light yellow crystal, expiry date: April 2006). DNCB was dissolved in olive oil for the first induction (intradermal induction) and the second induction (topical induction), and dissolved in ethanol for the challenge. The dosages of DNCB for the first and second inductions were both 0.1 w/v%. Those for the challenge were 0.1 and 0.01 w/v%. It was known that the dosages used would show skin sensitizing reactions. The DNCB solutions were prepared at each use.

3. Immunoenhancer and Enhancer for Sensitizing Potency

For the first induction (intradermal induction), Freund's complete adjuvant (hereafter referred to as FCA; lot no. 166864; manufacturer: Difco Lab.) was used as an immunoenhancer. Equal volumes (v/v) of FCA and water for injection or L-PMB were taken into two lure-locked syringes connected with a polyethylene tube, and were mixed into a water-in-oil (w/o) type emulsion. Equal volumes of FCA and DNCB were mixed. These mixtures were prepared at each use.

In order to enhance sensitizing potency, 10 w/w% sodium lauryl sulfate (hereafter referred to as 10 w/w% SLS) was pretreated at the second induction. The 10 w/w% SLS consisted of Vaseline (a base) and SLS (lot no. ACE1216; manufacturer: Wako Pure Chemical Industries) and was stored in a refrigerator until use.

4. Animals and Breeding

Four-week-old Hartley guinea pigs (Std: Hartley, clean animals) were purchased from Japan SLC. The purchased animals were quarantined and acclimatized for seven days, including the day of arrival. Thereafter, the animals were grouped and were further acclimatized until the day before the starting day of treatment. Neither general condition nor body weight gain in any of the animals showed any abnormalities during the acclimatization period. Details of the purchased animals are shown below.

Date of arrival, number of animals at arrival, sex and their body weights

Date of arrival:	July 10, 2003
Number of animals at arrival and sex:	28 females (nulliparous and not pregnant)
Body weights at arrival:	249-276 g
Body weights at the end of quarantine:	296-353 g
Body weights of animals for the preliminary test on the day of treatment (6 animals):	345-394 g
Body weights of animals for the main test on the starting day of the experiment (20 animals):	378-450 g

The breeding room was environmentally conditioned with the permissible room temperature of 21.0 to 25.0°C, the permissible relative humidity of 40.0 to 75.0%, a preset ventilation exchange rate of approximately 15 times/hour, and a 12-hour light/12-hour dark cycle (lighting from 7:00 to 19:00; no lighting from 19:00 to 7:00). The animals were housed in metal hanging cages with a metal-mesh bottom (260 W×380 D×200 H mm). Two or three animals were housed in each cage during the quarantine period, and then they were housed individually from the day of grouping. They were provided with pellet feed (RC4, Oriental Yeast) and allowed to receive drinking water (Hadano City municipal water) *ad libitum*.

The measured values for room temperature and relative humidity in the animal room during the breeding period were 22.5 to 24.0°C and 54.5 to 70.5%, respectively, and both were within the permissible

ranges. Analyses for the pellet feed and the drinking water revealed that they had no contamination that might affect the results of the present test.

5. Grouping and Identification of Animals

Animals were assigned to groups by the method of stratified random sampling on the basis of their body weights at the end of quarantine. Among the surplus animals of the main test, six animals were selected for the preliminary test in descending order of body weight. For the identification of animals in the same cage during the quarantine period, their heads and dorsa were painted with an oily marker pigment. After grouping, the individual animal number of each animal was painted on its dorsal auricle with the oily marker pigment. For the identification of cages during the quarantine period, the animal card was attached on which project number and arrival animal numbers were written. After grouping, differently colored animal cards were attached on which project number, animal number and name of test article were written. The cages were arranged in order of animal numbers. The surplus animals and the animals used in the preliminary test were euthanized using carbon dioxide gas on the day of the first induction.

6. Preliminary Test

In order to determine concentrations of L-PMB for each application in the main test, the irritation of the skin and systemic toxicity of L-PMB in guinea pigs were examined in accordance with the guideline.

Topical application	
Test material:	L-PMB
Concentrations (v/v%):	100, 50, 25 and 10
Vehicle:	Water for injection

Intradermal injection	
Test material:	L-PMB
Concentrations (v/v%):	100, 50, 25, 10, 5, 1, 0
Vehicle:	Water for injection

The hair of the treatment region was clipped and shaved with a hair clippers and a shaver on the day before topical application and intradermal injection. A volume of 0.1 mL of L-PMB of each concentration (see above) was applied to the lateral abdomen of three animals with occlusive contact for 24 hours, or was injected intradermally in the dorsal region of the other three animals according to the application methods for the main test. As a result, no systemic toxicity was observed by any route of application. The skin

reactions at administered sites were evaluated 24 and 48 hours after removal of the patches and dressings or 24 and 48 hours after intradermal injection against the criteria for the main test. As a result, L-PMB caused no irritation reaction by any route of application.

From the results of the preliminary test, 100 v/v% L-PMB was selected for the first induction (intradermal induction) and the second induction (topical induction). For the challenge, 100 v/v% L-PMB was selected as the most concentrated test solution, and 50, 25, 12.5 and 6.25 v/v% L-PMB aqueous solutions and water for injection were selected as the test solutions.

7. Main Test

1) Reasons for selection of the test method

Based on the property of L-PMB and its solubility in the vehicle, it was judged that L-PMB could be given intradermally. Therefore, this study adopted the Maximization test[1)] in accordance with the guideline. The dose levels, method of administration, route of administration, frequency of administration and duration of administration were conducted according to the methods described in the guideline.

2) Group constitution and number of animals

Group		Number of animals
Group I:	L-PMB treated group	10
Group II:	Negative control group	5
Group III:	Positive control group	5
	Total	20 animals

3) Observation of general condition and body weight measurements

The general condition of all the animals was checked once a day throughout the breeding period. All the animals were weighed on the day when animals for the preliminary test were treated, the starting day of the experiment [the day of the first induction (the day of intradermal induction, Day 1 of the experiment)], on the starting day of the second induction (the starting day of topical induction, Day 9 of the experiment), on Day 15 of the experiment, on the starting day of challenge (Day 22 of the experiment) and on the final day of the experiment (the reading day of skin reactions 48 hours after removal of the patches and dressings, Day 25 of the experiment). The mean and standard deviation of the body weights in each group were calculated.

4) First induction (intradermal induction)

The hair in the cranial part of the scapular region was clipped off with a hair clippers on the day before intradermal induction. On Day 1 of the experiment, after marking the six sites (symmetrically aligned A to C in Fig. 1) in an approximately 2×4 cm area in the cranial part of the scapular region with the oily marker pigment, 0.1 mL of each test solution (A to C, see below) was injected intradermally.

A (Left and right sides of the cranial part)

Groups I to III: Water-in-oil (w/o) type emulsion of FCA and water for injection (1:1)

B (Left and right sides of the middle part)

Group I: 100 v/v% L-PMB

Group II: Water for injection

Group III: 0.1 w/v% DNCB solution in olive oil

C (Left and right sides of the caudal part)

Group I: Water-in-oil (w/o) type emulsion of FCA and 100 v/v% L-PMB (1:1)

Group II: Water-in-oil (w/o) type emulsion of FCA and water for injection (1:1)

Group III: Mixture of FCA and 0.2 w/v% DNCB solution in olive oil (1:1)

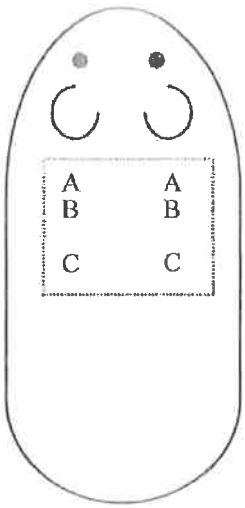

Fig. 1

5) Second induction (topical induction)

On Day 8 of the experiment, 7 days after the first induction (intradermal induction), the area including the intradermal injection sites (i.e., the area surrounded with dotted line in Fig. 1), where the hair had been clipped and shaved off with a hair clippers and a shaver on the day before, was treated with 10 w/w% SLS without covering.

On the following day, Day 9 of the experiment, after the SLS was wiped off, a patch of filter paper absorbing 0.2 mL of each test solution (see below) was placed on the skin where the SLS had been applied, and was held in place using an elastic adhesive bandage. The patch and dressing were removed after 48 hours occlusive contact. The application site was not wiped off because no residue of test solution was observed after removal of the patch and dressing.

Group I: 100 v/v% L-PMB

Group II: Water for injection

Group III: 0.1 w/v% DNCB solution in olive oil

6) Challenge phase

On Day 22 of the experiment, 13 days after the starting day of the second induction (topical induction), lint patches absorbing 0.1 mL of each test solution (see below) were placed on the left and right sides of the lateral abdomen (sites 1 to 6, shown in Fig. 2) of each animal, in areas where the hair had been clipped and shaved off with a hair clippers and a shaver on the day before. The patches were covered with elastic adhesive bandages and held in place for 24 hours.

After removal of the patches and dressings, four corners of the challenged sites of each test solution were marked with the oily marker pigment, then the hair of the challenged sites and their surrounding was shaved lightly with a shaver. The patched sites were not wiped off because no residue of test solution was observed after removal of the patches and dressings.

Groups I and II:

[Left lateral abdomen]

Cranial part		
Ventral site	1	100 v/v% L-PMB
Dorsal site	2	50 v/v% L-PMB aqueous solution
Caudal part	3	25 v/v% L-PMB aqueous solution
[Right lateral abdomen]		
Cranial part		
Dorsal site	4	12.5 v/v% L-PMB aqueous solution
Ventral site	5	6.25 v/v% L-PMB aqueous solution
Caudal part	6	Water for injection

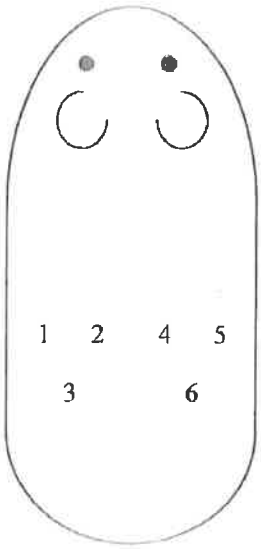

Fig. 2

Group III:

[Left lateral abdomen]

Ventral site	1	0.1 w/v% DNCB solution in ethanol
Dorsal site	2	0.01 w/v% DNCB solution in ethanol
[Right lateral abdomen]		
	4	Ethanol

7) Reading of reactions and evaluation

The appearance of the skin at each challenged sites was evaluated 24 and 48 hours after removal of the patches and dressings using the following classification system by the Draize method (1959).

(1) Erythema and eschar formation (erythema)	Numerical grading
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema to slight eschar formation (reflecting deep injury)	4
	[Maximum: 4]

(2) Edema formation (edema)	Numerical grading
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond exposure area)	4
	[Maximum: 4]
	[Total maximum for (1) and (2): 8]

Animals that showed reactions of grade 1 or greater were regarded as positive. The fractional response and the mean response were calculated by the following formulae:

Fractional response:

(Number of positive animals in the group/Total number of animals in the group) × 100

Mean response:

Sum of numerical grades in the group/Total number of animals in the group

The skin sensitizing potency of L-PMB was determined comprehensively using the results of the fractional response and the mean response, their time courses and dose-responses considering the responses of the negative and positive control groups.

8) Photographs

Color photographs of the test sites of all the animals were taken at the reading made 24 hours after removal of the patches and dressings, as supplemental records.

[Unexpected Conditions That Might Have Affected the Quality of the Study and Deviations from the Protocol]

During the test period, there were no unexpected situations that might have affected the quality of the study nor were there any deviations from the protocol, except for the deviations stated below.

The concentrations of Lipidure-PMB for the challenge phase should have been 100, 20, 4, 0.8 and 0.16 v/v%. Nevertheless, the challenge treatment was actually performed with the concentrations of 100, 50, 25, 12.5 and 6.25 v/v% on August 19, 2003. However, it was judged that this deviation had not affected the evaluation of this study because positive response was not observed at the highest concentration for the

challenge phase (100 v/v% L-PMB). In addition, it was judged that the data of the test article on stability test (non-GLP data) had not affected the reliability of the test results because they were confirmed and provided from the sponsor with the responsibility.

[Results of the Study and Discussion]

Neither mortality nor changes in general condition attributable to the administration of the test article were observed during the test period. Individual body weights of the animals of this study are shown in Table 1. No animals showed abnormal body weight gain.

The results of the skin sensitization test are summarized in Table 2. Tables 3-1 to 4-2 show the individual skin reactions graded numerically by reading the reactions 24 and 48 hours after removal of the patches and dressings. Photographs of representative cases in each group, which were taken at the reading made 24 hours after removal of the patches and dressings, are attached to this report (Photos 1 to 6).

When the animals in the L-PMB treated group were challenged with 100, 50, 25, 12.5 or 6.25 v/v% L-PMB, no positive reaction (erythema or edema) was observed at any time-point. The same animals did not show any positive reaction to the challenge with water for injection.

When the animals in the negative control group were challenged with 100, 50, 25, 12.5 or 6.25 v/v% L-PMB or water for injection, none of them showed positive reaction.

When the animals in the positive control group were challenged with 0.1 w/v% DNCB, all of them showed positive reactions (100%) at both time-points and the mean responses were 6.0 and 6.2 at 24- and 48-hour readings, respectively. In addition, when these animals were challenged with 0.01 w/v% DNCB, all of them showed positive reactions (100%) at both time-points and the mean responses were 4.8 and 5.0 at 24- and 48-hour readings, respectively. The same animals did not show any positive reaction to the challenge with ethanol.

From these results, L-PMB caused no positive reaction under the condition of this study. Thus, it was concluded that Lipidure-PMB exhibited no skin sensitizing potency in guinea pigs under the condition of this study.

[References]

1) Magnusson, B., Kligman, A.M.: The identification of contact allergens by animal assay. The guinea pig maximization test. J. Invest. Derm. 52: 268-276 (1969)

Table 1 Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)
Individual body weight (g)

Group	Animal No.	The day when animals for the preliminary test were treated	Day 1 of the experiment (The day of the first induction)	Day 9 of the experiment (The starting day of the topical induction)	Day 15 of the experiment	Day 22 of the experiment (The starting day of the challenge)	Day 25 of the experiment (The Reading day of the skin reactions 48 hours after removal of the patches and dressings)
I L-PMB	I- 1	361	421	463	483	502	490
	I- 2	378	427	444	488	538	517
	I- 3	383	444	489	504	542	547
	I- 4	369	428	464	493	532	522
	I- 5	352	396	450	439	480	483
	I- 6	402	450	498	535	577	582
	I- 7	373	400	454	465	500	505
	I- 8	374	409	467	486	528	529
	I- 9	369	417	455	491	523	511
	I- 10	374	407	462	475	512	507
	Mean	374	420	465	486	523	519
	S.D.	±13	±18	±17	±25	±27	±29
II Negative Control	II- 1	378	431	471	493	515	527
	II- 2	378	378	421	459	466	472
	II- 3	364	414	466	495	538	540
	II- 4	363	413	446	474	507	512
	II- 5	378	437	475	525	560	562
	Mean	372	415	456	489	517	523
	S.D.	±8	±23	±22	±25	±35	±34
III Positive Control	III- 1	356	406	430	453	470	474
	III- 2	369	429	456	471	518	505
	III- 3	373	409	442	463	513	502
	III- 4	359	384	445	482	513	508
	III- 5	377	436	495	499	555	555
	Mean	367	413	454	474	514	509
	S.D.	±9	±21	±25	±18	±30	±29

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Table 2 Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)

Summary of the test result

Group	Induction treatment			Challenge treatment		Skin reactions			
		Concentration (v/v%)				Reading at 24-hour [a]		Reading at 48-hour [a]	
	Treatment substances	The first	The second	Treatment substances	Concentration (v/v%)	Fractional response	Mean response	Fractional response	Mean response
I L-PMB	L-PMB	100	100	L-PMB	100	0	0.0	0	0.0
					50	0	0.0	0	0.0
					25	0	0.0	0	0.0
					12.5	0	0.0	0	0.0
					6.25	0	0.0	0	0.0
					0*				
II Negative Control	water for injection			L-PMB	100	0	0.0	0	0.0
					50	0	0.0	0	0.0
					25	0	0.0	0	0.0
					12.5	0	0.0	0	0.0
					6.25	0	0.0	0	0.0
					0*				
III Positive Control	DNCB (w/v%)	0.1	0.1	DNCB (w/v%)	0.1	100	6.0	100	6.2
					0.01	100	4.8	100	5.0
					0**	0	0.0	0	0.0

Fractional response = (Number of positive animals in the group/Total number of animals in the group) × 100

Mean response = Sum of numerical grades in the group/Total number of animals in the group

[a] Elapsed time after removal of the patches and dressings

*Water for injection

**Ethanol

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Table 3-1 Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)
Individual data of the reading made 24 hours after removal of the patches and dressings

Group	Animal No.	Substances for the challenge											
		100 v/v% L-PMB		50 v/v% L-PMB		25 v/v% L-PMB		12.5 v/v% L-PMB		6.25 v/v% L-PMB		Water for injection	
		Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
I L-PMB	I - 1	0	0	0	0	0	0	0	0	0	0	0	0
	I - 2	0	0	0	0	0	0	0	0	0	0	0	0
	I - 3	0	0	0	0	0	0	0	0	0	0	0	0
	I - 4	0	0	0	0	0	0	0	0	0	0	0	0
	I - 5	0	0	0	0	0	0	0	0	0	0	0	0
	I - 6	0	0	0	0	0	0	0	0	0	0	0	0
	I - 7	0	0	0	0	0	0	0	0	0	0	0	0
	I - 8	0	0	0	0	0	0	0	0	0	0	0	0
	I - 9	0	0	0	0	0	0	0	0	0	0	0	0
	I -10	0	0	0	0	0	0	0	0	0	0	0	0
	F.R.[a]	0		0		0		0		0		0	
	M.R.[b]	0.0		0.0		0.0		0.0		0.0		0.0	
II Negative Contrtol	II - 1	0	0	0	0	0	0	0	0	0	0	0	0
	II - 2	0	0	0	0	0	0	0	0	0	0	0	0
	II - 3	0	0	0	0	0	0	0	0	0	0	0	0
	II - 4	0	0	0	0	0	0	0	0	0	0	0	0
	II - 5	0	0	0	0	0	0	0	0	0	0	0	0
	F.R.[a]	0		0		0		0		0		0	
	M.R.[b]	0.0		0.0		0.0		0.0		0.0		0.0	

Classification system

Erythema and eschar formation (erythema)	Numerical grading
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema to slight eschar formation (reflecting deep injury)	4

Edema formation (edema)	Numerical grading
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond exposure area)	4

[a] Fractional response = (Number of positive animals in the group/Total number of animals in the group) x 100
[b] Mean response = Sum of numerical grades in the group/Total number of animals in the group

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Table 3-2 Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)
Individual data of the reading made 48 hours after removal of the patches and dressings

Group	Animal No.	Substances for the challenge											
		100 v/v% L-PMB		50 v/v% L-PMB		25 v/v% L-PMB		12.5 v/v% L-PMB		6.25 v/v% L-PMB		Water for injection	
		Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
I L-PMB	I - 1	0	0	0	0	0	0	0	0	0	0	0	0
	I - 2	0	0	0	0	0	0	0	0	0	0	0	0
	I - 3	0	0	0	0	0	0	0	0	0	0	0	0
	I - 4	0	0	0	0	0	0	0	0	0	0	0	0
	I - 5	0	0	0	0	0	0	0	0	0	0	0	0
	I - 6	0	0	0	0	0	0	0	0	0	0	0	0
	I - 7	0	0	0	0	0	0	0	0	0	0	0	0
	I - 8	0	0	0	0	0	0	0	0	0	0	0	0
	I - 9	0	0	0	0	0	0	0	0	0	0	0	0
	I -10	0	0	0	0	0	0	0	0	0	0	0	0
	F.R.[a]	0		0		0		0		0		0	
	M.R.[b]	0.0		0.0		0.0		0.0		0.0		0.0	
II Negative Contrtol	II - 1	0	0	0	0	0	0	0	0	0	0	0	0
	II - 2	0	0	0	0	0	0	0	0	0	0	0	0
	II - 3	0	0	0	0	0	0	0	0	0	0	0	0
	II - 4	0	0	0	0	0	0	0	0	0	0	0	0
	II - 5	0	0	0	0	0	0	0	0	0	0	0	0
	F.R.[a]	0		0		0		0		0		0	
	M.R.[b]	0.0		0.0		0.0		0.0		0.0		0.0	

Classification system of the skin reactions is referred to Table 3-1
[a] Fractional response
[b] Mean response

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Table 4-1 Skin Sensitization Test of Lipidure-PMB in Guinea Pigs
(Maximization Test)
Individual data of the reading made 24 hours after removal of the patches and dressings

Group	Animal No.	Substances for the challenge					
		0.1 w/v% DNCB		0.01 w/v% DNCB		Ethanol	
		Erythema	Edema	Erythema	Edema	Erythema	Edema
III Positive Control	III- 1	4	2	2	1	0	0
	III- 2	4	2	3	2	0	0
	III- 3	4	2	4	2	0	0
	III- 4	4	2	3	2	0	0
	III- 5	4	2	3	2	0	0
	F.R.[a]	100		100		0	
	M.R.[b]	6.0		4.8		0.0	

Classification system of the skin reactions is referred to Table 3-1.
[a] Fractional response
[b] Mean response

Table 4-2 Skin Sensitization Test of Lipidure-PMB in Guinea Pigs
(Maximization Test)
Individual data of the reading made 48 hours after removal of the patches and dressings

Group	Animal No.	Substances for the challenge					
		0.1 w/v% DNCB		0.01 w/v% DNCB		Ethanol	
		Erythema	Edema	Erythema	Edema	Erythema	Edema
III Positive Control	III- 1	4	2	2	1	0	0
	III- 2	4	2	4	2	0	0
	III- 3	4	2	4	2	0	0
	III- 4	4	3	3	2	0	0
	III- 5	4	2	3	2	0	0
	F.R.[a]	100		100		0	
	M.R.[b]	6.2		5.0		0.0	

Classification system of the skin reactions is referred to Table 3-1.
[a] Fractional response
[b] Mean response

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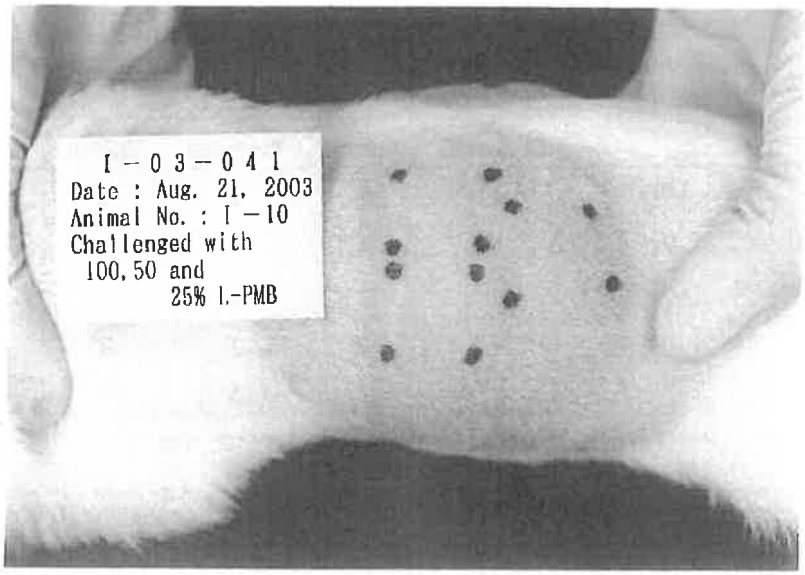

Photo 1 Photo of the left lateral abdomen of an animal in the L-PMB treated group (Animal No. I-10, photographed at the reading made 24 hours after removal of the patches and dressings)

Substances for the challenge (numerical grade):

Cranial part:	Dorsal site:	50 v/v% L-PMB	(Erythema, 0; Edema, 0)
	Ventral site:	100 v/v% L-PMB	(Erythema, 0; Edema, 0)
Caudal part:		25 v/v% L-PMB	(Erythema, 0; Edema, 0)

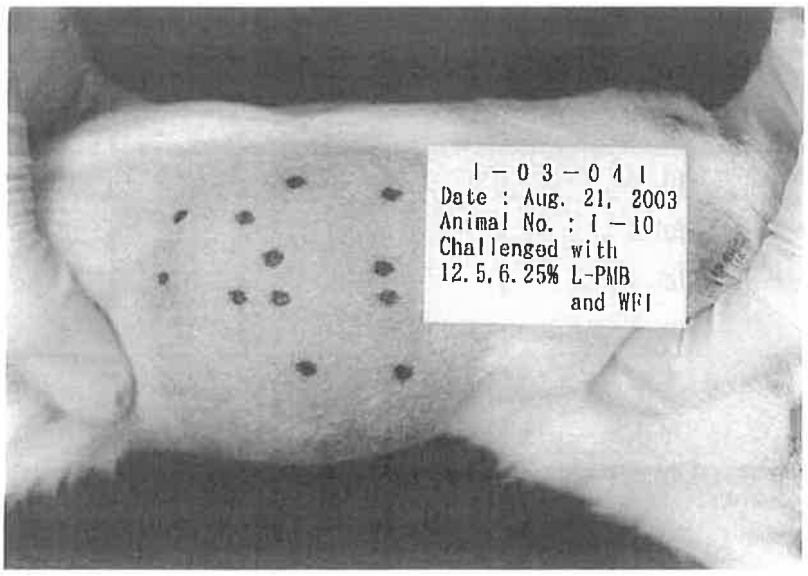

Photo 2 Photo of the right lateral abdomen of an animal in the L-PMB treated group (Animal No. I-10, photographed at the reading made 24 hours after removal of the patches and dressings)

Substances for the challenge (numerical grade):

Cranial part:	Dorsal site:	12.5 v/v% L-PMB	(Erythema, 0; Edema, 0)
	Ventral site:	6.25 v/v% L-PMB	(Erythema, 0; Edema, 0)
Caudal part:		Water for injection	(Erythema, 0; Edema, 0)

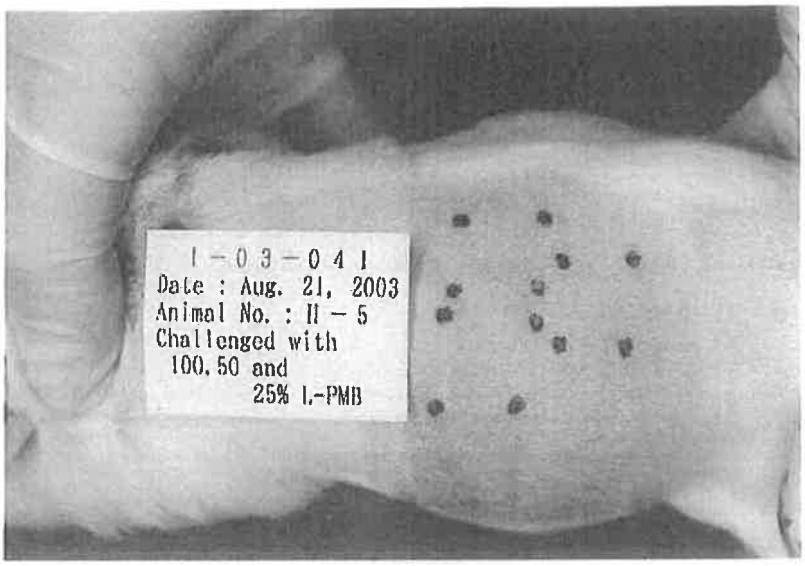

Photo 3 Photo of the left lateral abdomen of an animal in the negative control group (Animal No. II-5, photographed at the reading made 24 hours after removal of the patches and dressings)

Substances for the challenge (numerical grade):

Cranial part:	Dorsal site:	50 v/v% L-PMB	(Erythema, 0; Edema, 0)
	Ventral site:	100 v/v% L-PMB	(Erythema, 0; Edema, 0)
Caudal part:		25 v/v% L-PMB	(Erythema, 0; Edema, 0)

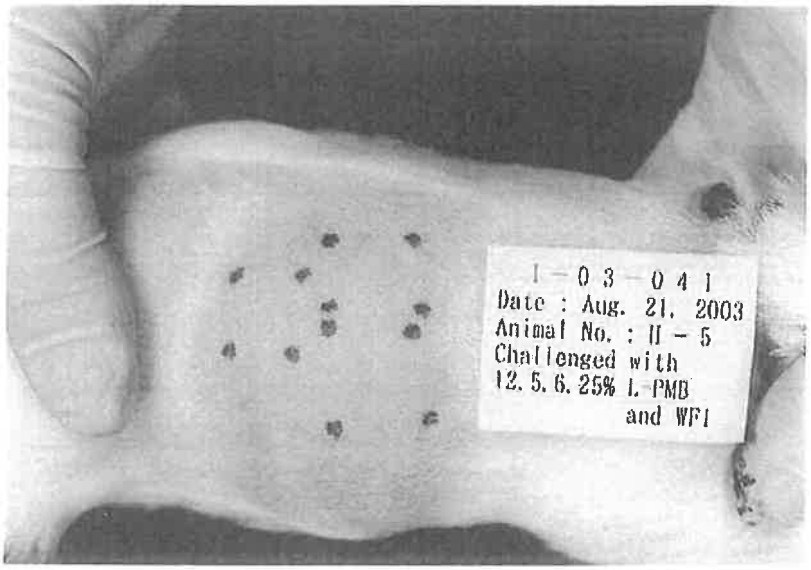

Photo 4 Photo of the right lateral abdomen of an animal in the negative control group (Animal No. II-5, photographed at the reading made 24 hours after removal of the patches and dressings)

Substances for the challenge (numerical grade):

Cranial part:	Dorsal site:	12.5 v/v% L-PMB	(Erythema, 0; Edema, 0)
	Ventral site:	6.25 v/v% L-PMB	(Erythema, 0; Edema, 0)
Caudal part:		Water for injection	(Erythema, 0; Edema, 0)

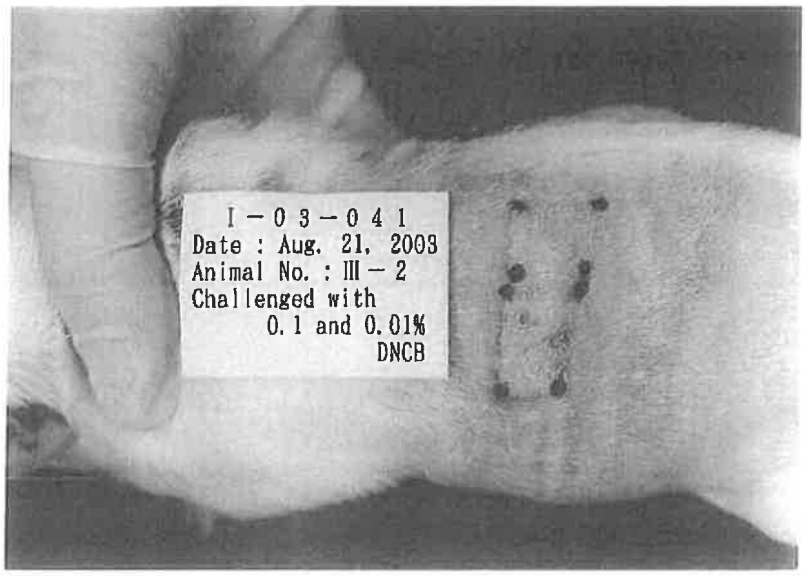

Photo 5 Photo of the left lateral abdomen of an animal in the positive control group (Animal No. III-2, photographed at the reading made 24 hours after removal of the patches and dressings)

Substances for the challenge (numerical grade):

Dorsal site:	0.01 w/v% DNCB	(Erythema, 3; Edema, 2)
Ventral site:	0.1 w/v% DNCB	(Erythema, 4; Edema, 2)

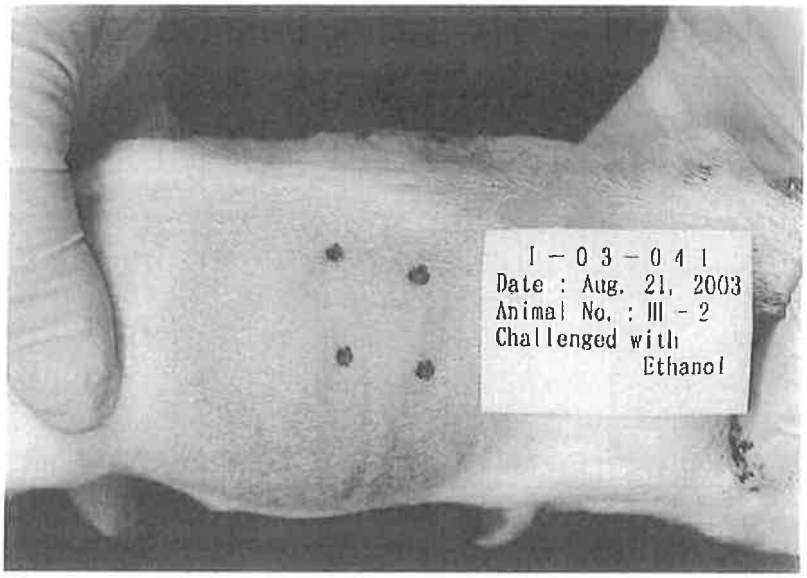

Photo 6 Photo of the right lateral abdomen of an animal in the positive control group (Animal No. III-2, photographed at the reading made 24 hours after removal of the patches and dressings)

Substance for the challenge (numerical grade):

Ethanol	(Erythema, 0; Edema, 0)

Statement for Translation

Title Skin Sensitization Test of Lipidure-PMB in Guinea Pigs (Maximization Test)

Project No. I-03-041

This translation of the original report in Japanese has been performed and approved by the following personnel.

Translated by T. Hara Date November 1, 2011

Takumi Hara, Ph.D.

Approved by Chiaki Matsuoka Date November 1, 2011

Chiaki Matsuoka

Study Director

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FINAL REPORT

CLIENT:

Creative Strategy, Inc.
High Park Nihonbashi Bldg. 4F
2-45-4 Nihonbashi-Hamacho
Chuo-ku, Tokyo 103-0007, Japan

SPONSOR:

NOF CORPORATION
5-10 Tokodai, Tsukuba-shi,
Ibaraki-ken, 300-2635, Japan

TEST:

Guinea Pig Adjuvant and Patch Test

TEST ARTICLE:

Lipidure - S

POSITIVE CONTROL ARTICLE:

1-Chloro-2,4-Dinitrobenzene, Lot# 03110TA

EXPERIMENT REFERENCE NUMBER:

T05-0034

Christine Hendricks 6/24/05
Christine Hendricks
Quality Assurance Associate

6/24/05
Steven Nitka
Vice President
Laboratory Director

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QUALITY ASSURANCE UNIT STATEMENT

Study No.: T05-0034

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. These studies have been performed with strict adherence to the Good Laboratory Practice Act (21 CFR 58) and in accordance to standard operating procedures and applicable standard protocols. The study is listed on this facility's Master Schedule. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date(s) listed below. The findings of these inspections have been reported to management and the Study Director. All materials and data pertinent to this study will be stored in the Archive Facility at 70 New Dutch Lane, Fairfield, New Jersey, 07004, unless specified otherwise, in writing by the Sponsor.

Dates of biophase/data inspection:

Biophase inspections: March 17, 2005, March 18, 2005, March 22, 2005, March 23, 2005, March 29, 2005, April 12, 2005, April 13, 2005, April 14, 2005, May 11, 2005, May 12, 2005, May 13, 2005, May 17, 2005, May 18, 2005, May 19, 2005, May 24, 2005, June 7, 2005, June 8, 2005, June 9, 2005

Data inspection: June 21, 2005

Professional personnel involved:

Steven Nitka, B.S.	-	Vice President Laboratory Director (Study Director)
Lillian Deniza, B.S.	-	Laboratory Supervisor
Melissa Pandorf, B.S.	-	Technician
Christine Hendricks	-	Quality Assurance Associate

The representative signature of the Quality Assurance Unit on the front page signifies that this study has been performed in accordance with standard operating procedures and applicable study protocols.

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Final Report Summary

CLIENT: Creative Strategy, Inc.
STUDY NO.: T05-0034
REFERENCE: Y. Yoshioka
TEST ARTICLE: Lipidure - S
TEST ARTICLE RECEIPT DATE: March 2, 2005
EXPERIMENTAL INTERVAL: May 11, 2005 to June 9, 2005

Guinea Pig Adjuvant and Patch Test

Method: Five (3M:2F) Hartley-strain albino, outbred, viral antibody free, guinea pigs (SPF Hartley guinea pig Aai: (HA) Outbred), 390 - 440 grams, were utilized as the test group. An additional five (2M:3F) Hartley-strain guinea pigs, 380 - 420 grams, were utilized as the control group. For induction, each animal in the test group received intradermal injections of an adjuvant/water emulsion, followed by three (3) topical applications of the test article. During the second week of the induction phase, another topical application of the test article was made to the induction site of each animal in the test group. Two (2) weeks after the topical induction applications, the challenge applications were made. These 24 hour challenge applications were made to virgin sites on the flank of each animal in the test and control groups, at 25% in petrolatum. Observations of erythema, edema and other effects were recorded 24 and 48 hours after the challenge applications.

Results:

	Challenge	
Index:	Incidence	Severity
Group	Test/Control	Test/Control
Scoring Interval:		
24 Hours:	0.00/0.00	0.00/0.00
48 Hours:	0.00/0.00	0.00/0.00

Conclusion: This test article, at the concentrations tested, is not a sensitizer in guinea pigs under the conditions of this test.

Incidence Index = Number of animals exhibiting a 1 or greater erythema score divided by the number of animals observed at challenge.
Severity Index = The sum of the erythema scores, 1 or greater, divided by the number of animals observed at challenge.

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Final Report Summary

CLIENT: Creative Strategy, Inc.
STUDY NO.: T05-0034
REFERENCE: Y. Yoshioka
POSITIVE CONTROL ARTICLE: 1-Chloro-2,4-Dinitrobenzene, Lot# 03110TA
TEST ARTICLE RECEIPT DATE: (in-house reagent)
EXPERIMENTAL INTERVAL: March 17, 2005 to April 14, 2005

Guinea Pig Adjuvant and Patch Test

Method: Five (3M:2F) Hartley-strain albino, outbred, viral antibody free, guinea pigs (SPF Hartley guinea pig Aai: (HA) Outbred), 372 - 434 grams, were utilized as the test group. An additional five (2M:3F) Hartley-strain guinea pigs, 348 - 412 grams, were utilized as the control group. For induction, each animal in the test group received intradermal injections of an adjuvant/water emulsion, followed by three (3) topical applications of the article. During the second week of the induction phase, another topical application of the article was made to the induction site of each animal in the test group. Two (2) weeks after the topical induction applications, the challenge applications were made. These 24 hour challenge applications were made to virgin sites on the flank of each animal in the test and control groups, at the screen determined, highest non-irritating concentration of 0.1%. Observations of erythema, edema and other effects were recorded 24 and 48 hours after the challenge applications.

Results:

	Challenge	
Index:	Incidence	Severity
Group	Test/Control	Test/Control
Scoring Interval:		
24 Hours:	1.00/0.00	2.40/0.00
48 Hours:	1.00/0.00	2.00/0.00

Conclusion: This positive control article, at the concentrations tested, is a sensitizer in guinea pigs under the conditions of this test.

Incidence Index = Number of animals exhibiting a 1 or greater erythema score divided by the number of animals observed at challenge.
Severity Index = The sum of the erythema scores, 1 or greater, divided by the number of animals observed at challenge.

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Guinea Pig Adjuvant and Patch Test

Objective:

This test was designed to determine if the test article is a potential contact sensitizer in guinea pigs. The method draws from that of Magnusson and Kligman[1] and Maguire and Cipriano[2]. This protocol was designed to satisfy the requirements of the Japanese Ministry of Health, Labor and Welfare.

Test System:

Hartley albino, outbred, viral antibody free, guinea pigs (SPF Hartley guinea pig Aai: (HA) Outbred), male and female, approximately four to six (4-6) weeks of age, were used. The animals were obtained through a suitably licensed dealer. They were carefully checked upon receipt and prior to test initiation for respiratory or intestinal disease, skin eruptions, mucosal membrane irritation, postural difficulties and general condition.

The animals were acclimated for at least seven (7) days prior to test initiation. They were housed in stainless steel cages in a temperature controlled room with a 12 hour light/dark cycle and were identified through individual markings as well as a cage label. The room temperature was controlled to comply with Animal Welfare regulations with an approximate range of 60° to 85° F. The humidity, with a preferred range of 30 to 70%, was also monitored. Diet consisted of Lab Diet Certified Guinea Pig Diet #5026, as well as water, *ad libitum*.

Guinea pig sensitization reactions are well documented in the scientific literature and have been used extensively in studies of this type.

Method:

Screening:

Prior to the induction phase of the test, topical screens were run. The highest non-irritating concentration (HNIC) for a topical application, under "open patch" conditions, of each of the articles was determined. Four (2M:2F) animals, for each article, were prepared by close-clipping the dorsal area of their trunks with an Oster® small animal clipper equipped with a #40 (surgical) head.

[1]Magnusson, B. & Kligman, A.M.: *Allergic Contact Dermatitis in the Guinea Pig.* (Thomas, Springfield 1970).
[2] Maguire, Jr, H.C. & Cipriano: *Split Adjuvant Technique.* Current Problems in Dermatology, vol. 14, pp. 107-113.

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During all shaving procedures, care was taken to avoid abrading the skin. On the same day, four (4) sites on each animal were treated with the appropriate article at decreasing concentrations, suspended or dissolved in petrolatum[3]. One-tenth (0.1) of a milliliter of appropriate article was applied to each site. After 24 hours, any excess article was wiped away with ethanol[4]. The test sites were scored (see Table 1) approximately 24 and 48 hours after article application.

As no irritation was observed on the test article animals, the challenge was to be conducted using the article at the maximum concentration (25%). Because irritation was observed on the positive control animals, the concentration below that which provides the least irritation was to be used for the challenge phase of the study (0.1%).

Induction:

Five (5) animals, mixed sex, were used for each of the test article and the positive control article test groups. Five (5) additional animals were used as negative control groups for each article. Only the test article and positive control article groups underwent the induction procedures. The negative control groups were not exposed to the articles until the challenge phase.

The induction phase of the test was divided into two (2) stages:

A) Intradermal Injection

A two by four (2 x 4) cm section of the shoulder area was shaved as detailed previously. Intradermal injections were made at each of the four (4) corners of the shaved area. Each injection consisted of one-tenth of one milliliter (0.1 ml) of a 50/50 emulsion of TiterMax® (TM)[5] and distilled water. Immediately after the injections were made, scratches in the shape of a grid were made with the same needle. The grid pattern was within the boundaries of the injections. Occlusive patches, containing the appropriate article (0.5 ml) at the maximum concentration (or in the case of the positive control, an exaggerated concentration), were then applied for 24 hours. The occlusive patch consisted of a 25 mm Hilltop Chamber (with the cotton patch). The animals were wrapped after dosing with a piece of three (3) inch Elastoplast® elastic tape (Beiersdorf Inc., Norwalk, CT), with a three (3) inch wide strip of Pure Latex Dental Dam (HCM - Hygenic Corporation, Malaysia). The scratching and occlusive patching procedures were repeated once per day for three (3) consecutive days.

[3]Vaseline® Pure Petroleum Jelly, Chesebrough Ponds Inc., Greenwich, Connecticut (or equivalent).
[4]Fisher Scientific, Pittsburgh, Pennsylvania
[5]Titermax Corporation, Inc. 6971 Peachtree Industrial Boulevard, Suite 103, Norcross, Georgia 30092.

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Induction (continued)

B) Topical Application

Because the screens showed that a maximum concentration of the test article is non-irritating, the same test area on the test article test animals was again shaved and then treated with ten (10) percent sodium lauryl sulfate (SLS)[6], in petroleum jelly, six (6) days after the injections were made. One-half of one milliliter (0.5 ml) of the SLS suspension was applied under "open patch" conditions. The SLS may have enhanced possible sensitization by provoking a mild inflammatory reaction.

Seven (7) days after the injections, the test article was suspended at 25% in petrolatum, and the positive control article was suspended in petrolatum at 0.25% weight per volume. Four-tenths (0.4) of a milliliter of each test article mixture was applied to each site via a 25 mm Hilltop Chamber (with the cotton patch). The animals were wrapped after dosing, with a piece of three (3) inch Elastoplast® elastic tape (Beiersdorf Inc., Norwalk, CT), that has been split at one (1) end and lined on the adhesive side, opposite the split, with a three (3) inch wide strip of Pure Latex Dental Dam (HCM - Hygenic Corporation, Malaysia). The wrap and patch were removed at 48 hours.

Challenge:

Two (2) weeks after the topical induction application, the challenge applications were made. Prior to dosing, a five by five (5 x 5) cm area of the flank of each guinea pig, in the test and positive control article groups, as well as the negative control groups, was shaved as detailed previously. The test or positive control article, at the screen determined highest non-irritating concentration, was applied to the flanks of the appropriate animals.

One-tenth (0.1) of a milliliter of appropriate article was applied to each site under "open patch" conditions. Approximately 24 hours after article application, remaining article was removed with an ethanol wipe and the test site was shaved if necessary. Each test site was then scored according to the attached Draize Scale (Table 1). Twenty-four hours later, each site was again scored.

[6]Sigma Chemical Company, St. Louis, Missouri.

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Two (2) indices were calculated from the erythema scores, one (1) to evaluate the incidence of erythema (reaction) and the other to evaluate the severity of erythema. The indices for incidence and severity were calculated for the control group and for the induction group from the erythema responses observed at the 24 and 48 hour post-challenge examinations. The incidence index was calculated by counting the number of animals showing an erythema response [one (1) or greater] for a specified time period and dividing by the number of test sites (animals) examined at the time period (# responses/# per group). The severity index was calculated by adding the erythema scores for a specified time period and dividing by the number of scores added (sum of erythema scores/# scores added). The two (2) indices were used to evaluate the sensitization potential of the test article. The edema scores were noted but were not used in the calculation of any indices. If there was any question as to the outcome of the test, the animals could have been rechallenged the following week.

Initial and terminal body weights were recorded for the non-screen animals. Sacrificing was accomplished via carbon dioxide asphyxiation. All animals appeared healthy throughout the study.

Characterization of the articles and/or any dilutions thereof, was not performed by this facility.

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Guinea Pig Adjuvant and Patch (Test Article)

The scoring scale used is presented in Table 1. Results of the screening procedures are presented in Table 2. Individual test group results are presented in Table 3. Individual control group results are presented in Table 4.

Guinea Pig Adjuvant and Patch (Positive Control Article)

The scoring scale used is presented in Table 1. Results of the screening procedures are presented in Table 5. Individual test group results are presented in Table 6. Individual control group results are presented in Table 7.

Summaries of all results are found preceding the text.

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Table 1

Scoring Criteria for Skin Reactions

ERYTHEMA FORMATION	
No erythema	0
Questionable erythema	T
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Total possible erythema score =	4

EDEMA FORMATION	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (area raised approximately 1 mm)	3
Severe edema (area raised approximately 1 mm and extending beyond area of exposure)	4
Total possible edema score =	4

Total possible primary irritation score = 8

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Table 2

Guinea Pig Adjuvant and Patch Topical Screen

Individual Results

Lipidure - S

Dosage: 0.1 ml

Animal #/Sex	Site / Concentration	1 25%	2 10%	3 5%	4 1%
		Scores			
1M	24 Hours	0/0	0/0	0/0	0/0
	48 Hours	0/0	0/0	0/0	0/0
2F	24 Hours	0/0	0/0	0/0	0/0
	48 Hours	0/0	0/0	0/0	0/0

Animal #/Sex	Site / Concentration	3 25%	4 10%	1 5%	2 1%
		Scores			
3M	24 Hours	0/0	0/0	0/0	0/0
	48 Hours	0/0	0/0	0/0	0/0
4F	24 Hours	0/0	0/0	0/0	0/0
	48 Hours	0/0	0/0	0/0	0/0

Raw Data Page: 058703

Scores = Erythema/Edema
All concentrations are dilutions of the test article, in petrolatum.

Table 3

Guinea Pig Adjuvant and Patch

Lipidure - S

Test Group

Animal No./Sex	Initial Wt.(g)	INDUCTION Injection & Topical Dose[1] 1 2 3	Day 6[2] SLS Treatment	Day 7[3] Topical Application	Remove Wrap @ 48 hrs	CHALLENGE Challenge[4] Application	Ethanol Wipe @24 hrs
1 M	440	X X X	X	X	X	X	X
2 M	414	X X X	X	X	X	X	X
3 M	390	X X X	X	X	X	X	X
4 F	408	X X X	X	X	X	X	X
5 F	390	X X X	X	X	X	X	X

Raw Data Page: 058728

[1]1st: TiterMax®/distilled water (1:1) x 4 (0.1 ml inj.) & topical dosage (0.5 ml) @ 25% in petrolatum
2nd: topical dosage (0.5 ml) @ 25% in petrolatum
3rd: topical dosage (0.5 ml) @ 25% in petrolatum
[2]Sodium lauryl sulfate @ 10% in petroleum jelly (0.5 ml/dose)
[3]Test article at 25% in petrolatum (0.4 ml/dose)
[4]Test article at 25% in petrolatum (0.1 ml/dose)
X = Procedure completed

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Table 3
(continued)

Guinea Pig Adjuvant and Patch

Lipidure - S

Test Group

Animal No./Sex	Scores @ 24 hrs	48 hrs	Terminal Wt. (g)
1 M	0/0	0/0	492
2 M	0/0	0/0	412
3 M	0/0	0/0	466
4 F	0/0	0/0	474
5 F	0/0	0/0	480

Raw Data Page: 058728

Scores = Erythema/Edema

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Table 4

Guinea Pig Adjuvant and Patch

Control Group

Lipidure - S

Animal No./Sex	Initial Wt. (g)	CHALLENGE Challenge[1] Application	Ethanol Wipe @ 24 hrs	Scores @ 24 hrs	Scores @ 48 hrs	Term Wt. (g)
1 M	398	X	X	0/0	0/0	552
2 M	420	X	X	0/0	0/0	548
3 F	390	X	X	0/0	0/0	472
4 F	380	X	X	0/0	0/0	430
5 F	400	X	X	0/0	0/0	466

Raw Data Page: 058729

Scores = Erythema/Edema

[1]Test article at 25% in petrolatum (0.1 ml/dose)

X = Procedure completed

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Table 5

Guinea Pig Adjuvant and Patch Topical Screen

Individual Results

1-Chloro-2,4-Dinitrobenzene, Lot# 03110TA

Dosage: 0.1 ml

Animal #/Sex	Site / Concentration	1 / 1.0%	2 / 0.5%	3 / 0.25%	4 / 0.1%
		Scores			
1M	24 Hours	2/2	3/2	2/1	T/0
	48 Hours	2/2B	3/3B	1/0	0/0
2F	24 Hours	2/1	2/1	1/0	0/0
	48 Hours	2/2	2/1	0/0	0/0

Animal #/Sex	Site / Concentration	3 / 1.0%	4 / 0.5%	1 / 0.25%	2 / 0.1%
		Scores			
3M	24 Hours	2/1	2/1	2/0	T/0
	48 Hours	2/1	2/1	1/0	0/0
4F	24 Hours	2/1	1/0	1/0	0/0
	48 Hours	2/1	1/0	T/0	0/0

Raw Data Page: 058506

Scores = Erythema/Edema
All concentrations are dilutions, in petrolatum, of the test article.
B = Blanching

Table 6

Guinea Pig Adjuvant and Patch

1-Chloro-2,4-Dinitrobenzene, Lot# 03110TA

Test Group

		INDUCTION						CHALLENGE	
Animal No./Sex	Initial Wt.(g)	Injection & Topical Dose[1] 1	2	3	Day 6[2] SLS Treatment	Day 7[3] Topical Application	Remove Wrap @ 48 hrs	Challenge[4] Application	Ethanol Wipe @24 hrs
1 M	398	X	X	X	N/A	X	X	X	X
2 M	434	X	X	X	N/A	X	X	X	X
3 M	396	X	X	X	N/A	X	X	X	X
4 F	388	X	X	X	N/A	X	X	X	X
5 F	372	X	X	X	N/A	X	X	X	X

Raw Data Page: 058511

[1]1st: TiterMax®/distilled water (1:1) x 4 (0.1 ml inj.) & topical dosage (0.5 ml) @ 0.25% in petrolatum
2nd: topical dosage (0.5 ml) @ 0.25% in petrolatum
3rd: topical dosage (0.5 ml) @ 0.25% in petrolatum
[2]Sodium lauryl sulfate @ 10% in petroleum jelly (0.5 ml/dose)
[3]Test article at 0.25% in petrolatum (0.4 ml/dose)
[4]Test article at 0.1% in petrolatum (0.1 ml/dose)
X = Procedure completed
N/A = Not applicable

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Table 6
(continued)

Guinea Pig Adjuvant and Patch

1-Chloro-2,4-Dinitrobenzene, Lot# 03110TA

Test Group

Animal No./Sex	Scores @ 24 hrs	48 hrs	Terminal Wt. (g)
1 M	2/1	2/2	496
2 M	3/2	2/2	518
3 M	3/2	2/2	484
4 F	2/1	2/1	492
5 F	2/1	2/1	494

Raw Data Page: 058511

X = Procedure completed
Scores = Erythema/Edema

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Table 7

Guinea Pig Adjuvant and Patch

Control Group

1-Chloro-2,4-Dinitrobenzene, Lot# 03110TA

			CHALLENGE				
Animal No./Sex		Initial Wt. (g)	Challenge[1] Application	Ethanol Wipe @ 24 hrs	Scores @ 24 hrs	48 hrs	Term Wt. (g)
1	M	412	X	X	0/0	0/0	564
2	M	406	X	X	0/0	0/0	601
3	F	348	X	X	0/0	0/0	451
4	F	366	X	X	0/0	0/0	489
5	F	356	X	X	0/0	0/0	462

Raw Data Page: 058512

Scores = Erythema/Edema

[1]Test article at 0.1% in petroleum jelly (0.1 ml/dose)

X = Procedure completed

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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: April 29. 2021

SUBJECT: Polyquaternium-51

Anonymous. 2012. Repeated insult patch test (Marzulli and Maibach Method) (serum containing 0.12% Polyquaternium-51).

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COPY

[redacted]

Final Report

Repeated Insult Patch Test
(Marzulli and Maibach Method)

CLIENT: [redacted]

ATTENTION: [redacted]

TEST MATERIAL: [redacted]

Serum containing 0.12% Polyquaternium-51

[redacted] **STUDY NUMBER:** [redacted]

AUTHORIZED SIGNATURES:

[redacted]

[redacted] **M.D.**
President/Medical Director

[redacted] **Ph.D.**
Executive Vice President/COO

[redacted] **M.D.**
Dermatologist

REPORT DATE: **April 25, 2012**

[redacted]

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[redacted]

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: [redacted]

Start Date: February 6, 2012

Completion Date: April 13, 2012

The clinical study listed above was conducted in accordance with [redacted] Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

[redacted]

April 25, 2012
Date

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[redacted]

FINAL REPORT

REPEATED INSULT PATCH TEST (MARZULLI AND MAIBACH METHOD)

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

INVESTIGATIVE SITE

[redacted]

TEST MATERIAL

The following test material was provided by [redacted] and received by [redacted] on January 6, 2012:

Test Material	Test Condition	Patch Type
[redacted]	Test as Received	Occlusive*

The test material was coded with the following [redacted] identification number:

[redacted]

STUDY DATES

This study was initiated on February 6, 2012 and was completed on April 13, 2012.

* Occlusive Strip with Flexcon® (Brady Medical, Mesquite,TX)

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[redacted]

PANEL SELECTION

Each subject was assigned a permanent [redacted] identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Panelist Profile/Medical History Form provided by [redacted] prior to the study (Subject Demographics - Appendix I). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

Inclusion Criteria

a. Male and female subjects between the ages of 18 and 70 years;

b. Subjects who do not exhibit any skin diseases which might be confused with a skin reaction from the test material;

c. Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;

d. Subjects who agree to refrain from getting patches wet during the course of the study;

e. Subjects willing to sign an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

f. Subjects who have completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

g. Subjects in generally good health who have a current Subject Profile/Medical History on file;

h. Subjects who are dependable and able to follow directions as outlined in the protocol.

Exclusion Criteria

a. Female subjects who are pregnant or nursing;

b. Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

c. Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

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TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back, between the scapulae and the waist, lateral to the midline.

The test material was applied to the same site three times per week (Monday, Wednesday, and Friday) for a total of nine applications. However, the schedule may have been modified to accommodate inclement weather, holidays, or missed applications. At the discretion of the Study Director, the test material may have been applied on two consecutive days during the Induction Phase or a makeup day may have been added at the end of the Induction Phase.

The sites were graded by a [redacted] technician for dermal irritation and sensitization 48 hours after application of the patches on Monday and Wednesday and 24 hours after removal of the patches on Sunday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scores

-	= 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

If a "++" reaction or greater occurred, the test site did not receive any further Induction Phase patches, and the test material was instead applied to an adjacent virgin site. If a "++" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than "++" may have been changed.

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[redacted]

TEST METHOD (Continued)

Following a 2-week rest period, the challenge patches were applied to the previously treated test sites on the back (original) and to newly defined sites, previously unexposed (virgin). After 48 hours, the patches were removed by a [redacted] technician, and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 72 and 96 hours.

STUDY RELATED COMMENT

Due to an early closing, nine subjects could not return for the 96 hour evaluation.

RESULTS

This study was initiated with 227 subjects. Fifteen subjects discontinued study participation for reasons unrelated to the test material. A total of 212 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 212 subjects and under the conditions of this study, the sample identified as [redacted] was dermatologist tested and did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by [redacted] as specified in [redacted] Standard Operating Procedures [redacted], unless designated otherwise by the Sponsor.

[redacted]

TABLE I

Tabulation of Individual Scores

Test Material:	[redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
1A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9A	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
10A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17A	?	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
19A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
26A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29A	-	-	-	-	-	+	?	-	-	-	-	-	-	-	-
30A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
31A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
32A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
35A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
36A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
37A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
38A	-	Discontinued													
39A	Discontinued														
40A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
43A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
45A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46A	-	-	-	-	Discontinued										
47A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
49A	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
50A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
51A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
52A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
53A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
54A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
55A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
56A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
57A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
58A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
59A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
60A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
61A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
62A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
63A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
64A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
65A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
66A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
67A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
68A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
69A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
70A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
71A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
73A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
74A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
75A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
76A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
77A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
78A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
79A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
80A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
81A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
82A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
83A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
84A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
85A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
86A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
87A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
88A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
89A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
90A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
91A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
92A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
93A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
94A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
95A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
96A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
97A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
98A	-	-	?	?	-	-	-	-	-	-	-	-	-	-	-
99A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
100A	-	Discontinued													

O = Original Site
V = Virgin Site

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
101A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
102A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
103A	-	-	-	-	-	-	-	-	-	-	-	-	?	-	?
104A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
105A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
106A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
107A	Discontinued														
107RA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
108A	-	-	-	-	-	-	Discontinued								
109A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
110A	-	-	-	-	-	-	-	-	-	-	-	-	?	-	-
111A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
112A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

R = Replacement Subject
O = Original Site
V = Virgin Site

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
1B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5B	-	-	-	-	-	-	-	-	-	X	X	-	-	-	-
6B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13B	-	-	-	-	-	Discontinued									
14B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17B	-	-	-	-	-	-	Discontinued								
18B	-	-	-	-	-	-	-	-	-	X	X	-	-	-	-
19B	Discontinued														
19RB	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
20B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22B	Discontinued														
22RB	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

R = Replacement Number
X = Subject Absent
O = Original Site
V = Virgin Site

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
26B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
30B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
31B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
32B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
35B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
36B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
37B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
38B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
39B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
40B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
43B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
45B	-	-	-	-	-	-	-	-	-	Discontinued					
46B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
47B	-	-	-	-	-	-	-	Discontinued							
48B	-	-	-	-	-	-	-	-	-	-	-	X	X	-	-
49B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

X = Subject Absent
O = Original Site
V = Virgin Site

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
51B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
52B	-	-	Discontinued												
53B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
54B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
55B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
56B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
57B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
58B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
59B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
60B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
61B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
62B	-	-	Discontinued												
63B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
64B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
65B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
66B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
67B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
68B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
69B	-	-	-	Discontinued											
70B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
71B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
73B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
74B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
75B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

X = Subject Absent
O = Original Site
V = Virgin Site

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
76B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
77B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
78B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
79B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
80B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
81B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
82B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
83B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
84B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
85B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
86B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
87B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
88B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
89B	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
90B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
91B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
92B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
93B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
94B	-	-	-	-	-	-	-	-	-	-	+	-	?	-	-
95B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
96B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
97B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
98B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
99B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
100B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

X = Subject Absent
O = Original Site
V = Virgin Site

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
101B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
102B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
103B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
104B	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-
105B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
106B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
107B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
108B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
109B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
110B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
111B	-	-	+	?	-	-	-	-	-	-	-	-	-	-	-
112B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

X = Subject Absent
O = Original Site
V = Virgin Site

[redacted]

Appendix I

Subject Demographics

Subject Number	Subject Initials	[redacted] ID #	Age	Sex
1A	WS	17503	64	F
2A	KB	29152	58	F
3A	DD	19959	51	F
4A	KW	08856	53	M
5A	MV	02436	65	F
6A	CC	28293	62	M
7A	MP	05273	55	F
8A	SK	24596	42	F
9A	MR	18041	52	F
10A	HS	29427	24	F
11A	EJ	13188	63	F
12A	CG	10981	62	F
13A	VM	25890	64	F
14A	MR	23590	63	F
15A	MP	28968	50	F
16A	CY	29605	40	F
17A	DP	23728	41	M
18A	CD	22327	59	F
19A	TD	25458	29	M
20A	AS	02343	62	F
21A	JL	26570	50	M
22A	RW	26017	58	M
23A	MB	18220	65	F
24A	JG	27625	60	F
25A	JH	05348	62	F
26A	NT	29337	63	F
27A	ML	24392	54	F
28A	DS	07961	54	F

Subject Number	Subject Initials	[redacted] ID #	Age	Sex
29A	DD	01937	55	F
30A	JW	29470	36	F
31A	LG	27694	69	M
32A	PG	27693	60	F
33A	PL	25562	56	F
34A	JB	27897	57	F
35A	DT	13190	60	M
36A	DS	11179	55	F
37A	JJ	29220	27	F
38A	KH	29028	32	F
39A	TP	24013	22	M
40A	JH	15091	55	M
41A	GP	27457	65	F
42A	MC	26344	46	F
43A	SP	28365	50	F
44A	CC	25057	65	F
45A	LS	29285	53	F
46A	MS	27321	69	F
47A	PF	28140	60	F
48A	JA	15371	42	F
49A	DK	28732	47	M
50A	SB	27935	39	F
51A	EB	28440	47	F
52A	AB	28081	22	M
53A	EA	17153	43	F
54A	MW	28454	53	F
55A	MA	03833	56	F
56A	CB	24697	60	F

[redacted]

Appendix I
(Continued)

Subject Demographics

Subject Number	Subject Initials	[redacted] ID #	Age	Sex
57A	AJ	01976	69	M
58A	TP	02453	52	M
59A	KS	18451	52	F
60A	SS	02364	28	M
61A	JS	00467	50	F
62A	JC	02268	37	F
63A	LB	13590	50	F
64A	DD	04567	52	F
65A	BW	26154	59	F
66A	BM	25149	20	M
67A	AK	06659	55	F
68A	DT	27954	36	F
69A	LT	12033	64	F
70A	JW	08904	53	F
71A	CA	08192	21	F
72A	DW	20399	51	F
73A	ML	17765	41	F
74A	JG	27647	29	F
75A	PR	23390	28	F
76A	JM	07179	51	F
77A	SW	28565	45	F
78A	BB	04876	62	F
79A	NP	27720	52	F
80A	BN	26497	49	F
81A	WF	05485	45	F
82A	GM	22057	42	M
83A	NF	14449	55	F
84A	GG	20604	46	F

Subject Number	Subject Initials	[redacted] ID #	Age	Sex
85A	SJ	20470	43	F
86A	AR	17119	41	F
87A	DG	16950	53	F
88A	JM	23779	52	F
89A	DJ	07997	44	F
90A	VC	29579	20	F
91A	DJ	27946	42	F
92A	MS	26669	46	M
93A	VH	29382	56	F
94A	FK	04033	63	M
95A	RS	01529	57	F
96A	KC	25528	36	F
97A	NA	28912	50	M
98A	CY	14780	56	F
99A	FR	26715	47	F
100A	JS	24794	30	F
101A	PA	29294	48	M
102A	FR	24101	41	M
103A	DL	27410	50	F
104A	TT	24709	61	F
105A	PP	29069	42	F
106A	SR	26541	48	F
107A	SM	27829	53	F
107RA	EJ	29514	37	F
108A	GV	29435	62	M
109A	NR	29461	47	M
110A	JH	10120	53	F
111A	KB	26002	50	F
112A	DG	27992	46	F

[redacted]

Appendix I
(Continued)

Subject Demographics

Subject Number	Subject Initials	[redacted] ID #	Age	Sex
1B	MG	28729	58	M
2B	JB	29563	52	M
3B	EL	18765	47	F
4B	LL	10549	35	F
5B	IF	28475	19	M
6B	RF	28256	53	F
7B	DS	22694	43	M
8B	KL	29373	33	M
9B	RM	21100	58	M
10B	RV	29265	64	F
11B	VD	23036	55	F
12B	MN	24264	29	F
13B	MH	28023	24	F
14B	DS	25223	48	F
15B	OJ	27802	64	M
16B	SH	17712	52	M
17B	SD	27633	58	F
18B	FN	23990	23	M
19B	DP	16953	53	F
19RB	DS	19108	41	F
20B	SG	23926	49	F
21B	TD	22974	39	F
22B	YM	27424	43	F
22RB	AK	21288	65	F
23B	LN	28468	18	F
24B	DR	29570	59	F
25B	CL	09171	39	F
26B	AB	20464	43	F
27B	VW	24745	57	F

Subject Number	Subject Initials	[redacted] ID #	Age	Sex
28B	BA	22252	65	F
29B	DG	16132	59	F
30B	NC	10624	33	F
31B	JM	27719	64	F
32B	DT	01334	54	F
33B	SF	29522	22	F
34B	AF	29526	42	F
35B	PB	27868	54	F
36B	BM	18748	64	F
37B	RC	28393	48	F
38B	AS	29062	38	F
39B	SP	27818	68	F
40B	GH	28483	62	F
41B	JS	02800	55	F
42B	GG	29681	47	F
43B	HH	28978	18	M
44B	IN	28003	30	F
45B	KP	22597	50	M
46B	FB	17272	67	F
47B	RS	21709	23	M
48B	DM	19176	50	F
49B	DS	19839	34	F
50B	BF	27894	53	F
51B	MF	01230	47	F
52B	CS	28087	27	F
53B	BW	28412	18	F
54B	LC	22990	36	F
55B	SW	01329	61	F
56B	MC	25723	45	F

[redacted]

Appendix I
(Continued)

Subject Demographics

Subject Number	Subject Initials	[redacted] ID #	Age	Sex
57B	MC	25724	22	F
58B	RD	23029	63	M
59B	RC	28608	55	F
60B	TM	27658	20	M
61B	NP	29249	33	F
62B	PB	04703	45	F
63B	EK	21440	65	F
64B	BS	28576	59	F
65B	LM	22551	34	F
66B	LL	27911	28	F
67B	KL	26716	23	F
68B	JL	13253	27	M
69B	RL	27571	48	M
70B	VL	26981	47	F
71B	BE	26475	55	F
72B	LG	21496	52	M
73B	SS	23756	56	F
74B	AP	26576	68	M
75B	YR	29359	45	F
76B	AB	19290	42	F
77B	AD	28496	41	F
78B	JB	24280	54	F
79B	DP	04921	47	F
80B	SS	10495	67	F
81B	PE	25599	50	F
82B	RA	23557	40	F
83B	KP	27396	20	F
84B	NS	24150	21	F

Subject Number	Subject Initials	[redacted] ID #	Age	Sex
85B	ZA	15076	47	F
86B	TH	17294	49	F
87B	BA	29629	48	M
88B	CK	08194	53	F
89B	MH	21487	28	M
90B	AP	26554	57	F
91B	BP	29422	43	M
92B	JP	29387	53	M
93B	CM	29173	54	F
94B	FG	27993	47	M
95B	SB	22953	64	F
96B	AF	22934	25	F
97B	JG	24987	52	M
98B	LN	24351	45	F
99B	HP	29071	35	F
100B	KC	18653	43	F
101B	MF	04348	57	F
102B	DH	25303	20	M
103B	BM	24122	70	F
104B	CB	24215	49	F
105B	SS	28416	59	M
106B	CS	27750	62	F
107B	CE	27144	67	F
108B	RS	05543	46	M
109B	MA	24169	56	M
110B	PB	28542	58	F
111B	FM	02793	55	M
112B	CK	02313	51	F

2021 FDA VCRP Data

Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer

No FDA data

C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer

No FDA data

Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer

No FDA data

Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer

No FDA data

Polyphosphorylcholine Glycol Acrylate

Eye Lotion	03D	1
Tonics, Dressings, and Other Hair Grooming Aids	05G	6
Cleansing	12A	1
Face and Neck (exc shave)	12C	2
Moisturizing	12F	1
Night	12G	1
Total		**12**

Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer

No FDA data

Polyquaternium-51

Eye Shadow	03C	6
Eye Lotion	03D	8
Eye Makeup Remover	03E	1
Other Eye Makeup Preparations	03G	8
Hair Conditioner	05A	1
Shampoos (non-coloring)	05F	4
Tonics, Dressings, and Other Hair Grooming Aids	05G	1
Face Powders	07B	3
Foundations	07C	40
Makeup Fixatives	07H	1
Other Makeup Preparations	07I	4
Bath Soaps and Detergents	10A	4
Other Personal Cleanliness Products	10E	2
Shaving Cream	11E	1
Cleansing	12A	15
Face and Neck (exc shave)	12C	66
Body and Hand (exc shave)	12D	22

Moisturizing	12F	66
Night	12G	8
Paste Masks (mud packs)	12H	2
Skin Fresheners	12I	4
Other Skin Care Preps	12J	8
Total		**275**

Polyquaternium-61

Face and Neck (exc shave)	12C	1
Night	12G	1
Total		**2**