Safety Assessment of Polyquaternium-6 as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 20, 2021
Panel Date: September 13-14, 2021

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

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

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

Date: August 20, 2021

Subject: Safety Assessment of Polyquaternium-6 as Used in Cosmetics

Enclosed is a Draft Final Report of the Safety Assessment of Polyquaternium-6 (*polyqu092021rep*) as Used in Cosmetics. A Tentative Report with a conclusion stating that Polyquaternium-6 is safe in cosmetics in the present practices of use and concentration described in the safety assessment was issued at the December 2020 Panel meeting. Comments on the Tentative Report (*polyqu092021pcpc*) that was issued at the December 2020 Panel meeting have been addressed, and the Draft Final Report has been revised accordingly. This report has also been revised to include the 2021 FDA VCRP data (*polyqu092021FDA*) (highlighted in the report text) that are included for the Panel's review.

Also included in this package for your review are the report history (*polyqu092021hist*), flow chart (*polyqu092021flow*), literature search strategy (*polyqu092021strat*), ingredient data profile (*polyqu092021prof*), and Panel meeting minutes of the December 2020 Panel meeting (*polyqu092021min).*

After reviewing these documents, as well as the Abstract, Discussion, and Conclusion , the Panel should issue a Final Report with the conclusion that is stated in the first paragraph above.

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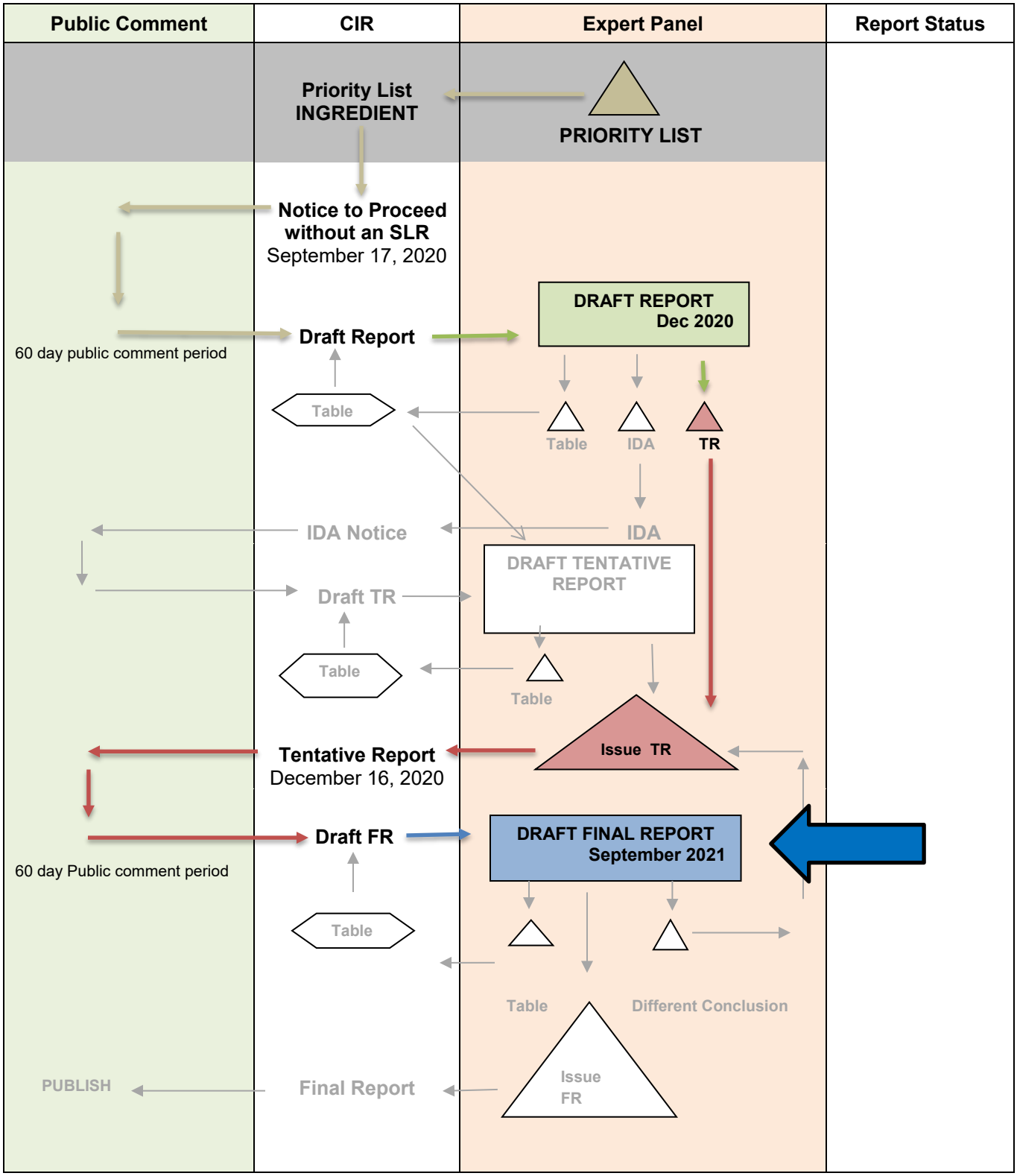
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Polyquaternium-6

MEETING September 2021



CIR History of:

Polyquaternium-6

A Scientific Literature Review (SLR) Notice to Proceed (NTP) on Polyquaternium-6 was issued on September 17, 2020.

Draft Report, Teams/Panel: December 7-8, 2020

The draft report also contains the following unpublished data that were received from the Council:

- Use concentrations
- Molecular weight
- Method of manufacture, composition, and impurities
- Acute dermal, oral, and inhalation toxicity; skin irritation (animal), and ocular irritation (animal)
- Short-term oral toxicity
- Subchronic dermal toxicity
- In vitro genotoxicity
- Skin irritation and sensitization (animal)
- Skin sensitization (human)
- Photoallergenicity (animal)
- Ocular irritation

The Panel issued a tentative report for public comment with the conclusion that Polyquaternium-6 is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The Panel noted that most of the safety test data in this report are on high molecular weight Polyquaternium-6 (42%, MW 150,000 Da, 6.5% monomer content). It was agreed that, overall, the available data are not indicative of any safety concerns relating to skin sensitization, systemic toxicity, or other toxicity endpoints, while acknowledging the polymer and monomer content of the test substance administered. The Panel considered the limited, negative skin sensitization/photosensitization data in this safety assessment, but noted that potential concerns relating to systemic exposure, in the absence of additional data, would be mitigated because this ingredient would not be percutaneously absorbed.

The Panel discussed the issue of incidental inhalation exposure from the use of Polyquaternium-6 in hair sprays (pump sprays) at maximum use concentrations up to 0.5%. The Panel stated that droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of Polyquaternium-6. Finally, the Panel cautions that products containing Polyquaternium-6 should be formulated to avoid the formation of nitrosamines.

Draft Final Report, Teams/Panel: September 13-14, 2021

The draft final report has been revised to include 2021 FDA VCRP data and comments that were received from the Council.

Polyquaternium-6 Data Profile* –September13-14, 2021 – Wilbur Johnson, Jr.																														
						Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents	Impurities	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Polyquaternium-6	**149**		**X**	**X**	**X**			**X**	**X**	**X**	**X**	**X**				**X**					**X**	**X**		**X**	**X**	**X**		**X**		

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

Polyquaternium-6 – 8/10-13/20; 10/20/20; 6/7/21; 7/20/21

Ingredient	CAS #	InfoBase	SciFinder	PubMed		FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Polyquaternium-6 (Quaternium-40)	26062-79-3	Yes		7/422		Yes (indirect additive)	No	No	No	No	No	No	No	No	No	No	No	Yes

*ECHA – pre-registration process

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)
FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)
EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - 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/

DECEMBER 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team –December 7, 2020

DR. BELSITO: So then we're going to polyquaternium-6. Okay. So this is the first time that we're looking at this ingredient. So on PDF page 8, it says the presence of nitrosamines in polyquaternium-6 has not been determined. And my question was would we expect it to be present? This is right at the bottom of PDF 8.

DR. KLAASSEN: I don't think it's a problem.

DR. BELSITO: And how would we address that, or do we just strike that sentence?

DR. KLAASSEN: I guess why was it added in the first place I wonder? How did that come about?

DR. BELSITO: I don't know. Wilber, can you tell us?

MR. JOHNSON: That statement was included in the industry submission.

DR. BELSITO: So industry was concerned that there could be nitrosamines or -- based upon the method of manufacturer that we have here, would you expect those to be formed, Curt or Dan?

DR. EISENMANN: Dr. Liebler, you're muted.

DR. LIEBLER: I'm sorry. Thank you, Carol. So this is Dan. I normally would not expect nitrosamines to be formed -- you normally think of those from secondary amines. However, I googled quaternary amines, nitrosamine precursors. And there's a paper in a 2010 issue of the ACS Journal, Environmental Science and Technology. And there's a couple lines in the abstract that are highlighted here. "Experiments indicated that nitrosamines form in low yield from quaternary amines, and that the nitrosamines form from the quaternary amines themselves not just lower order amine impurities."

So I haven't had a chance to read the paper. And it would be interesting to see what Lisa thought of this. So I think that it's okay to leave the language in. Because, essentially, what it's saying is that nitrosamines have not been determined. I mean that basically says it was not attempted to measure them.

DR. BELSITO: So then do we need something in the discussion with our usual nitrosation caveat?

DR. LIEBLER: Yes.

DR. BELSITO: Okay.

DR. KLAASSEN: We'll have to look and see what Ron has to say tomorrow also, but this is a -- it's not just the quat. It's a polyquat.

DR. BELSITO: Yeah.

DR. KLAASSEN: Which would probably decrease the problem, potential problem.

DR. BELSITO: Okay. Well, let's wait and see. And then we have --

DR. SNYDER: It's also happened before.

DR. BELSITO: Okay, yeah. Because we had that sub-chronic toxic dermal that included --

DR. SNYDER: Yeah. Negative up to 40 percent.

DR. BELSITO: And it was also on abraded skin.

DR. SNYDER: Yeah.

DR. BELSITO: For genotox, do we need mammalian? We don't have it. Or again, because it's not absorbed or not that -- well, but we still have skin (audio skip).

DR. LIEBLER: I didn't flag it. I don't think it's going to be -- I think a mammalian test is going to be -- at least done from dermal administration -- is going to be negative because this material will not be absorbed it's so big.

DR. BELSITO: Okay. So we're fine with that.

DR. LIEBLER: I think so.

DR. KLAASSEN: Especially because they've done the four different AMES tests or strains, and that's about as good as you can get.

DR. BELSITO: Okay. So I thought overall we could go with a safe as used. And in the discussion, the aerosol boilerplate, nitrosation, the molecular weight, Kow and subchronic dermal mitigate tox studies, limited sensitization, but not expected to get past the stratum corneum.

DR. LIEBLER: I do have another question on PDF page 11, top of the page, third line.

DR. BELSITO: Yeah?

DR. LIEBLER: It says the skin irritation potential of a similar substance was evaluated. It doesn't appear to say what the similar substance was.

MR. JOHNSON: That information is not included in the industry submission.

DR. LIEBLER: Take it out.

DR. KLAASSEN: Yeah.

MR. JOHNSON: Okay.

DR. EISENMANN: Actually, that says -- there is other places where it was. But that one is -- from reference 17 -- that is the polymer with the higher level of monomer. If that's from reference 17, Wilbur, that's the higher-level monomer.

DR. LIEBLER: Yeah. It is. So we could clarify that --

DR. EISENMANN: So that's incorrect. That, you know the compound. You don't know the compound for an acute oral. And there's dermal irritation and a mucous membrane irritation. That should be taken out.

DR. LIEBLER: Reference eight.

DR. EISENMANN: Right.

DR. LIEBLER: Yeah. Okay.

DR. EISENMANN: But reference 17 you know the compounds.

MR. JOHNSON: Okay. thank you.

DR. BELSITO: So we do know this compound. Is that what you're saying, Carol?

DR. EISENMANN: Yes. That's the larger molecular weight compound with the high level of monomer.

DR. BELSITO: Okay.

DR. KLAASSEN: So that needs to be inserted.

DR. BELSITO: Yeah.

MR. JOHNSON: Okay.

MS. FIUME: Were you discussing the ocular irritation study? I'm sorry.

DR. BELSITO: No. The dermal irritation at the top of page 11, Monice.

MS. FIUME: Okay. Thank you.

DR. BELSITO: But I don't really think, you know, since it has a high level of monomer, do we really need to put that in the discussion? I don't think so. I think we just need to make it clear, under Sensitization and Irritation, what that material was. Would you agree, team?

DR. LIEBLER: Yes. I agree.

DR. BELSITO: Okay. So then safe as used. Aerosol boilerplate, nitrosation, lack of dermal absorption, limited sensitization but not expected to get past the stratum corneum.

DR. LIEBLER: So one other item that might come up -- don't know if the other teams ever flagged this -- having to do with the residual monomer. There are, at least -- I think there are three different versions described residual monomer under Composition Impurities on Page 8. The first one says, not to exceed one percent by weight. And then the next one says up to 0.5 percent. And then the last one, which is at the top of PDF nine, free unreacted monomer six and a half percent maximum.

So I thought about the monomer a little bit. The monomer itself, I think it probably poses little risk. It is itself non-reactive towards proteins without metabolism. The monomer would be kind of like that structure in the -- that showed on the report, but with alkenes or double bonds in those side chains. The (audio skip) in the skin if possible, but the likelihood's unknown.

We wrestled with this a lot in RIFM, when trying to assess whether a molecule belongs in the reactive or nonreactive dermal sensitization threshold scheme. We would probably use reactive DST for this and RIFM, because we'd be kind of overly conservative, Don. But I think that the likelihood of direct skin reaction with this monomer is nil in contrast to many of the monomers we talk about. So I'm not concerned about this but in case the monomer discussion comes up, that's kind of where I am to begin with.

DR. BELSITO: Okay. Well, I'll make a note of that. If it comes up in the discussion, did Daniel address it?

DR. LIEBLER: Yeah.

DR. SNYDER: Hey, Don, on page 15 under table 4 -- oh never mind. I see it over there on the left. Okay. It was 42 percent. I didn't see what that sensitization study was. That was at 42 percent. Never mind. I thought I had 4.2 percent, but it's 42 percent.

DR. BELSITO: Okay. Anything else here? Okay. Wilbur, you're all set with this?

MR. JOHNSON: Yes. I am, thank you.

DR. BELSITO: Okay.

MS. FIUME: Don, can I just ask for clarification because I see it's in the report in several places? Was it said that when it states that a similar substance, that was not identified is included, that that information should be removed from the report?

DR. BELSITO: Carol says we know what that substance is.

MR. JOHNSON: Yes.

MS. FIUME: I think for Reference 17, right? But is it with Reference 8, it says the test substance was unidentified?

MR. JOHNSON: Yeah. For Reference 8 that statement stands. But for the Reference 17, we know the molecular weight and the monomer content of that.

DR. BELSITO: So then Monice's question, I guess, to our team is if we don't know what was tested, do we put that data in? I think if we don't know what's tested, we really -- it shouldn't be in the report.

DR. SNYDER: Correct.

DR. LIEBLER: So we just reviewed this with Carol. And it was in Reference 17 we do know what was tested.

DR. BELSITO: Exactly.

DR. LIEBLER: And in Reference 8 we do not know. So that one should come out.

DR. BELSITO: Okay. So where is that in the report exactly?

MS. FIUME: I believe there's several occurrences. Is that correct, Wilbur? I know it's under Ocular Irritation.

MR. JOHNSON: I recall the Ocular Irritation, but maybe other sections also.

DR. LIEBLER: Dermal Irritation on the top of PDF 11.

MS. FIUME: Dermal Irritation.

DR. EISENMANN: And I think Acute Oral.

DR. BELSITO: Okay. Anything else? Okay. So we're going to delete everything that has to do with Reference 8. So my quick scan, we still have sufficient information to go with the safe as used. Okay?

MR. JOHNSON: Dr. Belsito, just one question. Specifically, what do you want to be stated about nitrosation in the discussion?

DR. BELSITO: That if in fact the material contains nitrosamine, the usual boilerplate.

MR. JOHNSON: Okay. Thank you.

DR. BELSITO: Okay. Anything else? We're all set?

DR. LIEBLER: That's it. It's good.

Cohen Team – December 7, 2020

DR. COHEN: So next on the list is Polyquaternium-6. So this is Wilbur's. This is a draft report. It's the first time we're reviewing this. It's a single ingredient used as a skin conditioning agent. Its max use is three percent in rinse off and 1.2 percent in leave on. It's in three percent in a hair straightener.

We have method of manufacturing. There was a late-breaking memo from the Council, which had some clarifications that I thought were fine, and some specification about using a similar substance which was the Polyquaternium-6. And then there's some residual monomer of 0.5 percent. So comments from the team. Lisa, what do you think?

DR. SHANK: I think we have --

DR. PETERSON: Actually, I think that there are some reports of the monomer being up to 6.5 percent. And my review of the literature is that the monomer is toxic, could be irritant. And I was wondering if it's actually -- what's responsible for the varying effects reported for irritation in the subsequent things. So, I mean, otherwise, I have no concern.

It was just I was trying to understand why there was a varied response in the dermatological testing. And, given a wide range of -- I mean, there is one report, and it's on PDF Page 9 at the top, the maximum concentration. Again, I could be -- I just feel like the resid- -- if there's residual monomer of substantial amount, it is toxic. And so it could be respon- -- it could explain some of the inconsistencies seen in some of the dermal irritation stuff. Yeah.

And because, if it's six and a half percent, in a 1.2 percent solution, it's 0.07 percent, so it would be significant.

DR. COHEN: Yeah. It's consequential.

DR. PETERSON: That's my only comment on this whole thing. I have some minor edits for the (audio skip).

DR. COHEN: Yes, you're right. I'd like to (inaudible) it's 6.5 percent. Ron?

DR. SHANK: Yes.

DR. COHEN: What are your thoughts and comments on the tox package here?

DR. SHANK: I think we have enough tox data. We have 90-day dermal, genotox, irritation and sensitization. We don't have developmental reproductive toxicity, but this is a large molecule. It's positively charged, a little skin penetration is expected, so I don't think we need DART. I don't know about the reacted monomer. The toxicology data looked pretty good.

DR. COHEN: Tom? Tom? Tom, are you able to hear us?

DR. SLAGA: Tom Slaga here. I basically agree that I think we have enough tox data. The irritation/sensitization data, to me, is okay. The genotox is okay and the general toxicity. Also, it should be known that, obviously, this is a FD- -- come again?

DR. COHEN: No, proceed.

DR. SLAGA: Can you hear me?

DR. COHEN: Yes, proceed.

DR. SLAGA: Hello?

DR. COHEN: We can hear you.

DR. SLAGA: Can you hear me? My speaker's on.

DR. COHEN: We can hear you.

DR. SHANK: I can hear you, Tom.

DR. BERGFELD: Yes. Yes. Yes.

DR. PETERSON: Yeah, we can hear you.

DR. SLAGA: Hello? Hello?

DR. SHANK: Yeah, we can hear you.

DR. COHEN: Tom, we can hear you.

DR. SLAGA: Okay.

DR. BERGFELD: Hello?

DR. SLAGA: It's also an FDA-approved indirect food additive. Okay. The toxicology is all okay.

DR. COHEN: Lisa, any suggestions or concerns about the residual monomer and how -- is there any other information?

DR. SLAGA: Okay. Thanks.

DR. PETERSON: No.

DR. COHEN: You need to -- you need it?

DR. PETERSON: No, I don't have any real significant concerns. I just was pointing out that it seemed like -- somewhere I had gotten the impression that there was some irritation, and I just was thinking that I would say the irritation is --

DR. SLAGA: I didn't have any problem.

DR. PETERSON: I don't have really have any problem. I just was thinking, given all of the data, that in some of the reports there was small amounts of irritation. And my only comment was that the monomer is toxic and could be responsible for that. So I don't know that this needs to go beyond this conversation. My only comment, I thought it was overall clean.

DR. COHEN: Yeah.

MR. JOHNSON: Dr. Cohen, I have a comment.

DR. COHEN: We need the HRIPT? I'm sorry, Wilbur?

MR. JOHNSON: Yeah, I have a comment. Most of the tox data in the report are on the 115 thousand Dalton molecular weight compound with the 6.5 percent monomer content. And those studies are associated with Reference 17. So anywhere you see Reference 17, that means that the 115 thousand molecular weight compound, with a 6.5 percent monomer, is being tested.

DR. PETERSON: Cool. Then I think you can say that there is no concerns. Because there's no con- -- I mean, the data is very clean.

DR. BERGFELD: That can get in the discussion. You can put that in the discussion.

DR. COHEN: Yeah, that would be good for the discussion. The 50 subjects didn't show any signals. There was a phototox with natural light. It looked okay. If there's nothing right now, do we proceed with safe as used in the present practice and proceed?

DR. SHANK: Yes.

DR. BERGFELD: Yes.

DR. SHANK: Yes.

DR. COHEN: Okay. So it advances to a draft final report? A draft report -- not a draft report.

MR. JOHNSON: I think it would advance to a draft tentative report.

DR. BERGFELD: Tentative final.

DR. COHEN: Give me that again, Wilbur.

DR. HELDRETH: No, what will happen is --

MR. JOHNSON: It would advance to a tentative report, if approved by the Panel.

DR. COHEN: (Inaudible).

DR. HELDRETH: Actually, it will skip over the draft, Wilbur, and it goes straight to a tentative report.

MR. JOHNSON: Yes. Mm-hmm. Thank you.

DR. BERGFELD: And a final.

DR. COHEN: Because we don't have any issues, right?

DR. BERGFELD: Right.

MR. JOHNSON: Right.

DR. COHEN: Okay. We'll have one more crack at it as the draft final report, right? Okay. The next one is Dimethicone, Methicone, and Substituted-Methicone Polymers.

Full Panel – December 8, 2020

DR. BELSITO: Yeah, so this is the first time the Panel is reviewing the safety of this single ingredient. It's always nice to have just one ingredient to look at. And it's used in 282 cosmetic products, primarily rinse-offs and more diluted for bath use. Maximum concentration of use in a leave-on is 1.2 percent.

We looked at all the data and felt that because of the relative lack of absorption of this material, in fact it's not likely to get pass the stratum corneum, that this was safe as used.

DR. BERGFELD: And that's a motion?

DR. BELSITO: Yes.

DR. BERGFELD: Second?

DR. COHEN: Second.

DR. BERGFELD: Any further discussion on this --

DR. COHEN: Second.

DR. BERGFELD: Yes, I have it. Any further discussion on this ingredient then?

DR. BELSITO: Yes --

DR. BERGFELD: Anything after discussion?

DR. BELSITO: In the discussion, the molecular weight, the KOW, and the sub-chronic dermal mitigate tox studies. There's limited sensitization but not expected to pass the stratum corneum. And that there was a question about nitrosation, but we could put that in the discussion, using our usual boilerplate for nitrosation. Also needs the aerosol boilerplate. And we thought that reference eight could be deleted in the reports since we don't know what the materials are.

DR. BERGFELD: Any comment, Dr. Cohen?

DR. COHEN: Yes, so, we agree with your conclusion, Don. And, I guess, one item that came up in conversation, perhaps for the discussion, was the 6.5 percent residual monomer in the 150,000 Dalton product. But, we didn't see any signals in the irritancy or sensitization part, so it was just a matter of discussion and it didn't affect our final.

DR. BELSITO: And this is where Dan has a comment.

DR. BERGFELD: All right, Dan.

DR. LIEBLER: Well, the residual monomer in this case is a lot less reactive, chemically reactive, but for proteins then it would be, you know, acrylates or other things like that. So, I noted that high residual monomer concentration, but there's no evidence to suggest it's causing a problem if it is that high.

DR. BERGFELD: It could be put in the discussion for that as a disclaimer though.

DR. LIEBLER: Yeah. Correct.

DR. BERGFELD: Let's do that then. Any other comments or discussion? I'm going to move the question then. All those opposed to passing this as a safe with the discussion being outlined as discussed? Hearing none, moving on, this is unanimous approval. The next one is interesting, Sugarcane, or table sugar, Dr. Cohen presenting.

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Panel Date: September 13-14, 2021

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

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ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of Polyquaternium-6 as used in cosmetic formulations. This ingredient is reported to function as an antimicrobial agent, antistatic agent, film former, and hair fixative in cosmetics. The Panel cautions that Polyquaternium-6 should not be used in cosmetic products in which *N*-nitroso compounds can be formed. The Panel reviewed data relevant to the safety of this ingredient in cosmetic formulations, and concluded that Polyquaternium-6 is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The safety of Polyquaternium-6 as used in cosmetics is reviewed in this safety assessment. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Polyquaternium-6 is reported to function as an antimicrobial agent, antistatic agent, film former, and hair fixative in cosmetics.[1]

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

CHEMISTRY

Definition and Structure

Polyquaternium-6 (CAS No. 26062-79-3) is defined as a polymeric quaternary ammonium salt of diallyldimethyl ammonium chloride (DADMAC).[1] The idealized chemical structure is presented in Figure 1.

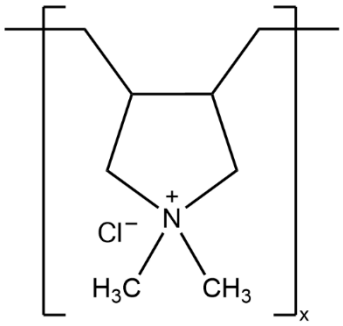

Figure 1. Polyquaternium-6 is the vinyl-type, homopolymer of DADMAC, wherein x is variable.

Chemical Properties

According to an analysis report from the cosmetics industry, Polyquaternium-6 has an average formula weight of 294,000 Da.[2] Additionally, it is soluble in water.[3] According to another source, 2 separate products identified as Polyquaternium-6 have typical molecular weights (MW) of 15,000 Da and 150,000 Da.[4] These and other properties are presented in Table 1.[2,3,5-7]

Method of Manufacture

Polyquaternium-6 is produced by the polymerization of DADMAC (21 CFR 176.170).

A cosmetics industry source indicates that the origin of the starting material for production of Polyquaternium-6 is synthetic, and that, as stated above, the production process involves polymerization of DADMAC.[8] This process does not involve the incorporation of additives such as preservatives, antioxidants, bleaching agents, or fragrances. Furthermore, the following by-products are not expected from the Polyquaternium-6 production process: 1,4-dioxane, ethylene oxide, monochloroacetic acid, dichloroacetic acid, phthalates, pesticides, glycol ethers, and residual solvents.

According to a manufacturer of 2 other products that are identified as Polyquaternium-6, both are produced by polymerization of DADMAC in an aqueous solution.[4] (Composition data on these 2 products are included at the end of the following section.)

Composition/Impurities

For use as an indirect food additive, the finished resin resulting from the polymerization of DADMAC has a nitrogen content of 8.6 6 ± 0.4% on a dry weight basis and the level of residual monomer is not to exceed 1% by weight of the polymer (dry basis) (21 CFR 176.170).

According to one supplier, Polyquaternium-6 contains 40 to 42% Polyquaternium-6 and 58% to 60% water.[8,9] The residual monomer content is up to a maximum of 0.5% dimethyldiallylamine, and data on other components are as follows: amines (maximum of 0.2%), sodium chloride (maximum of 1.5%), allyl alcohol (maximum of 250 ppm), allyl chloride (maximum of 50 ppm), and methyl chloride (< 2 ppm). Heavy metals content is up to a maximum of 10 ppm, and each of the following elements is present at concentrations of < 1 ppm: nickel, chromium, cobalt, cadmium, mercury, lead, arsenic, and antimony. The presence of nitrosamines in Polyquaternium-6 has not been determined.

Polyquaternium-6 (MW of 150,000 Da), produced by another company, contains Polyquaternium-6 (42%), water (< 58%), and free unreacted DADMAC (6.5% maximum).[4,10] Another product identified as Polyquaternium-6 (MW of 15,000 Da) manufactured by the same company, has the following composition: Polyquaternium-6 (33%), water (< 67%), acetic acid (0.65%), and free unreacted DADMAC (1.5% maximum).[4,10] Both have the same structure, and vary by the amount of repeated monomer units to achieve the desired MW.

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this safety assessment is evaluated based, in part, on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[11] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[12]

According to 2021 VCRP data, Polyquaternium-6 is reported to be used in 149 cosmetic products (10 leave-on products, 138 rinse-off products, and 1 product diluted for bath use; Table 2).[11] The results of a concentration of use survey completed in 2019 - 2020, and provided by the Council in 2020, indicate that Polyquaternium-6 is being used at maximum use concentrations up to 1.2% in leave-on products (tonics, dressings, and other hair grooming aids) and at maximum use concentrations up to 3% in rinse-off products (hair straighteners).[12] Cosmetic products containing Polyquaternium-6 may be applied to the skin/hair (at concentrations up to 3%) or, and may come in contact with mucous membranes (at concentrations up to 0.25% in bath soaps and detergents). Products containing Polyquaternium-6 are not typically applied more than once per day, and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Polyquaternium-6 is reported to be used in aerosol hair sprays (pump sprays) at maximum use concentrations up to 0.5%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[13-16] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[13,14]

Polyquaternium-6 is not restricted from use in any way under the rules governing cosmetic products in the European Union.[17]

Non-Cosmetic

Polyquaternium-6 is an FDA-approved indirect food additive for use as a component of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170). As a pigment dispersant and/or retention aid in the manufacture of paper, Polyquaternium-6 is used at a level not to exceed 10 pounds of active polymer per ton of finished paper and paperboard. As a pigment dispersant in coatings, it is used at a level not to exceed 3.5 pounds of active polymer per ton of finished paper and paperboard. For use only as a flocculant in the manufacture of paper and paperboard, it is used at a level not to exceed 10 mg/l (10 ppm) of influent water.

TOXICOKINETIC STUDIES

Dermal Penetration

Dermal penetration studies on Polyquaternium-6 were neither found in the published literature, nor were these data submitted.

Absorption, Distribution, Metabolism, and Excretion (ADME)

ADME studies on Polyquaternium-6 were neither found in the published literature, nor were these data submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Acute toxicity studies are presented in Table 3.

Dermal

The acute dermal toxicity of Polyquaternium-6 (MW and monomer content not stated) was evaluated in rats (number and strain not stated).[6] An LD_{50} of > 2 g/kg was reported. An acute dermal toxicity study on Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was performed using 4 groups of 4 rabbits (strain not stated).[10] The test substance was administered at the following doses, and the animals were wrapped in binders for the duration of the 24-h application period: 2.15 g/kg , 4.64 g/kg, 10.0 g/kg, and 21.5 g/kg. The LD_{50} was estimated to be > 21.5 g/kg, and no consistent test substance-related signs of systemic toxicity were observed.

Oral

The acute oral toxicity of Polyquaternium-6 (MW and monomer content not stated) was evaluated in a study involving mice (number and strain not stated). An LD_{50} of 1.72 g/kg was reported, and respiratory depression was observed.[18] Acute oral toxicity studies on Polyquaternium-6 (MW and monomer content not stated) were performed using rats (number and strain not stated).[3,18] An LD_{50} of 3 g/kg was reported in both studies. Respiratory depression was noted in one of the studies.[18] In another acute oral toxicity test on Polyquaternium-6 (MW and monomer content not stated) involving rats (number and strain not stated), an LD_{50} of > 2 g/kg was reported.[6] The acute oral toxicity of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using 6 groups of 5 male albino rats.[10] The animals received doses up to 14.7 g/kg via oral intubation. Necropsy findings were normal, and an LD_{50} of 8.71 g/kg was reported. An acute oral toxicity study on 42% aqueous Polyquaternium-6 (contained ~ 40% solids; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was performed using 4 groups of albino rats (5 males and 5 females per group).[10] The animals received doses up to 9.62 ml/kg via oral intubation. An acute oral LD_{50} of 3.15 ml/kg was reported. In an acute oral toxicity study on Polyquaternium-6 (MW and monomer content not stated) involving guinea pigs (number and strain not stated), an LD_{50} of 3.25 g/kg was reported.[18] Respiratory depression was observed.

Inhalation

The acute inhalation toxicity of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using 10 CD rats (5 females and 5 males).[10] The aerosolized test substance (1:1, in distilled water) was introduced into the breathing zone of each animal. The animals were exposed to the test substance at an average analytical concentration of 0.2 mg/l, with a nominal exposure concentration of 28 mg/l of diluted test substance. There was no evidence of inhalation toxicity.

Short-Term Toxicity Study

Oral

The short-term oral toxicity of Polyquaternium-6 (40% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using 5 groups of rats (strain not stated; 10 males and 10 females per group).[10] The test substance was fed in the diet at concentrations of 0, 330, 1000, 3300, and 10,000 ppm for 28 consecutive days. Feeding with the highest concentration caused depression of body weight gain, increased water consumption, and a decrease in diet efficiency. The maximum no-effect dosage of the test substance was estimated to be 3300 ppm for both male (280 mg/kg/d) and female (295 mg/kg/d) rats.

Subchronic Toxicity Study

Dermal

The subchronic dermal toxicity of Polyquaternium-6 (40% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using groups of rabbits (strain not stated; 10 males and 10 females per group).[10] For 89 to 92 consecutive days, the test substance was applied topically to abraded and intact skin at doses 0.25, 0.75, or 2.25 ml/kg/d. Negative control rabbits received physiological saline at a dose of 2.25 ml/kg/day. Each day the treatment area (test animals only) was cleaned with lukewarm tap water after 5 to 6 h of exposure. There was no evidence of systemic toxicity in any treatment group.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies on Polyquaternium-6 were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

In Vitro

The genotoxicity of Polyquaternium-6 (40 to 42%; number average MW (Mn) of 15,100 and residual monomer (dimethyldiallylamine) at 0.5%) was evaluated in the Ames test (Organisation for Economic Co-operation and Development test guideline (OECD TG) 471) using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, and TA1537.[19] The test substance was evaluated at doses ranging from 4 to 5000 µg/plate, with and without metabolic activation. The positive control with metabolic activation was 2-aminoanthracene, and the positive controls without metabolic activation were sodium azide, 9-aminoacridine, and 2-nitrofluorene. The test substance did not cause a dose-dependent increase in the

number of revertants in any of the bacterial strains, with or without metabolic activation. It was concluded that Polyquaternium-6 (40 to 42%) was not genotoxic in this assay, with or without metabolic activation. The positive controls were genotoxic.

CARCINOGENICITY STUDIES

Carcinogenicity studies of Polyquaternium-6 were neither found in the published literature, nor were these data submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal irritation and sensitization data summarized below are presented in detail in Table 4.

In a study involving 4 groups of 4 rabbits, Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was applied to the skin for 24 h at doses up to 21.5 g/kg.[10] Slight to severe erythema was observed. The skin irritation potential of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated in 6 rabbits.[10] After a 24-h application period, the test substance was not irritating to abraded or intact skin. In another study, the skin irritation potential of 42% aqueous Polyquaternium-6 (contained ~ 40% solids; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated in 3 rabbits (strain not stated).[10] After 24 h of application, very slight erythema was observed at abraded sites, but not at intact sites. The skin irritation potential of Polyquaternium-6 (MW 150,000, maximum DADMAC concentration of 6.5%) was evaluated using groups of rabbits (10 males and 10 females per group).[10] For 89 to 92 consecutive days, the test substance was applied topically to abraded and intact skin at a dose of 0.25, 0.75, or 2.25 ml/kg/d. Skin irritation was not observed at intact skin sites, but was observed at abraded sites. The Buehler test method (OECD TG 406) was used to evaluate the skin sensitization potential of Polyquaternium-6 (41% active in water; Mn of 15,100 and residual monomer (dimethyldiallylamine) at 0.5%), using 20 Pirbright-White guinea pigs. [20] Repeated 6-h applications were made to the skin, and reactions were classified as negative. The skin irritation and sensitization potential of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated in a human repeated insult patch test (24-h applications) involving 50 subjects.[10] Results were classified as negative.

Photosensitization/Phototoxicity

The photoallergenicity of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using 29 subjects.[10] During induction, the test substance (0.3 ml) was applied for 24 h, under a patch, to 2 x 2 cm^2 areas of skin. The test site was then exposed to natural sunlight for 30 to 40 min (between 11:00 AM and 3:00 PM). Applications and sunlight exposures were repeated for a total of 9 times. At challenge, a single application of the test substance, under sets of duplicate patches, was made to new sites. One of the replicate patch test sites in each set was used in the photoallergenicity evaluation, and another was used to evaluate contact sensitization. The test substance did not induce contact irritation, sensitization or photoallergy in any of the subjects tested.

OCULAR IRRITATION STUDIES

Ocular irritation studies summarized below are presented in detail in Table 5.

The ocular irritation potential of Polyquaternium-6 (MW and free unreacted monomer not stated) was evaluated using rabbits (number and strain not stated).[6] The test substance caused slight ocular irritation. The ocular irritation potential of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated in 6 New Zealand white rabbits [10] The test substance (0.1 ml) was instilled into the left conjunctival sac of each animal. Reactions were scored at 24 and 72 h. Ocular irritation was not observed. In another study, the ocular irritation potential of 42% aqueous Polyquaternium-6 (contained ~ 40% solids; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was studied in 3 male and 3 female rabbits.[10] The test substance (0.1 ml) was instilled into the left conjunctival sac. Reactions were evaluated over a 14-d period. The test substance induced transient, slight ocular irritation.

SUMMARY

Polyquaternium-6, a polymeric quaternary ammonium salt of diallyldimethyl ammonium chloride (DADMAC), is reported to function as an antimicrobial agent, antistatic agent, film former, and hair fixative in cosmetics. A cosmetics industry source indicates that the origin of the starting material for production of Polyquaternium-6 is synthetic, and that the production process involves polymerization of DADMAC. The residual monomer content is up to a maximum of 0.5% dimethyldiallylamine. According to the same source, Polyquaternium-6 is supplied as a solution consisting of 40 to 42% Polyquaternium-6 and 58 to 60% water.

According to a manufacturer of 2 other products (cationic homopolymers) that are each identified as Polyquaternium-6, both are produced by polymerization of DADMAC in an aqueous solution. One product contains Polyquaternium-6 (42%; MW of 150,000 Da), water (< 58%), and free unreacted DADMAC (6.5% maximum). The other product has the following

composition: Polyquaternium-6 (33%; MW of 15,000 Da), water (< 67%), acetic acid (0.65%), and free unreacted DADMAC (1.5% maximum).

For use as an FDA-approved indirect food additive, the finished resin resulting from the polymerization of DADMAC has a nitrogen content of 8.6 6 ± 0.4% on a dry weight basis and the level of residual monomer is not to exceed 1% by weight of the polymer (dry basis).

According to 2021 VCRP data, Polyquaternium-6 is reported to be used in 149 cosmetic products (10 leave-on products, 138 rinse-off products, and 1 product diluted for bath use). The results of a concentration of use survey provided by the Council in 2020 indicate that Polyquaternium-6 is being used at maximum use concentrations up to 1.2% in leave-on products (tonics, dressings, and other hair grooming aids) and at maximum use concentrations up to 3% in rinse-off products (hair straighteners).

Polyquaternium-6 is an FDA-approved indirect food additive for use as a component of paper and paperboard in contact with aqueous and fatty foods.

The acute dermal toxicity of Polyquaternium-6 was evaluated in a study involving rats (protocol details not stated). An LD_{50} of > 2 g/kg was reported. An acute dermal toxicity study on Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was performed using 4 groups of 4 rabbits (strain not stated). The LD_{50} was estimated to be > 21.5 g/kg, and no consistent test substance-related signs of systemic toxicity were observed.

In an acute oral toxicity study on Polyquaternium-6 involving mice, results yielded an LD_{50} of 1.72 g/kg. An LD_{50} of 3/g/kg for Polyquaternium-6 was reported in 2 acute oral toxicity studies involving rats (protocol details not stated). The acute oral toxicity of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using 6 groups of 5 male albino rats; an acute oral LD_{50} of 8.71 g/kg was reported. The acute oral toxicity of 42% aqueous Polyquaternium-6 (contained ~ 40% solids; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using 4 groups of albino rats (5 males and 5 females per group). Results indicated an acute oral LD_{50} of 3.15 ml/kg. In an acute oral toxicity study involving guinea pigs (protocol details not stated), an LD_{50} of 3.25 g/kg was reported.

The acute inhalation toxicity of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using 10 CD rats. The animals were exposed to the test substance at an average analytical concentration of 0.2 mg/l, with a nominal exposure concentration of 28 mg/l of diluted test substance. There was no evidence of acute inhalation toxicity.

The short-term oral toxicity of Polyquaternium-6 (40% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated using 5 groups of rats (strain not stated; 10 males and 10 females per group). The test substance was fed in the diet at concentrations of 330, 1000, 3300 and 10,000 ppm for 28 consecutive days. The maximum no-effect dosage of the test substance was estimated to be 3300 ppm for both male (280 mg/kg/d) and female (295 mg/kg/d) rats.

Subchronic dermal toxicity of Polyquaternium-6 (40% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was studied using groups of rabbits (strain not stated; 10 males and 10 females per group). The test substance was applied to abraded and intact skin at doses 0.25, 0.75 or 2.25 ml/kg/d for 89 to 92 d. There was no evidence of systemic toxicity.

The genotoxicity of Polyquaternium-6 (40 to 42%) was evaluated in the Ames test at doses up to 5000 µg/plate, using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. Results were negative, with and without metabolic activation.

In a study involving 4 groups of 4 rabbits, Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was applied to the skin for 24 h at doses up to 21.5 g/kg. Slight to severe erythema and necrosis were observed. The 24-h application of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) to the skin of 6 rabbits in another study did not cause skin irritation at intact or abraded skin sites. The skin irritation potential of 42% aqueous Polyquaternium-6 (contained ~ 40% solids; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated in 3 rabbits. Very slight erythema at 2 abraded sites, but not at any intact sites, was observed at 24 h post-application and persisted for 5 d. In a study involving groups of rabbits (10 males and 10 females per group), Polyquaternium-6 (40% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was applied to abraded and intact skin at doses up to 2.25 ml/kg/d for 89 to 92 consecutive days. Skin irritation was observed at abraded sites, but not at intact skin sites.

The Buehler test method was used to evaluate the skin sensitization potential of Polyquaternium-6 (41% active in water) using 30 guinea pigs (20 test and 10 controls). There was no evidence of skin sensitization. The skin irritation and sensitization potential of Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated in a repeated insult patch test involving 50 subjects. The dose per application was 0.1ml/cm^2, and results were negative. Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) did not induce, irritation, sensitization, or photoallergy in a repeated insult patch test involving 29 subjects.

The ocular irritation potential of Polyquaternium-6 was evaluated using rabbits (protocol details not stated). The test substance caused slight ocular irritation. The ocular irritation potential of Polyquaternium-6 (42%; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max) was evaluated in 6 New Zealand white rabbits, and results were negative. In another study, transient ocular irritation was observed in 6 rabbits tested with 42% aqueous Polyquaternium-6 (contained ~ 40% solids; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max).

DISCUSSION

This assessment reviews the safety of Polyquaternium-6 as used in cosmetic formulations. The Panel concluded that the data included in this review are sufficient for determining the safety of these ingredients as reportedly used in cosmetics.

The Panel noted that most of the safety test data in this report are on high MW Polyquaternium-6 (42%, MW 150,000 Da, 6.5% DADMAC content). It was agreed that, overall, the available data are not indicative of any safety concerns relating to the toxicity endpoints evaluated, while acknowledging the polymer and monomer content of the test substances administered. Furthermore, it was agreed that concern over the DADMAC residual monomer content is not warranted because it is the opinion of the Expert Panel that this monomer is non-reactive to proteins without bioactivation. Regarding the issue of potential systemic toxicity, the Panel agreed that there was no evidence of this effect in the subchronic dermal toxicity study that was reviewed. The Panel considered the limited, negative skin sensitization data in this safety assessment, but noted that sensitization (or any other potential concerns relating to safety in the absence of additional data) would be mitigated because it is not likely that this high MW polymer would move past the stratum corneum.

The Panel discussed the issue of the potential for incidental inhalation exposure from the use of Polyquaternium-6 in hair sprays (pump sprays) at maximum use concentrations up to 0.5%. The Panel noted that in aerosol products, 95% – 99% of droplets/ particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns (e.g., data available from an acute inhalation toxicity study suggest little potential for respiratory effects at relevant doses). Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

Finally, the Panel cautions that Polyquaternium-6 should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Polyquaternium-6 is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

TABLES

Table 1. Chemical Properties

Property	Value/Results	Reference
Form	Liquid; clear, light yellow liquid	3,5
Number average MW (Mn) (Da)	15,100	2
Weight average MW (Mw) (Da)	294,000	2
Higher average MW (Mz) (Da)	1,010,000	2
Polydispersity (Mw/Mn)	19.47	2
Typical MW (Da) of material that typically contains 42% Polyquaternium-6	150,000	4
Typical MW (Da) of material that typically contains 33% Polyquaternium-6	15,000	4
Stability	Stable. Incompatible with strong oxidizing agents, iron and iron salts, steel, copper, copper alloys, and aluminum.	5
Water solubility	Completely soluble	3
log K_{ow}	< 10; -2.301	3,7
Density (g/ml @ 25ºC)	1.09; 1.015	3,5,6
Specific gravity (@ 25ºC)	1.04	7
Refractive index (n20/D)	1.417; 1.375	5,7
Freezing point (ºC)	100	5
Melting range (ºC)	-2.8 - 0.0	3
Boiling point (ºC @ 1,013 hPa (760 mmHg))	100	3
Flash point (ºC, closed cup)	> 100	3
Flash point (ºC, tag closed cup)	0	7
Vapor pressure (hPa @ 25ºC)	20 - 30	3

Table 2. Frequency (2021)[11] and concentration (2020)[12] of use of Polyquaternium-6 according to duration and exposure

	# of Uses	Max Conc of Use (%)
Totals*	**149**	**0.0004-3**
Duration of Use		
Leave-On	*10*	*0.0004-1.2*
Rinse-Off	*138*	*0.04-3*
Diluted for (Bath) Use	*1*	*NR*
Exposure Type		
Eye Area	NR	NR
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	9[a];1[b]	0.067-0.5; 0.41-1.2[a]
Incidental Inhalation-Powder	1[b]	NR
Dermal Contact	9	0.2-0.25
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	79	0.067-3
Hair-Coloring	61	0.04-0.99
Nail	NR	0.0004
Mucous Membrane	3	0.2-0.25
Baby Products	NR	0.13

*Because this 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 these products are 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
NR – not reported (use not reported in VCRP or Council survey data)

Table 3. Acute toxicity studies

Test Article	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
DERMAL						
Polyquaternium-6 (MW and monomer content not stated)	Rats (strain not stated)	Not stated	Not stated	Details relating to test protocol not included.	LD_{50} > 2 g/kg	[3]
Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	Rabbits (strain not stated)	4 groups of 4 rabbits	Water	Test substance administered at the following doses: 2.15 g/kg, 4.64 g/kg, 10.0 g/kg, and 21.5 g/kg. After application, animals wrapped in binders for 24 h. Dosing followed by 14-d observation period	LD_{50} estimated at 21.5 g/kg. No consistent test substance-related signs of systemic toxicity observed. (Dermal irritation results are presented in Table 4.)	[10]
ORAL						
Polyquaternium-6 (MW and monomer content not stated)	Mice (strain not stated)	Not stated	Not stated	Details relating to test protocol not stated	LD_{50} = 1.72 g/kg. Respiratory depression noted.	[18]
Polyquaternium-6 (MW and monomer content not stated)	Rats (strain not stated)	Not stated	Not stated	Details relating to test protocol not included	LD_{50} = 3 g/kg	[3]
Polyquaternium-6 (MW and monomer content not stated)	Rats (strain not stated)	Not stated	Not stated	Details relating to test protocol not stated	LD_{50} = 3 g/kg. Respiratory depression noted	[18]
Polyquaternium-6 (MW and monomer content not stated)	Rats (strain not stated)	Not stated	Not stated	Details relating to test protocol not stated	LD_{50} > 2 g/kg	[3]
Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC)	Albino rats (male)	6 groups of 5	Water	Doses via oral intubation: 2.15 g/kg, 3.16 g/kg, 4.46 g/kg, 6.81 g/kg, 10.0 g/kg, and 14.7 g/kg. Dosing followed by 14-d observation period	LD_{50} = 8.71 g/kg. Necropsy findings for animals that survived to day 14 were normal.	[10]
Polyquaternium-6 (42% aqueous contained ~ 40% solids; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	Albino rats	4 groups (5 males and 5 females per group)	Water	Doses via oral intubation: 1.99 ml/kg, 3.37 ml/kg, 5.69 ml/kg, and 9.62 ml/kg. Dosing followed by 14-d observation period	LD_{50} = 3.15 ml/kg	[10]
Polyquaternium-6 (MW and monomer content not stated)	Guinea pigs (strain not stated)	Not stated	Not stated	Details relating to test protocol not stated.	LD_{50} = 3.25 g/kg. Respiratory depression noted	[18]
INHALATION						
Polyquaternium-6 (42% aqueous; MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	CD rats	5 males and 5 females	Water	Aerosolized test substance (1:1, in distilled water) introduced into breathing zone of each animal. Animals exposed to test substance at average analytical concentration of 0.2 mg/l, with a nominal exposure concentration of 28 mg/l of diluted test substance.	All animals survived through 14-day post-exposure period. No evidence of inhalation toxicity	[10]

Table 4. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
Polyquaternium-6 (MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	42% in water	4 groups of 4 rabbits (strain not stated)	Test substance applied to skin (for 24 h, under binder) at the following doses: 2.15 g/kg, 4.64 g/kg, 10.0 g/kg, and 21.5 g/kg.	Signs of dermal irritation included slight to severe erythema, slight edema, blanching, and necrosis. Relationship between doses administered and reactions observed not stated	[10]
Polyquaternium-6 (MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	42% in water	6 rabbits (strain not stated)	Testing performed according to Federal Hazardous Substances Labeling Act specifications (16 CFR 1500). Test substance (0.5 ml) applied for 24 h to intact and abraded skin; 1 in^2 square gauze patch secured with nonabsorbent binder. Reactions evaluated after 24 h and 72 h.	Nonirritating to abraded or intact skin	[10]
Polyquaternium-6 (MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	42% in water (contained ~ 40% solids)	3 rabbits (strain not stated)	The test material (0.5 ml) applied for 24 h, under occlusive dressing, to intact and abraded skin sites. Reactions evaluated over 2-wk period.	Very slight erythema at 2 abraded sites observed at 24 h post-application, and persisted for 5 d. Skin irritation not observed at intact sites or at abraded sites in other animals	[10]
Polyquaternium-6 (MW 150,000, maximum DADMAC concentration of 6.5%)	40% in water	Rabbits (strain not stated; 10 males and 10 females per group).	For 89 to 92 consecutive days, test substance applied topically to abraded and intact skin at doses 0.25, 0.75 or 2.25 ml/kg/d. Negative control rabbits received physiological saline at dose of 2.25 ml/kg/d. Each day, treatment area (test animals only) cleaned with lukewarm tap water after 5 to 6 h of exposure	Skin irritation was not observed at intact skin sites. At abraded sites, varying amounts of erythema and edema observed along the lines of abrasion. Doses associated these findings not identified	[10]
Polyquaternium-6 (number average MW (Mn) of 15,100 and residual monomer (dimethyldiallylamine) at 0.5%)	41% active in water	30 Pirbright-White guinea pigs (20 test and 10 controls)	Buehler test method (OECD TG 406) used to evaluate skin sensitization potential. Test substance applied to 20 guinea pigs on days 1, 8, and 15 of induction; challenged on day 29. Each induction and challenge exposure (0.5 ml) involved 6-h application, under 2 x 2 cm^2 occlusive patch, to clipped flank skin. Control animals treated with vehicle only during induction, and challenged test substance (41% active in water). Challenge sites evaluated at 24 h and 48h after patch removal.	No positive reactions in test or control animals. Classified as a non-sensitizer	[20]
			HUMAN		
Polyquaternium-6 (MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	42% in water	50 subjects	During induction, test substance (0.1ml/cm^2) applied for 24 h under occlusive dressing. Series of 12 applications made. At challenge, a series of 4 doses applied to new sites.	No evidence of skin irritation or sensitization	[10]

Table 5. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
		ANIMAL			
Polyquaternium-6 (MW and free unreacted monomer not stated)	Not stated	Rabbits (strain not stated)	Details relating to test protocol not included	Slight ocular irritation observed	[3]
Polyquaternium-6 (MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	42% in water	6 New Zealand white rabbits	Tested according to specifications of Federal Hazardous Substances Act (16 CFR 1500). Test substance (0.1 ml) instilled into left conjunctival sac of each animal; right eye served as control. Reactions scored at 24 h and 72 h	No evidence of ocular irritation	[10]
Polyquaternium-6 (MW of 150,000 Da and free unreacted monomer (DADMAC) at 6.5% max)	42% in water (contained ~ 40% solids)	6 rabbits (strain not stated; 3 males and 3 females)	Test substance (0.1 ml) instilled into left conjunctival sac; right eye served as untreated control. Reactions evaluated over 14-d period	Test substance induced slight ocular irritation. Slight conjunctival injection and discharge (moderate) observed in all animals. By 48 h, all reactions had cleared.	[10]

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2021 VCRP Data

Polyquaternium-6

Other Bath Preparations	02D	1
Hair Conditioner	05A	5
Hair Straighteners	05C	2
Shampoos (non-coloring)	05F	64
Tonics, Dressings, and Other Hair Grooming Aids	05G	6
Other Hair Preparations	05I	2
Hair Dyes and Colors (all types requiring caution statements and patch tests)	06A	61
Bath Soaps and Detergents	10A	2
Aftershave Lotion	11A	1
Cleansing	12A	4
Body and Hand (exc shave)	12D	1
Total		**149**

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 11, 2021

SUBJECT: Tentative Report: Safety Assessment of Polyquaternium-6 as Used in Cosmetics (release date: December 16, 2020)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Polyquaternium-6 as Used in Cosmetics.

Composition/Impurities – It would be helpful to note that the specifications listed for Polyquaternium-6 in 21CFR 176.170 are for the use of this material as an indirect food additive.

Acute, Oral; Summary – Although references 3 and 18 do not provide sufficient information to determine if the rat LD_{50} of 3 g/kg is from the same primary reference, the sources of this information are not transparent. Reference 3 is an MSDS that cites the LD_{50} to another safety data sheet. Reference 18 cites the study to a 1988 English translation of a Russian journal Gigiena I Sanitarya. Are these acceptable references for a CIR report?

Summary – In the Summary, it would be helpful to note the monomer limit for the ingredient when used as an indirect food additive.

Discussion - It is not clear why the Discussion suggests that DADMAC may be reactive to proteins with “bioactivation”. There is no information presented earlier in the report concerning the potential of DADMAC to react with proteins.

As only one acute inhalation study on Polyquaternium-6 is included in the CIR report, “limited data available from inhalation studies” needs to be revised.

Table 3 – The rat study with an LD50 of 3 g/kg is incorrectly cited to reference 5 in this table (it should be reference 3).