Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: May 23, 2022
Panel Meeting Date: June 16-17, 2022

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

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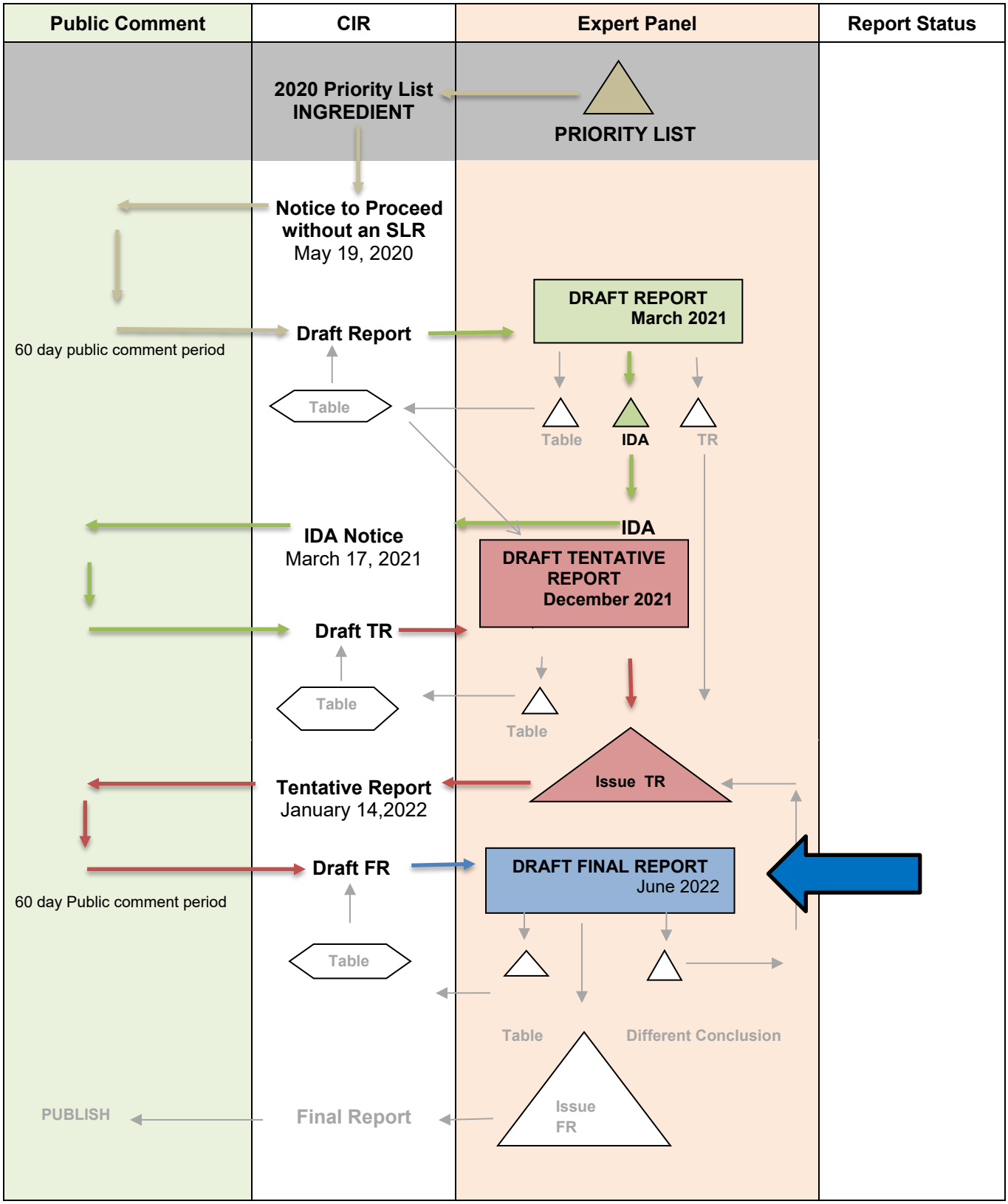
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Acryloyloxyethyl Phosphorylcholine Polymers

MEETING June 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Regina Tucker, M.S.
Scientific Analyst/Writer, CIR

Date: May 23, 2022

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

Enclosed is the Draft Final Report of the Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics (*report_AcryloyloxyethylPhosphorylcholinePolymers_062022*). At the December 2021 meeting, the Expert Panel for Cosmetic Ingredient Safety (Panel) issued a Tentative Report for public comment with the conclusion that the acryloyloxyethyl phosphorylcholine polymer ingredients reviewed in the safety assessment are safe in the present practices of use and concentration.

Included in this packet are the report history (*history_AcryloyloxyethylPhosphorylcholinePolymers_062022*), a data profile (*dataprofile_AcryloyloxyethylPhosphorylcholinePolymers_062022*), the search strategy (*search_AcryloyloxyethylPhosphorylcholinePolymers_062022*), transcripts of previous meeting (*transcripts_AcryloyloxyethylPhosphorylcholinePolymers_062022*), and flow chart (*flow_AcryloyloxyethylPhosphorylcholinePolymers_062022*).

Updated 2022 FDA VCRP data were received and incorporated into the report (*VCRP_AcryloyloxyethylPhosphorylcholinePolymers_062022*). These data were similar to 2021 FDA VCRP data, with negligible changes in the reported uses from the previous year. Total reported uses of Polyquaternium-51 increased from 275 to 317 formulations, while Polyquaternium and Phosphorylcholine Glycol Acrylate use remained mostly the same. Changes reflecting updated VCRP data and newly added data are highlighted in yellow. Additionally, changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review.

In addition, comments on the Tentative Report that were provided from the Council (*PCPCcomments_AcryloyloxyethylPhosphorylcholinePolymers_062022*), as well as responses to these comments (*response-PCPCcomments_AcryloyloxyethylPhosphorylcholinePolymers_062022*) are also attached.

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: January 27, 2022

SUBJECT: Tentative Report: Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics (release date: January 13, 2022)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics.

Introduction – If the paragraph on sources of information is going to identify the ingredients for which published data were found, it would also be helpful to identify the ingredients for which industry information was submitted (Polyphosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61).

Definition and Structure – In the second paragraph, the names of the two ingredients without structures (Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer and Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer) are stated twice.

Method of Manufacture – Please define “RAFT”

Dermal Penetration – It currently states: “from the skin surface to 0 µm thickness”. Was the thickness really stated as “0”?

Subchronic and Chronic Toxicity – Please correct “an” to “and”

Dermal Irritation and Sensitization – Please state the concentration(s) of Polyquaternium-51 used in the guinea pig maximization test.

Summary – The sixth paragraph of the Summary appears to describe the same study (mice injected with human breast tumor fragments) twice.

Table 5 – The descriptions of the maximization studies in guinea pigs should include the induction doses/concentrations in the Concentration/Dose column, rather than in the Procedure column.

Acryloyloxyethyl Phosphorylcholine Polymers - June 2022 – Regina Tucker	
Comment Submitter: Personal Care Products Council **Date of Submission: January 27, 2022**	
Comment	**Response/Action**
Introduction – If the paragraph on sources of information is going to identify the ingredients for which published data were found, it would also be helpful to identify the ingredients for which industry information was submitted (Polyphosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61)	Addressed
Definition and Structure – In the second paragraph, the names of the two ingredients without structures (Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer and Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer) are stated twice.	Addressed
Method of Manufacture – Please define "RAFT"	Addressed
Dermal Penetration – It currently states: "from the skin surface to 0 µm thickness". Was the thickness really stated as "0"?	The thickness was stated as described. Please see ***Observation of Permeation Pathway in the Skin Barrier by a CLSM*** as follows**…….**"Skin surface was washed with distilled water after 6 h-permeation experiment and fluorescence (from the skin surface to 0 mm thickness) was observed under a CLSM (MRC-600 confocal system, Bio-Rad, Hercules, CA, U.S.A)
Subchronic and Chronic Toxicity – Please correct "an" to "and"	Addressed
Dermal Irritation and Sensitization – Please state the concentration(s) of Polyquaternium-51 used in the guinea pig maximization test.	Addressed
Summary – The sixth paragraph of the Summary appears to describe the same study (mice injected with human breast tumor fragments) twice	Addressed
Table 5 – The descriptions of the maximization studies in guinea pigs should include the induction doses/concentrations in the Concentration/Dose column, rather than in the Procedure column.	Addressed

CIR History of:

Acryloyloxyethyl Phosphorylcholine Polymers

May 2020

- A Scientific Literature Review (SLR) Notice to Proceed (NTP) issued.

March 2021

- Expert Panel reviews Draft Report. 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

December 2021

- Expert Panel reviews Draft Report and issues a Tentative Report for public comment

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

- Method of manufacture and impurities data on Phosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61
- Weight average molecular weight data on Phosphorylcholine Glycol Acrylate, Polyquaternium-51, and Polyquaternium-61
- Negative guinea pig maximization test on Polyquatermium-51 (challenge concentrations up to 100%) (Hatano Research Institute,2003)
- Negative guinea pig adjuvant and patch test on Polyquaternium-61 (challenge concentration of 25%) (Consumer Product Testing Company, 2005)
- Negative human repeated insult patch test on an undiluted serum containing 0.12% Polyquaternium-51 (Anonymous, 2012)

The structures for Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer and Polyquaternium10/Phosphorylcholine Glycol Acrylate Copolymer were not provided.

January 2022

- Council comments on Tentative Report received and addressed
- Updated 2022 FDA VCRP data received

Data is similar to 2021 data; Total reported uses of Polyquaternium-51 increased from 275 to 317 formulations, while Polyquaternium and Phosphorylcholine Glycol Acrylate use remained mostly the same.

June 2022

- Expert Panel reviews Draft Final Report

Acryloyloxyethyl Phosphorylcholine Polymers Data Profile* -June 2022-Writer, Regina Tucker (and previously, Wilbur Johnson)																															
						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.

DECEMBER 2021 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – December 6, 2021

DR. BELSITO: Okay, so this is Wilbur. So at the March 2021 meeting we issued an IDA to come to a conclusion of safety. We asked for composition impurities, molecular weight, averages in distributions, skin sensitization for polyquaternium-51, chemical structures for hydroxyethylcellulose/phosphorylcholine glycol acrylate copolymer and polyquaternium 10/phosphorylcholine glycol acrylate copolymer.
In response, we received a number of unpublished data that have been incorporated into the report. And I won't review all of those because we will be doing that when we look at the document. So let me close out the last and find this one. We also got Wave 2 data on this. It seems that we've gotten composition impurities data, but not on all ingredients. And we're told that we're not going to get structures because they're crude mixtures. Otherwise, a lot of what we asked for is there. Except we asked for composition impurities just for polyquaternium-51, correct?
DR. LIEBLER: Right, and that's been added.

DR. BELSITO: Right, and we got an HRIPT to 0.12 percent, but we also have animal data for sensitization to 100 percent. And according to Wave 2 -- I guess I didn't follow this -- it said there was no acrylate, but we have this ingredient that's called hydroxyethylcellulose phosphorylcholine glycol acrylate copolymer. So what were they telling us in Wave 2 about acrylates in this?
DR. HELDRETH: So there was two parts to the information we received from the INCI folks. One was to explain how the cellulose type polymers were being copolymerized with these vinyl type polymers. So that's one step that speaks to those two ingredients that we didn't have a structure for.
DR. BELSITO: Right.
DR. HELDRETH: The other part that they wanted to mention was for those two ingredients, instead of actually using acrylate monomers in there, they used methacrylate monomers.
DR. BELSITO: Okay. So there is an acrylate in the polymer, it's just that it's a methacrylate monomer that's used in the manufacturing?
DR. HELDRETH: That's correct. Along that vinyl type polymer backbone, in some places where you would have expected to see a hydrogen poking up, there's a methyl group poking up instead.
DR. BELSITO: Okay. And do we need the composition and impurities for poly phosphorylcholine glycol acrylate? Or I guess we have those, right?
DR. LIEBLER: It's there. It's been added.
DR. BELSITO: Yep. We have those and we have the composition and impurities for polyquaternium-51 and 61. Is that sufficient for the entire group?
DR. LIEBLER: I thought it was.
DR. BELSITO: Okay.
DR. LIEBLER: I would point out there's one thing, I flagged it in the report, Wilbur, but under the phosphorylcholine glycol acrylate for composition/impurities, it's highlighted yellow.
MR. JOHNSON: Yeah.
DR. LIEBLER: And the last item listed was and methyl 0.15 percent, so methyl what?
DR. EISENMANN: Paraben.
DR. LIEBLER: Methylparaben? Okay.
MR. JOHNSON: Yes.
DR. LIEBLER: So we just need to add that in.
MR. JOHNSON: Okay.
DR. BELSITO: That was a PCPC comment. So, then, let's go to PDF Page 22 under the "Definition." The third line down that starts, "in common, these phosphorylcholine substituted…" Should that now become methacrylate monomers? Is that what you were saying, Bart?
DR. HELDRETH: I mean, for those two ingredients I leave it to the panel's discretion. I mean, methacrylates actually fall into the demo category of acrylates.
DR. BELSITO: Right.
DR. HELDRETH: But outside of those two ingredients, we don't have any information to suggest that they're methacrylates instead of acrylates. So, as far as we know, we have both methacrylates for those two ingredients, or acrylates for the other ingredients in this group.
DR. BELSITO: Okay, so then why don't we -- my viewpoint would be why don't we just go with the generic acrylate, but, Dan?
DR. LIEBLER: I'm comfortable with as currently written.
DR. BELSITO: Okay. Paul? Curt?
DR. SNYDER: Yeah, no further comment.
DR. KLAASSEN: That's fine.
DR. BELSITO: And, Dan, you said you're comfortable with the method of manufacturing, even though it's sort of generic?
DR. LIEBLER: That's right.
DR. BELSITO: Okay. So, for the dermal penetration, is that data on PDF Page 24 sufficient to assume that none of these would penetrate the stratum corneum? And, so, that local (audio skip) effects are not needed?
DR. LIEBLER: Yeah. I think they used an FITC, or fluorescent isothiocyanate-labeled polymer and it was found on the skin surface only. And when they used just the label, it distributed into the corneum sites. So it's a good control, it shows that there's no penetration.
DR. BELSITO: Okay.
DR. SNYDER: We also used that read-across from polyquaternium-51.
DR. LIEBLER: Yeah.
DR. BELSITO: The six-hour dermal penetration?
DR. LIEBLER: Yeah, I think that's a good experiment. I don't have a problem with that.
DR. BELSITO: Okay.

DR. BELSITO: So we don't need anything more. So this read -- PDF Page 25 for this hemolytic activity to look at ocular irritation, I could not find any evidence that it's a validated test. So do we reference tests that aren't validated in the report? Just a question for the team.
DR. LIEBLER: Yeah, I don't think so. And particularly, when we're going to use data from a read-across molecule, I mean, usually a read-across becomes valuable when you've got data from a validated test for one of our endpoints. And I don't think this meets that criteria.
DR. BELSITO: So we would delete that?
DR. LIEBLER: I would delete this whole Hemolytic Activity section.
DR. BELSITO: Okay. Paul and Curt, are you -- that's what I felt too, but --
DR. SNYDER: I'm fine with that.
DR. BELSITO: Okay.
DR. KLAASSEN: Yeah, it's not (audio skip).
DR. BELSITO: Wilbur, we're going to be deleting that.
MR. JOHNSON: Okay.
DR. BELSITO: So it looks like you're not going to be able to retire when you planned to, you've got about (audio skip). So, then, we got -- I just have a question here. I don't know why I had this question, how we deal with Wave 2. Okay. So is this safe as used? And how do we deal with the apparently two misnamed ingredients? And I'm not, again, I reviewed this a long time ago so I'm not -- what two ingredients were misnamed? Can someone help me out there?
DR. HELDRETH: Yeah, if we're talking about the two ingredients where the folks from the nomenclature committee told us that it was actually methacrylate instead of acrylate monomers used.
DR. BELSITO: Yes.
DR. HELDRETH: I don't think that they intend to change the name because acrylate technically covers it. I think they just plan to change the definition. So there won't be anything changed in the report except for our definition.
DR. BELSITO: Okay. Yeah, those were the two I guess I was referring to. Is our conclusion safe as used? And do we need to add the respiratory boilerplate there?
DR. SNYDER: I thought we received all of our IDA insufficient data announcement needs, and I was safe as used.
DR. LIEBLER: Yes, I was the same place.
DR. BELSITO: So we have some incidental inhalation, so what are we doing in both sprays and powders for phosphorylcholine glycol acrylate and polyquaternium-51? And also with polyquaternium-61? So what are we doing with the respiratory boilerplate here?
DR. SNYDER: So this one, I think works, for this one because it's in the -- we specifically -- it's labeled to the ones, the face -- the powder and the spray. There's no aerosolized spray use, right?
DR. BELSITO: No, there is, no?
DR. SNYDER: Aerosolized hairspray, but that's different, right, than the deodorant?
DR. BELSITO: Right.
DR. SNYDER: I mean, we give the concentrations -- I mean, they're way out there.
DR. LIEBLER: Yep, they're very low.
DR. SNYDER: Yeah, so this is one -- again, I like the way this one's done because we deal with it, and this is ingredient-specific. These are -- they're used in these categories, there's no category here that, you know, like airbrush use or deodorant, aerosolized deodorants. And the maximum concentrations for those are very, very low, so we're not worried. I mean, yeah, I think we have data to suggest that there's no issue. And it's very well -- this is tailored to this ingredient group.
DR. BELSITO: Okay, so then do we need to put that in the discussion?
DR. SNYDER: It is in the discussion, there in yellow.
MR. JOHNSON: Last paragraph.
DR. SNYDER: Last paragraph. That's what I'm saying, I like this one very much. You can go last paragraph, right, the last paragraph before the conclusion.
DR. LIEBLER: Yeah, I think it's fine.
DR. SNYDER: Yeah, I do too.
DR. LIEBLER: So we have it in the discussion and it's appropriate in this context.
DR. BELSITO: Okay.
DR. SNYDER: The only paragraph under discussion I didn't like was I thought the second paragraph -- or the third paragraph where it starts off, "also take into consideration…," I thought that all could be eliminated because -- or reduced down to saying there are no -- I mean, after that, the last sentence of the paragraph above where it says, "furthermore, the panel agrees that the skin penetration data essentially eliminate the need for systemic toxicity data…." Then you could also have a sentence that says, "The panel also could not identify any structural alerts for genotoxicity."
DR. LIEBLER: Okay.
DR. SNYDER: Eliminating the need for genotoxicity data. Then just leave it at that, not all that -- I don't care about all that tumor IP, blah, blah, blah, blah, blah.

DR. LIEBLER: Yeah, agree.
DR. BELSITO: So you're starting, you're just putting that sentence into the paragraph above it?
DR. SNYDER: Correct.
DR. BELSITO: Okay. So it would just, also taken into consideration were the absence of structural alerts for genotoxicity in the polymers reviewed. On page --
DR. SNYDER: It's just too many words. Just say the absence of structural alerts for genotoxicity. Don't put up -- take out that -- don't use that also taken into consideration were. Just start with, "The absence of structural alerts for genotoxicity in the polymers reviewed eliminate the need for genotoxicity data." Period.
DR. BELSITO: Okay. For some reason I'm having that same issue that you had.
DR. SNYDER: Yeah, a couple of these files were corrupted or something.
DR. BELSITO: Yeah.
DR. SNYDER: Editing them.
DR. LIEBLER: I had that on another document, but I'm making an edit on mine. I can edit. The absence of structure alerts for genotoxicity obviated the need for genotoxicity data, period?
DR. SNYDER: Yep. Because we already say in the previous one we didn't need the carcinogenicity data either, because it's not systemically absorbed. So the only genotox would be for skin, so.
DR. BELSITO: Okay. So, Dan, you were able to make those changes?
DR. SNYDER: I have them in mine also.
DR. BELSITO: Yeah. I could not go in and strikethrough that paragraph for some reason.
DR. LIEBLER: Yeah, well we don't want to strike out the whole thing, so we got what we need.
DR. BELSITO: Okay, so you took care of that.
DR. LIEBLER: And Wilbur's probably already made notes as well, so.
MR. JOHNSON: Yes.
DR. BELSITO: Okay. So we're just going safe as used without any caveats with respiration.
DR. SNYDER: Well, we have it. We have it in the boilerplate.
DR. BELSITO: Right, but not in the --
DR. LIEBLER: Not in the conclusion.
DR. SNYDER: Correct. That's correct.
DR. BELSITO: Okay. Any other comments on these acryloyloxyethyl phosphorylcholines?
MR. JOHNSON: Yes, I have a question, Dr. Belsito, relating to the data on the absence of the two structures that appear in Wave 2. Exactly, I know there's a few statements relating to that but, you know, which statement should be included in the report and where should that information appear?
DR. BELSITO: Okay. You're on Wave 2, Wilbur?
MR. JOHNSON: Yes. You know, the comments that Bart made relating to the --
DR. BELSITO: Oh, methacrylate rather than acrylate?
MR. JOHNSON: Yeah. Right.
DR. BELSITO: I think that we dismissed that, Wilbur, by saying we were comfortable just going with the generic use of the term acrylate.
MR. JOHNSON: Okay, so none of that information should be added to the report?
DR. LIEBLER: I didn't think it was necessary.
MR. JOHNSON: Okay. Thank you.
DR. LIEBLER: I mean, it depends on whether or not the other team feels that we need to explicitly put in some language adapted from the response that was shown in the Wave 2. If they want to, they probably have a proposal. And they can put it under composition and impurities I suppose. But I felt that the response in Wave 2 addressed the concern we had. I didn't feel we need an additional text added to the report. If they feel that they want to add text that's adapted from that Wave 2 response, I have no objection. I don't think there's any reason we'd need to object to it.
MR. JOHNSON: Yeah. And, just one more question, relating to the absence of those two structures. Should any language be included in the discussion relating to the fact that those structures are not available?
DR. LIEBLER: No.
MR. JOHNSON: Okay. Thank you.
DR. HELDRETH: Yeah, I would propose adding just a little bit of information about how they're synthesized from methacrylate and a little bit about how the cellulose in the vinyl type polymers are combined, in the definitions of those two ingredients in Table 1. Just minor edits, I think, would take care of that.
DR. LIEBLER: Yeah, good suggestion.
MR. JOHNSON: Okay. Well, I'll incorporate, you know, Bart's comments on that.
DR. LIEBLER: Good.
DR. BELSITO: Anything else on these? Okay. Not hearing anything, we'll move to the methacrylate ester monomers.

Cohen Team – December 6, 2021

DR. COHEN: This is acryloyloxyethyl Phosphorylcholine polymers. This is a draft tentative report. And in March we had an IDA for these ingredients -- there were eight of them -- requesting composition/impurities, molecular weight averages and distributions, sensitization data for a number of them. We've received method and manufacturing and impurities on phosphorylcholine glycol acrylate, polyquaternium-51 and -61. We got a number of molecular weights. We got guinea pig max and HRIPT on 0.12 percent polyquaternium-51 -- at 0.12, which is pretty close. And we received some Wave II information about the terminology and reaction products, and Wave III data we got some composition and impurities and some correction, I think. It's just a correction. Lisa, what did you think?
DR. PETERSON: I have no concerns. I actually thought it was ready for conclusion, safe as used.
DR. COHEN: Tom.
DR. SLAGA: For clarification, I thought we got everything we needed, but there was something we asked about two structures that the other team did that I didn't see those.
DR. COHEN: Are you talking about the polyquaternium-10/phosphorylcholine glycol acrylate copolymer and hydroxyethylcellulose?
DR. SHANK: Yes.
DR. COHEN: And I thought we got back something like it was difficult to determine the reaction product.
MR. JOHNSON: Yeah, the Wave II submission relates to that.
DR. SHANK: Well, if you don't know what the structures are, how can you talk about chemical activity and biological activity toxicity?
DR. PETERSON: Okay. I thought maybe they should be taken out of the report. I've got notes that are now -- we can see.
DR. SHANK: I agree. I thought it was confusing. Pardon me, we talk about sensitization tests on polyquaternium-51 and -61, but in fact, those were not tested. Compounds in similar structure were, but we keep referring it to sensitization studies on poly-Q 51 and poly-Q 61. You know, we shouldn't do that because that's not accurate unless I misread these studies.
DR. COHEN: We have 0.12 percent polyquaternium-51 HRIPT, right?
DR. SHANK: It wasn't that. My understanding -- oh, let me try to find it.
DR. COHEN: I'm going back myself now. It's on Table 5, PDF --
MS. FIUME: PDF page 35?
DR. COHEN: Yes. No, no, PDF 37.
DR. SHANK: 36.
DR. COHEN: 37. You see serum containing 0.12 percent?
DR. SHANK: I think when I went to see those actual data, it was listed as polyquaternium-51, but in fact it was a different compound with a very, very long name which is similar, but not the same.
DR. COHEN: Ron, go to PDF 88.
DR. SHANK: 8?
DR. COHEN: 88.
DR. SHANK: 88. Yeah, okay.
DR. COHEN: Does that persuade you?
DR. SHANK: I'm trying to find where it says what they tested.
DR. COHEN: The test material is all redacted, so I used what was written in in red on 88 that said serum containing 0.12 percent polyquaternium-51.
DR. SHANK: Okay.
MS. FIUME: What I think Ron may be referring to, PDF page 44.
DR. COHEN: 44.
DR. SHANK: 44.
MS. FIUME: And the studies associated with that where there are trade-in mixtures that contain a percent of polyquat-51?
DR. SHANK: Okay. Yes. There's the INCI name and then the CAS name. My understanding was the two compounds are similar but not the same.
DR. COHEN: You mean 51 and 61?
DR. SHANK: Yes.
DR. COHEN: Doesn't that get -- that goes to the read across, doesn't it?
DR. SHANK: Well, we shouldn't say sensitization tests on poly-Q 51 and 61 because the tests weren't done on those. They were done on the very similar compounds for which we use read across. Do I understand that correctly?
DR. COHEN: Yeah. I didn't remember if anyone said we had sensitization data on 61, but I would agree with your last statement.
DR. SHANK: Okay.
DR. COHEN: The question is, can -- with 51 can we read across the rest of them? Is the group suggesting we get rid of the

polyquaternium-10/phosphorylcholine glycol acrylate copolymer because we don't know as much about it? I need a little more information. Lisa, do you think that we could read across, or we need to get rid of that based on the Wave II data? I mean, was that concerning enough to want to pull that out?
DR. PETERSON: I am not fully understanding the issue. So, I apologize. Are you talking -- what are you -- can you please reorient me?
DR. COHEN: I think the easier question that I could articulate is, is the summary table -- can we read across with our polyquaternium-51 and 61 data? Just in general, can we read across the rest of this table?
DR. PETERSON: Well, I think that the two chemicals where we don't know the structure should be removed from the table. I mean, I think they should be removed for that report because we don't know what their chemical structure is, and it doesn't really quite make sense. And then, I think it's just --
DR. COHEN: Is that what Wave II is saying? It said something -- "It is difficult to say which reaction product, graft co-polymers or MPC homopolymers, would be the dominant reaction product." I was hoping you'd be able to translate some of that.
DR. PETERSON: I mean, I agree with that conclusion. I think without the chemical structures you don't really know what they are, and they're not used in anything. And I would argue that if they're going stay insufficient, they shouldn't be -- I wouldn't read across those two with the other ones. I mean, I agree with that. Sorry, I have something caught in my throat, and it's not clearing.
DR. COHEN: Yeah, I was trying to hold off calling on you because I saw you were trying to drink it down. So, it's number 4 and number 6 on the table. Is that what you're suggesting?
DR. PETERSON: It's the hydroxyethylcellulose and the quaternium-10.
DR. COHEN: Well, it's the phosphorylcholine glycol acrylate, right?
DR. PETERSON: Yeah. Yeah. And then the two phosphorylcholine. It's too bad I can't share my screen.
DR. COHEN: Oh, it's -- I'm sorry, one, two --
DR. PETERSON: I'm on page --
DR. COHEN: -- three, four, five.
DR. PETERSON: -- I'm on page 22 where I have them highlighted.
DR. COHEN: 22.
DR. PETERSON: And it's the third and the sixth one.
DR. JOHNSON: Mm-hmm.
DR. COHEN: The hydroxyethylcellulose?
DR. JOHNSON: Yes.
DR. PETERSON: Yeah.
DR. COHEN: Okay. PDF 22. So, it's the hydroxy -- okay, I got that one. And the polyquaternium-10/phosphorylcholine glycol acrylate copolymer.
MR. JOHNSON: Yes, mm-hmm.
DR. COHEN: And they're not in use?
DR. PETERSON: They're not in use. I mean, I just would drop them because --
DR. COHEN: So, this is a draft tentative report. What are our options here? That we recommend dropping it, or we suggest that there's still insufficient data on those two with regard to structure? Wilbur, what kind of choices do we have for moving this tomorrow?
MR. JOHNSON: You could, you know, issue a tentative report with a safe conclusion on some of the ingredients. And for those two, you know, for which structures weren't provided you could state that the available data are insufficient for determining the safety of those. That is a possibility.
DR. SLAGA: I like that possibility.
DR. COHEN: I do too.
DR. PETERSON: Yeah, that's probably better than deleting it.
DR. SLAGA: Yes, that's better than deleting it.
DR. COHEN: And Lisa -- go ahead, Tom.
DR. SLAGA: No, no, I did -- I would go with what Wilbur stated. Safe, and the two that we don't have the structures on insufficient.
MR. JOHNSON: Mm-hmm.
DR. COHEN: And so, the insufficient data is exactly what? We --
DR. PETERSON: Chemical structure.
DR. SLAGA: We don't know the structure.
DR. COHEN: All right.
DR. PETERSON: Chemical structure.
DR. COHEN: Okay.
MR. JOHNSON: I guess you also have the option of, you know, just deleting those two from the safety assessment.

DR. COHEN: Okay. I think those are two good options we have tomorrow.
DR. SHANK: Good.
MR. JOHNSON: Dr. Cohen, I have one question about Dr. Shank's concern on PDF page 37, Table 5.
DR. COHEN: PDF 37, yes.
MR. JOHNSON: Yeah, in that study the test substance is identified as serum containing 0.12 percent polyquaternium-51. Should the name be changed, you know, based upon Dr. Shank's comments for further information on the identity of what is actually being tested?
DR. SHANK: I think being scientifically correct we have to say maybe a footnote or something because polyquaternium-51 was not tested itself. It was a very similar compound that was, unless I misunderstand the chemistry. So, to put it in the report and put it in the table poly-Q 51 was tested is not accurate.
DR. COHEN: Ron, how --
DR. SHANK: It's really not a big deal but --
DR. COHEN: How did you -- from page 88, I'm assuming that the table that Wilbur just highlighted is referencing PDF page 88 on.
DR. SHANK: Yes.
DR. COHEN: So, where's the suggestion that it wasn't polyquaternium-51? That's what I'm missing.
DR. SHANK: Okay. I have to find that table again. It was in the industry --
DR. COHEN: Oh, you mean in the --
DR. SHANK: -- position.
DR. COHEN: -- second Wave or third Wave?
DR. SHANK: Page 44.
MR. JOHNSON: 44, mm-hmm.
DR. COHEN: 44.
MS. FIUME: Ron, I think that information correlates to the irritation study on PDF page 35. And as I read that table, polyquaternium-51 was the INCI name which corresponded to that chemical name, and it's used at 0.5 percent the trade name mixture. I believe the sensitization data are referring to the study that David was looking at on PDF page --
DR. COHEN: 88.
MS. FIUME: -- 88. That's at least how I had interpreted the data when I had looked at it.
DR. JOHNSON: Mm-hmm.
DR. SHANK: Okay. There it's redacted. I can't tell. It just says serum containing 0.12 percent poly-Q 51. And we're sure it was? Well, maybe it's just a nomenclature problem for me. Does the INCI name and the CAS name refer to exactly the same chemical?
DR. COHEN: Oh.
MS. FIUME: So, that CAS number, according to the dictionary -- according to the dictionary that CAS number corresponds to polyquaternium-51.
DR. SHANK: Okay. Then forget everything I've said.
DR. COHEN: How far back do you want us to go, though?
MS. FIUME: I mean, that is a different chemical name but --
DR. SLAGA: Way to go, David.
DR. COHEN: I'm sorry. Go ahead, Monice, sorry.
MS. FIUME: I was saying the chemical name -- you know, I was just going on what was submitted to us that that chemical name was synonymous with the inky name based on the CAS number.
DR. SHANK: Okay. Thank you for clarifying that.
DR. COHEN: Okay. And Belsito's presenting that one tomorrow.
MR. JOHNSON: Okay. Dr. Cohen, so you really haven't determined -- you presented two options for tomorrow, but you haven't determined, you know, exactly what you think the conclusion should be?
DR. COHEN: I actually think we would go out with safe as used for the six of them and insufficient data on the Polyquaternium-10/phosphorylcholine and the hydroxyethylcellulose/phosphorylcholine. And the insufficient information would be better information on the chemical structures.
MR. JOHNSON: Mm-hmm.
DR. COHEN: So that's what we're going to go out with. If during the discussion the other team has some further information they want to discuss or there's a decision about deleting them or proposing that, I think I have the support of the team to do that.
MR. JOHNSON: Okay. Okay. Thank you.
DR. COHEN: Is that accurate, guys?
DR. SLAGA: Yes.
DR. SHANK: Yes.

Full Panel – December 7, 2021

DR. BERGFELD: It's 10:20. Everyone back? So we have reports advancing and quite a few of these. The first person up is Don again. I don't know if I can do this one, acryloyloxyethyl phosphorylcholine. This is a tentative report.
DR. BELSITO: Thank you. So this is acryloyloxyethyl phosphorylcholine. March 2021 we issued an IDA. To conclude safety we wanted composition, impurities, molecular weight averages, distribution, skin sensitization data for polyquaternium-51 and (audio skip) for hydroxyethyl cellulose, phosphorylcholine, glycol acrylate copolymer, and the quaternium-10/phosphorylcholine glycol acrylate polymer. We did get unpublished data. I won't review all of that, and we'll just look at whether that unpublished data helped us in getting to the conclusions here. So based upon the data that we received, we thought we could go ahead with a safe as used conclusion.
DR. BERGFELD: Is that a motion?
DR. BELSITO: That's a motion.
DR. BERGFELD: Okay. David?
DR. COHEN: I guess before I would second that we went out safe as used for six of the ingredients and an insufficient for two, but we could talk this through. For the polyquaternium-10 phosphorylcholine glycol acrylate copolymer and the hydroxyethyl cellulose phosphorylcholine glycol acrylate copolymer the team thought there was some ambiguity with the structures of those two. Maybe I can ask Lisa to comment a bit more on that.
DR. PETERSON: There was just -- because there was no clear structure that we thought that there would be insufficient, but I can be talked out of that.
DR. BELSITO: We were told the structures for those two were not possible; right?
DR. SLAGA: What do you mean by not possible?
DR. BELSITO: I don't know. I'll turn that over to the chemists, but we had a comment back in Wave II that the structures were not available -- or I guess the way -- I mean, Dan, you want to comment?
DR. LIEBLER: Yeah. So the page 2 of the Wave II document -- PDF page 2 has the summary of a memo from Bart saying that they inquired with the International Nomenclature Committee and that these two polymers don't have precise structures available that could be portrayed, but given the nature of the polymerization process, they provide a plausible explanation for how they may be cross-linked. There are multiple sites on hydroxyethyl cellulose, the quadertium-10, that would participate in the formation of the polymerization with the methacryloxyethyl phosphorylcholine. So I felt that that was good enough to include this in this set of ingredients. I mean, the essential chemical features or characteristics of these that unify these into the group are still there. It's the precise representation of how they're linked don't fit into this structural representations that we have in table one. But I don't think that was enough reason to exclude these.
DR. BERGFELD: Lisa?
DR. PETERSON: Yeah. I'm okay with that.
DR. BERGFELD: How would you propose putting that into the discussion?
DR. LIEBLER: Can you say that again? I heard a dog bark.
DR. BERGFELD: I don't have my mic. How would you propose putting that into the discussion? It should be discussed.
DR. LIEBLER: I think --
DR. SLAGA: It's hard to discuss.
DR. LIEBLER: Wilbur, I think what we can simply say is that the representation of the polymerization process of these two ingredients provided a plausible basis for including these with the other ingredients of more defined structure.
DR. PETERSON: That would be fine.
DR. COHEN: So, Dan, this comment about difficult to say which reaction product graph copolymer versus MPC homopolymers wouldn't change the way we're interpreting the dataset and the read across?
DR. LIEBLER: No, not at all.
DR. COHEN: That's key.
DR. BERGFELD: So you held back your motion to approve or not, David?
DR. COHEN: We can second the motion.
DR. BERGFELD: Okay. Is that Wilbur?
MR. JOHNSON: Yeah. Just one comment. The statement that was just made by Dr. Liebler, is that to be included in the discussion?
DR. BERGFELD: Yes.
MR. JOHNSON: And also, should there be any additional information for inclusion in the chemistry section?
DR. BERGFELD: Dan?
DR. SLAGA: It should be in the chemistry section too.
DR. LIEBLER: Taking a quick look, Wilbur.
MR. JOHNSON: Okay.
DR. BERGFELD: You'd have to say something about it.

DR. SLAGA: Yeah. If it doesn't follow the other compounds there should be something stated.
DR. LIEBLER: Right. Okay. There's nothing in the current definition section, so I think, Wilbur, I think you could adapt the language from the Wave II memo right in the middle where it starts with the bold-faced polyquaternium-10 phosphorylcholine glycerol acrylate copolymer and then the other hydroxyethylcellulose one and cellulose-derived polymers, lack acrylate groups that would be expected to copolymerize. However, the use of ammonium persulfate will generate -- I would say the polymerization process will also contain homopolymers. Let me see. Shoot, I hate wordsmithing on the fly here with the group. So, can I -- I'd rather owe it to you than cheat you out of it, as my business manager used to say. Can I give Wilbur some language to include in the chemistry section?
DR. BERGFELD: I think so. Yes.
DR. LIEBLER: When we see this again? I'll just adapt from that paragraph, though, but I'll just condense it so it's one or two sentences max.
MR. JOHNSON: Okay. Thank you.
DR. BERGFELD: So the motion has been made and seconded. Some discussion on the chemistry has been added to two areas, the chemistry and the discussion. Anything else we need to do?
DR. BELSITO: Yeah. Dan wanted to shorten this second full paragraph in the discussion or wordsmith it. Dan, you want to comment?
DR. LIEBLER: I was just starting to wordsmith the other. Okay. Let's see. What did I have? Oh, yeah.
DR. BELSITO: PDF page 28.
DR. LIEBLER: Yeah. PDF 28, the paragraph that starts "Also taken into consideration were." And I just shortened that to "The absence of structural alerts for genotox in the polymers reviewed eliminate the need for genotoxicity data."
MR. JOHNSON: Okay.
DR. BERGFELD: Okay. That's acceptable. Let's add the change.
MR. JOHNSON: And just one more comment about it, Dr. Bergfeld. In one of the teams it was mentioned that the section on hemolytic activity should be deleted.
DR. BELSITO: That was our team, Wilbur. It's not an acceptable method for assessing ocular irritation.
MR. JOHNSON: Okay.
DR. BERGFELD: David, do you agree?
DR. BELSITO: David, are you okay with that?
DR. COHEN: Yeah. I think that makes sense.
DR. BERGFELD: Anything else?
DR. SHANK: Can you go back to the paragraph in the discussion that Dr. Liebler wants to change? "Also taken into consideration were the absence of structural alerts." And just leave it at that? Why do want to take off the read across? Can you hear me?
DR. LIEBLER: Yeah. I'm trying to understand what you're saying here, Ron.
DR. BELSITO: Perhaps repeat your shorten version.
DR. LIEBLER: Yeah. Okay. So I'll just repeat my shortened version, Don. "The absence of structural alerts for genotoxicity in the polymers reviewed eliminated the need for genotoxicity data." Now, Ron's asking about the remainder of the paragraph or the rest of that sentence.
DR. SHANK: Correct.
DR. LIEBLER: "The absence of toxicity when the read across chemicals administered by a dermal absorption pathway" -- I think that our discussion --
DR. SNYDER: If I could interject here, as written it says "lack of support of concern over systemic toxicity." This is dealing with genotoxicity, not systemic toxicity; right?
DR. LIEBLER: I think I suggested striking that because it wasn't about the genotox.
DR. SHANK: We have not very often relied strictly on chemical structure only to determine genotoxicity. Have we? I don't think so.
DR. LIEBLER: No. You're right, Ron. You're correct. Chemical structure, lack of structural alerts isn't the only factor in play here. There's these large polymers unlikely to be -- I mean, not going to be absorbed.
DR. BERGFELD: Are you going to say that?
DR. SNYDER: It does in the preceding paragraph.
DR. BELSITO: Yeah. It says "These data indicate the absence of skin penetration," yada, yada, yada, in the first paragraph.
DR. BERGFELD: I see that, but if you're going to use it for genotox, maybe you have to add it there too. Comment, Dan, since you're wordsmithing it?
DR. LIEBLER: Questions for my colleagues Ron and Tom, if a chemical is not going to be absorbed because it's a large polymer, does that mitigate our concern about genotox data?
DR. SHANK: Yes.
DR. SLAGA: Yes.
DR. LIEBLER: Okay. I think we have our answer, and then it's just a question of where to put the text.

DR. BELSITO: In the absence of structural alerts for genotoxicity or systemic absorption in the polymers reviewed obviate the need for genotoxicity data -- no, that's not right.
DR. LIEBLER: Lisa, I didn't ask you as well. Do you concur with that -- with your colleagues?
DR. PETERSON: Yes.
DR. LIEBLER: Okay. Apologies. I'm sorry.
DR. SNYDER: I think it can just be added to the end of that pervious paragraph and say "Further, an absence of structural alerts for genotoxicity in the polymers reviewed further support the" --
DR. LIEBLER: The lack of need for genotox?
DR. SNYDER: Yeah. Much harder to do that on the fly than it is in -- yeah.
DR. BELSITO: Okay. So taking that paragraph and just making a sentence and moving it into the first paragraph where we already discussed lack of skin penetration.
DR. SHANK: Okay.
DR. BERGFELD: Does everyone approve of that editorial change?
DR. PETERSON: Yes.
DR. SLAGA: Yes.
DR. COHEN: Yeah.
DR. BERGFELD: Okay. So we have our motion that's been seconded. Any other discussion before we call it moot? Hearing none, all those opposed? Abstaining? Unanimously approved. All right. Moving on to zeolites. Dr. Cohen.

Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics

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

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 8 acryloyloxyethyl phosphorylcholine polymers as used 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 that the acryloyloxyethyl phosphorylcholine polymers are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

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. Please note, because little relevant data were available in the published literature, 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 and Structure

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 (for 6 of the ingredients), and available 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 (CAS No. 125275-25-4).

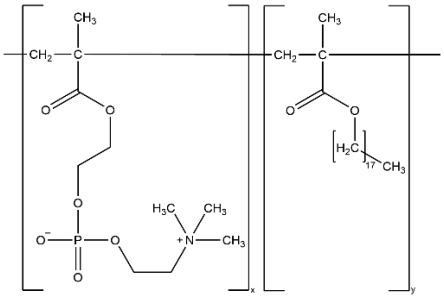


Figure 1. Polyquaternium-61

The chemical structures of Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer and Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer remain unknown. However, information provided by the International Nomenclature Committee (INC) indicate that Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer and Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer, the cellulose derived polymers (polyquaternium-10 and hydroxyethylcellulose), lack acrylate groups and are expected to copolymerize with methacryoyloxyethyl phosphorylcholine (MPC) (personal communication from the INC, November 22, 2021). Free radical reactions of polyquaternium-10 and hydroxyethylcellulose lead to the production of graft copolymers with the MPC.

Chemical Properties

Average molecular weights 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

Ammonium persulfate is used as an initiator for the polymerization of Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer and Hydroxyethylcellulose/ Phosphorylcholine Glycol Acrylate Copolymer (personal communication from the INC, November 22, 2021).

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 reversible-addition-fragmentation chain-transfer (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′- azoisobutyronitrile (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 methylparaben (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 include heavy metals (20 ppm max) and arsenic (2 ppm max).[6]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment 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, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Therefore, airbrush application of cosmetic products is not assessed by the Panel.

According to 2022 VCRP data, Polyquaternium-51 is reported to have the greatest frequency of use; it is reported to be in 317 cosmetic products, 279 of which are leave-on formulations (Table 3).[8] The results of a concentration of use survey provided by the Council in 2020 indicate that Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer has the highest reported use concentration; it is reported to be used at maximum concentrations of up to 0.18% in leave-on products (foundations).[9] Additionally, 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 listed in Table 4.

Cosmetic products containing acryloyloxyethyl phosphorylcholine polymers may incidentally come in contact with the eyes (e.g., 0.05% Polyquaternium-51 in eye makeup preparations) or mucous membranes (e.g., Polyquaternium-51 in bath soaps and detergents and personal cleanliness products [concentrations not reported]). Additionally, some of these ingredients are used in cosmetic sprays and powders and could possibly be inhaled; for example, Polyquaternium-61 is reported to be used in aerosol hair sprays at use concentrations up to 0.000006% and in face powders at up to 0.0069%. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. 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.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

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

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

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 and Chronic Toxicity Studies

Data on the subchronic and 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 provide additional information on the toxicity potential under circumstances of direct contact of Polyquaternium-51 with cells.

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.

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.[19] 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 SENSITIZATION STUDIES

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

A trade name mixture containing 1.4% Polyquaternium-51 was not an irritant in the Irrectection® assay when tested at doses of 25, 50, 75, 100, and 125 µl.[20] Polyquaternim-51 was not a sensitizer in an animal study (maximization test using groups of 10 Hartley guinea pigs of a tradename mixture containing 5% aqueous Polyquaternium-51)[21] or human studies (maximization test with 25 subjects of a foundation containing 0.08125% Polyquaternium-51;[22] human repeated insult patch test (HRIPT; occlusive patches) with 212 subjects of a serum containing 0.12% Polyquaternium-51[23]). Polyquaternium-61 (25% in petrolatum) was not a sensitizer in the guinea pig adjuvant and patch test (5 Aai: (HA) outbred albino guinea pigs).[24]

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.[20] 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 Polyphosphorylcholine Glycol Acrylate (40%), water (54.85%), 1,3-butylene glycol (5%), and methylparaben (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 2022 VCRP data, Polyquaternium-51 is reported to have the greatest frequency of use; it is reported to be used in 317 cosmetic products, 279 of which are leave-on formulations. The results of a concentration of use survey provided by the Council in 2020 indicate that Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer has the highest use concentration; it is reported to be used at maximum concentrations up to 0.18% in leave-on products (foundations).

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 d. 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 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 was 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 phosphoryl-choline-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) were implanted s.c. into 3 male 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.

A trade name mixture containing 1.4% Polyquaternium-51 was not an irritant in the Irrectection® assay when tested at doses of 25, 50, 75, 100, and 125 µl. Polyquaternim-51 was not a sensitizer in an animal study (maximization test using groups of 10 Hartley guinea pigs of a tradename mixture containing 5% aqueous Polyquaternium-51) or human studies (maximization test with 25 subjects of a foundation containing 0.08125% Polyquaternium-51; (HRIPT; occlusive patches) with 212 subjects of a serum containing 0.12% Polyquaternium-51). Polyquaternium-61 (25% in petrolatum) was not a sensitizer in the guinea pig adjuvant and patch test (5 (Aai: (HA) outbred albino guinea pigs).

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).

DISCUSSION

This assessment reviews the safety of 8 acryloyloxyethyl phosphorylcholine polymers, as used in cosmetic formulations. The Panel concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel considered the available data include in this assessment to be adequate for determining safety; data on poly (2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) were deemed appropriate for read across. Based on the molecular weights of the ingredients, significant skin penetration is not expected. The only skin penetration data in this report are on the read-across ingredient; these data demonstrate the absence of skin penetration. Furthermore, the Panel agreed that the expected absence of skin penetration essentially eliminates the need for systemic toxicity data (i.e., subchronic/chronic toxicity, carcinogenicity, and reproductive/developmental toxicity data) on the acryloyloxyethyl phosphorylcholine polymers. Furthermore, the absence of structural alerts for genotoxicity in the polymers reviewed mitigates the need for genotoxicity data.

Chemical characterization data provide an indication of residual monomer content. 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.

The Panel also discussed irritation and sensitization. Concern for the skin irritation and sensitization potential of these polymers was mitigated based on the negative irritation and sensitization data for Polyquaternium-51 and Polyquaternium-61, and the absence of skin penetration by these polymers.

The chemical structures for Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer and Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer were not found in the published literature, nor were these structures provided by the cosmetics industry. However, information relating to their chemistry was provided by the International Nomenclature Committee. After reviewing the information provided, the Panel agreed that the description of the polymerization process is a plausible basis for including Hydroxyethylcellulose/Phosphoryl-choline Glycol Acrylate Copolymer and Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer in this safety assessment.

The Panel expressed concern regarding heavy metals that may be present in these ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

Finally, the Panel discussed the issue of incidental inhalation exposure resulting from these ingredients ((Polyquaternium-61 is reported to be used in aerosol hair sprays at concentrations up to 0.000006%, and in face powders at concentrations up to 0.0069%.). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. As indicated in the respiratory exposure resource document and in the Cosmetic Use section of this report, airbrush application of cosmetic products is not assessed by the Panel. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 8 acryloyloxyethyl phosphorylcholine polymers are safe in cosmetics in the present practices of use and concentration described in the 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

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

TABLES

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

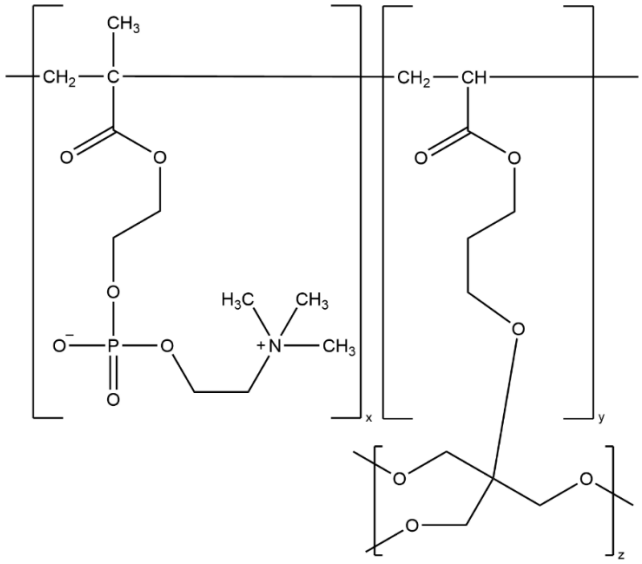
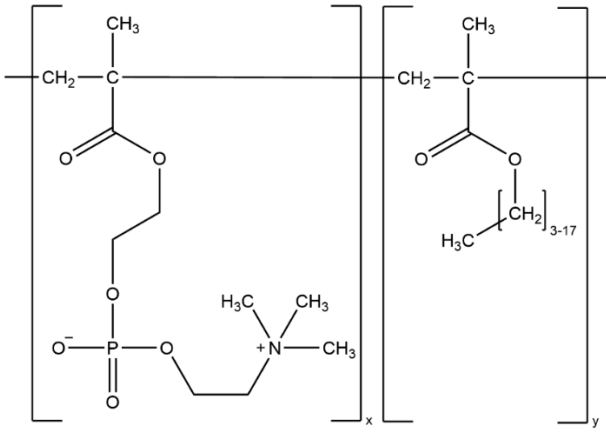
Ingredient/CAS No.	Definition & Structures	Function(s)
Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer	Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer is a copolymer formed from acrylic acid and phosphorylcholine glycol methacrylate, crosslinked with an allyl ether of pentaerythritol. 	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 is 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]

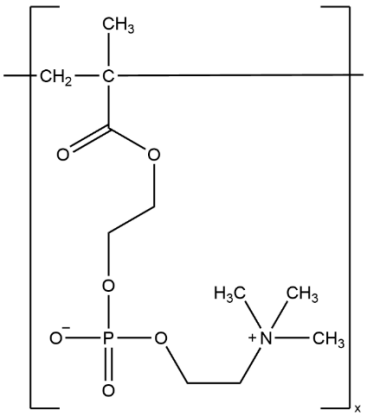
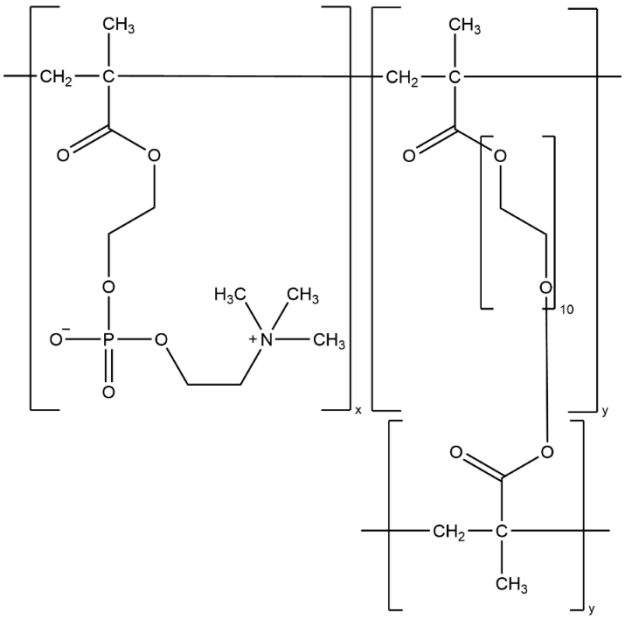
Ingredient/CAS No.	Definition & Structures	Function(s)
Polyphosphorylcholine Glycol Acrylate 67881-99-6	Polyphosphorylcholine Glycol Acrylate is the polymer that conforms generally to the formula: 	film formers; skin-conditioning agents - miscellaneous
Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate 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 is 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]

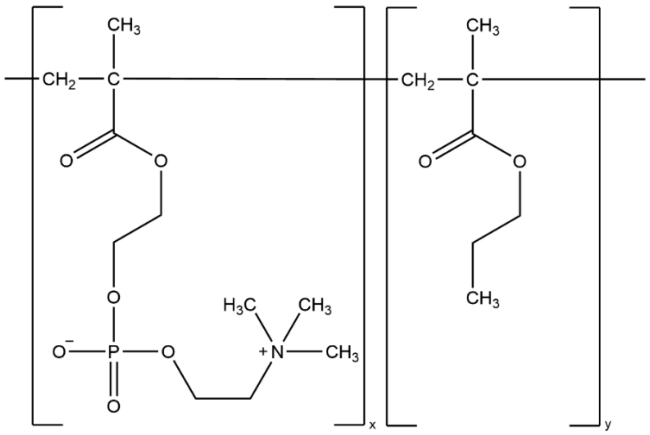
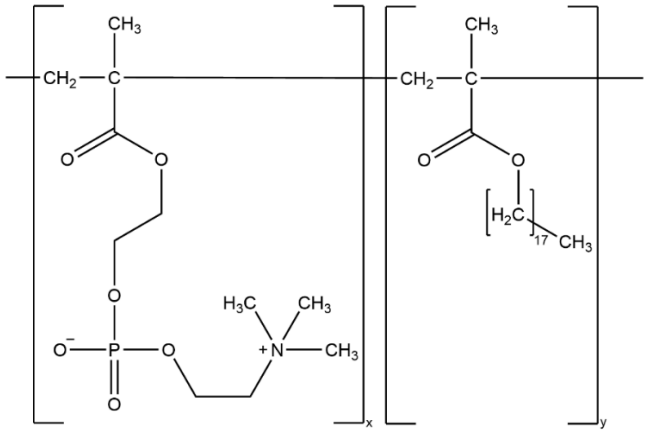
Ingredient/CAS No.	Definition & Structures	Function(s)
Polyquaternium-51 125275-25-4	Polyquaternium-51 is the polymeric quaternary ammonium salt that conforms generally to the formula: 	Film Formers; Skin-Conditioning Agents - Humectant
Polyquaternium-61	Polyquaternium-61 is the polymeric quaternary 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 (2022) 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**	**9**	**0.0005-0.075**	**317**	**0.000005-0.14**
Duration of Use						
Leave-On	*NR*	*0.13-0.18*	*8*	*0.0005-0.075*	*279*	*0.002-0.14*
Rinse off	*NR*	*NR*	*1*	*NR*	*38*	*0.000005-0.025*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	24	0.021-0.05
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation - Sprays	NR	NR	6[a];2[b]	0.0005[b]	1;97[a];95[b]	0.01[a]
Incidental Inhalation - Powders	NR	NR	2[b]	0.0005[b]	4;95[b]	0.008-0.14[c]
Dermal Contact	NR	0.13-0.18	4	0.0005-0.075	310	0.000005-0.14
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	5	NR	7	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	7	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Polyquaternium-61	
	# of Uses	Conc. (%)
Totals/Conc. Range	**3**	**0.000006-0.01**
Duration of Use		
Leave-On	*2*	*0.000006-0.0069*
Rinse off	*1*	*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	1	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	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; 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	[20]
			ANIMAL		
Polyquaternium-51 (tradename mixture; 5% aqueous)	Challenge: 6.25 v/v %, 12.5 v/v %, 25 v/v%, 50 v/v%, and 100 v/v% [For preparation of test solutions, 5% aq. Poly-quaternium-51was defined as 100 v/v% original solution. Thus, the highest test concentration was 100 v/v% solution.]	Hartley guinea pigs test group: 10 animals negative control (water) and positive control (1-choloro-2,4-dinitrobenzene [DCNB])groups: 5 animals each	Sensitization potential evaluated in maximization test. For intradermal induction (on day 1), the test group was injected in the cranial part of scapular region with Polyquaternium-51, Freund's complete adjuvant(FCA) and the test material (1:1), an d FCA and water (1:1). On day 8, the skin was pretreated with an open application of 10 w/w% sodium lauryl sulfate (SLS), and on day 9, an occlusive patch containing 0.2 ml of Polyquaternium-51 was applied for 48 h. On day 22 (challenge phase), occlusive patches containing 0.1 ml of the challenge solutions were applied for 24 h. Challenge sites were evaluated at 24 nd 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.	[21]
Polyquaternium-61	25% in petrolatum	5 albino guinea pigs (Aai: (HA) outbred)/group	Skin sensitization potential evaluated in guinea pig adjuvant and patch test. A negative control group (petrolatum; only applied during challenge phase) and a positive control (DNCB) group were included. 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. 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 (0.5 ml) on 3 consecutive days (1 application/day). Second week of induction involved pretreatment of patch application sites with SLS. Test substance (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, 0.1 ml) made to new site on flank (open patch, 5 cm x 5 cm area) of test animals. Negative control (petrolatum) was also applied to the flank (5 cm x 5 cm area) of each animal in negative control group. 1,2- DNCB (up to 1%) similarly applied to 5 positive control	Polyquaternium-61 was not a sensitizer in guinea pigs. DNCB induced sensitization.	[24]

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			animals. Observations relating to erythema, edema, recorded at 24 h and 48 h after challenge applications.		
			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) were 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 the test material (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. The test formulation did not possess contact-sensitizing potential and not likely to cause contact sensitivity reactions under normal use conditions	[22]
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 x/wk 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	[23]

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Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer

Total: 0

C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer

Total: 0

Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer

Total: 0

Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer

Total: 0

Polyphosphorylcholine Glycol Acrylate

Tonics, Dressings, and Other Hair Grooming Aids	5
Cleansing	1
Face and Neck (exc shave)	2
Moisturizing	1

Total: 9

Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer

Total: 0

Polyquaternium-51

Eye Shadow	7
Eye Lotion	7
Eye Makeup Remover	1
Other Eye Makeup Preparations	9
Other Fragrance Preparation	1
Hair Conditioner	2
Shampoos (non-coloring)	4
Tonics, Dressings, and Other Hair Grooming Aids	1
Face Powders	4
Foundations	43
Makeup Bases	3

Other Makeup Preparations	5
Bath Soaps and Detergents	5
Other Personal Cleanliness Products	2
Shaving Cream	1
Cleansing	22
Face and Neck (exc shave)	75
Body and Hand (exc shave)	20
Moisturizing	85
Night	7
Paste Masks (mud packs)	1
Skin Fresheners	4
Other Skin Care Preps	8

Total: 317

Polyquaternium-61

Other Hair Preparations	1
Face and Neck (exc shave)	1
Night	1

Total: 3