
Safety Assessment of Fatty Ester End-Capped Alkoxylates as Used in Cosmetics

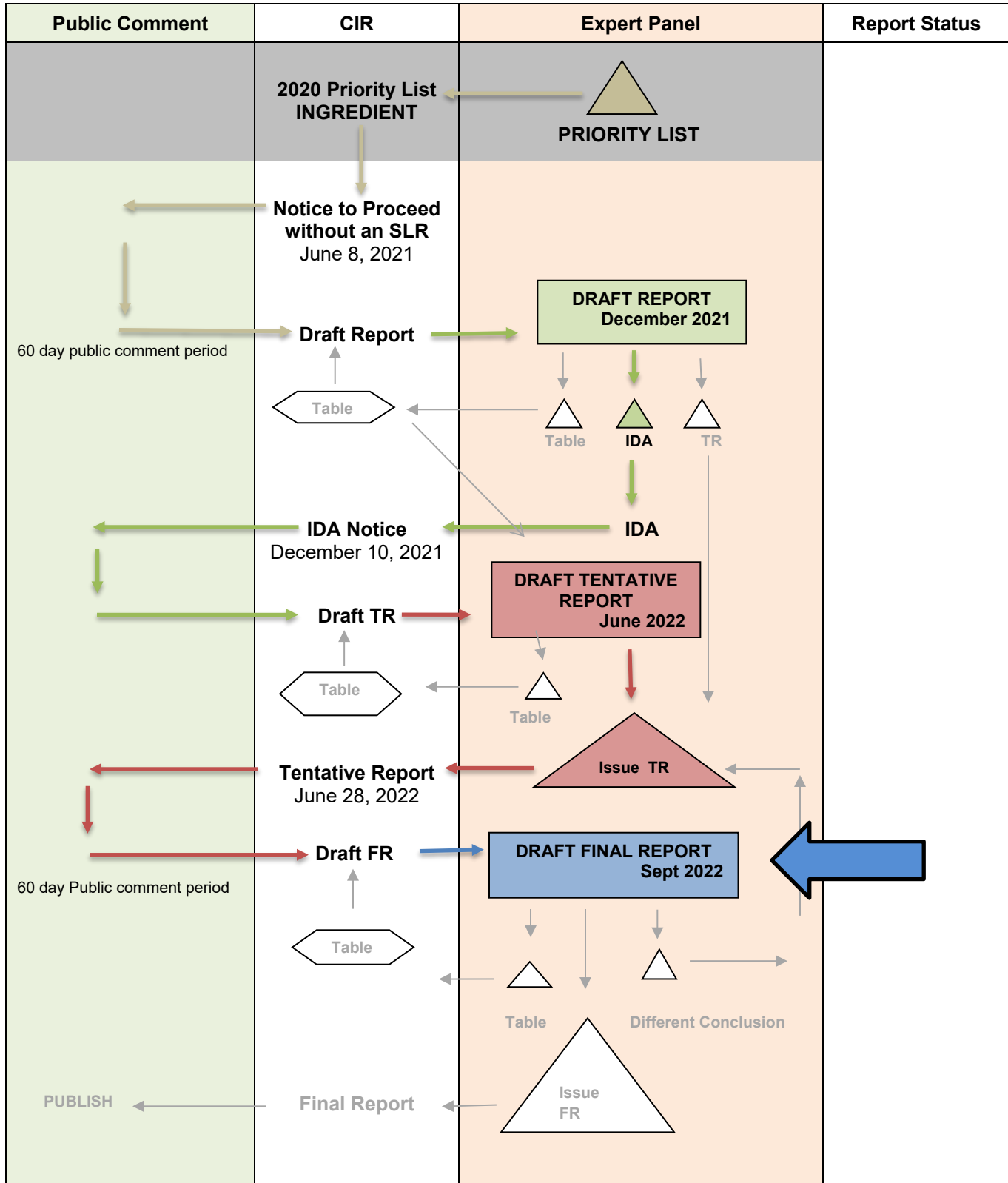
Status: Draft Final Report for Panel Review
Release Date: September 1, 2022
Panel Meeting Date: September 26-27, 2022

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.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Lisa A. Peterson, Ph.D. and Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer, CIR.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Fatty Ester End-Capped Alkoxylates

MEETING September 2022





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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst, CIR
Date: September 1, 2022
Subject: Safety Assessment of Fatty Ester End-Capped Alkoxylates as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Fatty Ester End-Capped Alkoxylates as Used in Cosmetics. (It is identified as *report_FattyEsterAlkoxylates_092022* in the pdf document.) At the June 2022 meeting, the Panel issued a Tentative Report with the conclusion that PEG/PPG-8/3 Diisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment. However, the Panel also concluded that the available data are insufficient to make a determination of safety for the remaining 13 fatty ester end-capped alkoxylated ingredients under the intended conditions of use in cosmetic formulations. The additional data needed to determine safety for these 13 cosmetic ingredients are:

- Method of manufacturing data
- Composition and impurities data

Since the June meeting, CIR has received method of manufacturing, composition, and impurities data for PEG-15 Butylene Glycol Diisostearate, PEG-10 Glyceryl Diisostearate, PEG-20 Glyceryl Diisostearate, PEG-30 Glyceryl Diisostearate, PEG-60 Glyceryl Diisostearate, and PEG-4 Glyceryl Distearate (*data_FattyEsterAlkoxylates_092022*). No method of manufacturing, composition, or impurities data have been received for PEG-15 Glyceryl Diisostearate, PEG-12 Glyceryl Dimyristate, PEG-12 Glyceryl Dioleate, PEG-3 Glyceryl Distearate, PEG-12 Glyceryl Distearate, PEG-23 Glyceryl Distearate, or PEG-4 Polyglyceryl-2 Distearate. No additional data were received and no formal comments were received from the Council. The new data have been incorporated into the report and have been **highlighted** to aid the Panel's review.

Additional supporting documents for this report package include a flow chart (*flow_FattyEsterAlkoxylates_092022*), report history (*history_FattyEsterAlkoxylates_092022*), a search strategy (*search_FattyEsterAlkoxylates_092022*), meeting transcripts (*transcripts_FattyEsterAlkoxylates_092022*), FDA VCRP raw data (*VCRP_FattyEsterAlkoxylates_092022*), and a data profile (*datapofile_FattyEsterAlkoxylates_092022*).

The Panel should review the Abstract, Discussion, and Conclusion, and issue a Final Report.

Fatty Ester End-Capped Alkoxylates History

June 8, 2021 – Notice to Proceed without the preparation of a Scientific Literature Review issued.

July 27, 2021 – Unpublished data received.

December 2021 – The Panel issued an IDA for the 14 fatty ester end-capped alkoxylates. The additional data needed to determine safety for these cosmetic ingredients are:

- Use concentrations for PEG/PPG-8/3 Diisostearate
- Method of manufacturing for all ingredients except PEG/PPG-8/3 Diisostearate
- Composition and impurities data for all ingredients except PEG/PPG-8/3 Diisostearate

February 17, 2022 – Unpublished data received.

June 2022 - The Panel issued a Tentative Report for public comment with the conclusion that PEG/PPG-8/3 Diisostearate is safe cosmetics in the present practices of use and concentration described in this safety assessment.

The Panel noted the lack of DART and genotoxicity studies for fatty ester end-capped alkoxylated ingredients. However, the Panel also noted these ingredients are large molecules (> 1600 Da) and are not likely to absorb readily through the skin. These factors, coupled with the favorable safety profile and lack of structural features associated with genotoxicity, mitigated the need for DART and genotoxicity data.

However, the data are insufficient to make a determination of safety for the remaining 13 fatty ester end-capped alkoxylates. The additional data needed to determine safety for these cosmetic ingredients are:

- Method and manufacturing
- Composition and impurities data

The Panel's respiratory exposure resource document (<https://www.cir-safety.org/cir-findings>) notes that airbrush delivery systems present a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

July 19, 2022 – Unpublished data received.

Fatty Ester End-Capped Alkoxylates Profile* - September 2022 - Christina Burnett

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies		
	Reported Use	Method of Mfg	Impurities	log P/log K _{ow}	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
PEG/PPG-8/3 Diisostearate	X	X	X		X			X															X			X				
PEG-15 Butylene Glycol Diisostearate		X	X																											
PEG-10 Glyceryl Diisostearate		X	X																											
PEG-20 Glyceryl Diisostearate		X	X																											
PEG-30 Glyceryl Diisostearate		X	X																											
PEG-60 Glyceryl Diisostearate		X	X																											
PEG-12 Glyceryl Dimyristate	X																										X			X
PEG-12 Glyceryl Dioleate								X																						
PEG-3 Glyceryl Distearate	X																													
PEG-4 Glyceryl Distearate		X	X																											
PEG-12 Glyceryl Distearate	X						X	X																						
PEG-23 Glyceryl Distearate							X																							
PEG-4 Polyglyceryl-2 Distearate																														
PEG-15 Glyceryl Diisostearate																														

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

Fatty Ester End-Capped Alkoxylates

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
PEG/PPG-8/3 Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-3 Glyceryl Distearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-4 Glyceryl Distearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-4 Polyglyceryl-2 Distearate	86360-24-9 or 72828-11-6	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-10 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-12 Glyceryl Dimyristate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-12 Glyceryl Dioleate		√	21CFR17 6.210? 21CFR17 7.2800	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-12 Glyceryl Distearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-15 Butylene Glycol Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-15 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-20 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-23 Glyceryl Distearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-30 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-60 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy***PubMed – 0 relevant hits using the following search terms:***

86360-24-9 or 72828-11-6

PEG/PPG-8/3 Diisostearate

PEG-3 Glyceryl Distearate

PEG-4 Glyceryl Distearate

PEG-4 Polyglyceryl-2 Distearate

PEG-10 Glyceryl Diisostearate

PEG-12 Glyceryl Dimyristate -

PEG-12 Glyceryl Dioleate

PEG-12 Glyceryl Distearate

PEG-15 Butylene Glycol Diisostearate

PEG-15 Glyceryl Diisostearate

PEG-20 Glyceryl Diisostearate

PEG-23 Glyceryl Distearate

PEG-30 Glyceryl Diisostearate

PEG-60 Glyceryl Diisostearate

Google Scholar using search terms used for PubMed got the following results:

PEG-12 Glyceryl Myristate – 5 potentially relevant hits
PEG-12 Glyceryl Distearate – 3 potentially relevant hits
PEG-23 Glyceryl Distearate – 2 potentially relevant hits

Internet searches using trade names and other technical names. No relevant hits.

LINKS

Search Engines

- Pubmed (- <http://www.ncbi.nlm.nih.gov/pubmed>)
- appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - <http://webdictionary.personalcarecouncil.org>
- FDA databases <http://www.ecfr.gov/cgi-bin/ECFR?page=browse>
- FDA search databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>;
- Substances Added to Food (formerly, EAFUS): <https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus>
- GRAS listing: <http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm>
- SCOGS database: <http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm>
- Indirect Food Additives: <http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives>
- Drug Approvals and Database: <http://www.fda.gov/Drugs/InformationOnDrugs/default.htm>
- FDA Orange Book: <https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm>
- (inactive ingredients approved for drugs: <http://www.accessdata.fda.gov/scripts/cder/iig/>)
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/opthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - <http://www.cdc.gov/niosh/>
- NTIS (National Technical Information Service) - <http://www.ntis.gov/>
 - technical reports search page: <https://ntrl.ntis.gov/NTRL/>
- NTP (National Toxicology Program) - <http://ntp.niehs.nih.gov/>
- Office of Dietary Supplements <https://ods.od.nih.gov/>
- FEMA (Flavor & Extract Manufacturers Association) GRAS: <https://www.femaflavor.org/fema-gras>
- EU CosIng database: <http://ec.europa.eu/growth/tools-databases/cosing/>
- ECHA (European Chemicals Agency – REACH dossiers) – <http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1>
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - <http://www.ecetoc.org>
- European Medicines Agency (EMA) - <http://www.ema.europa.eu/ema/>
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- <http://webnet.oecd.org/hpv/ui/Search.aspx>
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- <https://www.industrialchemicals.gov.au/>
- International Programme on Chemical Safety <http://www.inchem.org/>
- FAO (Food and Agriculture Organization of the United Nations) - <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/>
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

DECEMBER 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – December 6, 2021

DR. BELSITO: This is the first time that we're looking at this. Council provided concentration of use data, molecular weight, manufacturing, impurities, dermal penetration, acute oral, HRIPT, in vitro ocular on one particular one. We got some concentration of use and VCRP data.

We basically need to look at this document and decide is the data sufficient or not. This is under fatty acid. There we go. We have no concentration of use for PEG/PPG-8/3 diisostearate, which is the most used. I think we're sort of insufficient in that regard.

DR. LIEBLER: Right. That's what I flagged, as well, Don.

DR. BELSITO: Then it says that, at the time the safety assessment was written, PEG-3 glyceryl distearate was not listed in the dictionary, but it has reported use in the FDA VCRP. Are we including that in our list of materials we're reviewing or not?

MS. BURNETT: Yes, we are.

DR. BELSITO: Okay. Then, it should be up on the lists, no?

MS. BURNETT: Did I not? I'm sorry. I left that out.

DR. LIEBLER: It's the first one, isn't it?

DR. BELSITO: No, that's PEG/PPG-8/3. This is just PEG-3 glyceryl distearate. I don't see it in the introduction list.

DR. LIEBLER: Oh, yeah, it is. It's in the second column, third one down.

DR. BELSITO: Ah, yeah, there it is. Sorry. I'm just going blind.

DR. LIEBLER: It's just the way it is, grandpa.

DR. BELSITO: Yeah. With the method of manufacturing, are we comfortable with that? Or do we feel we need more specific information?

DR. LIEBLER: No, I was fine with the chemistry stuff: properties, method of manufacture. I would note that the PEG/PPG-8/3 diisostearate is 1,630 molecular weight, and that's one of the small ones. These are going to have little or no absorption.

DR. BELSITO: Okay.

DR. LIEBLER: I was fine with the method of manufacture, impurities, chemical properties.

DR. BELSITO: Okay. With the size? We have just expected not to penetrate the skin. We have no DART or mutagenicity data. Are we comfortable with that lack of penetration?

DR. KLAASSEN: I am.

DR. LIEBLER: Yep.

DR. BELSITO: Okay. Sorry. Other than for not having concentration of use for the most used, the PEG/PPG-8/3 diisostearate, do we have any other data needs for this?

DR. LIEBLER: I did not see any.

DR. BELSITO: Paul, Curt.

DR. KLAASSEN: It's fine for me.

DR. SNYDER: On page 12, Don, that human sensitization assay on 114 subjects, what was the concentration of the PEG-3 diisostearate that was used? I couldn't determine that. I couldn't find that.

MS. BURNETT: I don't believe I received that data. Let me see.

DR. BELSITO: What page you on, Paul?

DR. SNYDER: The bottom of page 12, there's a sensitization study with that 8/3 diisostearate with 114 subjects.

DR. BELSITO: Right.

DR. SNYDER: But it doesn't give the concentration. I queried what concentration was it?

MS. BURNETT: I don't believe it was part of the data package. The data we received on that starts at PDF page 28.

DR. SNYDER: If we're not worried about absorption, I guess that's a moot point.

DR. LIEBLER: I think you always need the concentration tested, especially for dermal sensitization.

DR. BELSITO: Yeah. I'm shocked that it's not there. We have an insufficient for the --

DR. LIEBLER: Sorry, Don. Sorry to interrupt, but this looks like it was done with a pure material. If you look at PDF 31, the study product is a cosmetic ingredient with an incubating CAS number description clear yellow oil as supplied. It strongly implies that it's just this chemical. It's not like a hair or a skin lotion with X percent of the PEG-8/3 diisostearate.

DR. BELSITO: What page you on, Dan?

DR. LIEBLER: PDF 31, Item 5.00, study products. When I look at those lines and the description, clear oil, it sounds like they're referring to the chemical listed, which is the PEG-8/3 diisostearate.

DR. BELSITO: Oh, you're right.

DR. LIEBLER: That's probably why they're not citing a concentration. It's not like they tested some skin lotion with two percent of this chemical in it.

DR. BELSITO: So it was 100 percent, or it was pure?

DR. LIEBLER: Yeah.

DR. SNYDER: Well, we should say that up there say it was neat or something -- use neat.

DR. BELSITO: Yeah.

MS. BURNETT: Yeah. I will add that.

DR. LIEBLER: Thank you.

DR. BELSITO: Okay. I guess it's not going to penetrate. Tom usually likes some data anyway on skin, but we're comfortable without the mutagenicity data because it's not going to get through the stratum corneum. Is that correct?

DR. LIEBLER: That was my interpretation. I think if it doesn't penetrate the stratum corneum, mutagenicity is moot. Let's see what Tom says. If he brings it up, we can discuss.

DR. BELSITO: Okay. Then, basically, again, we have an insufficiency, and that is for the concentration of use of PEG/PPG-3/8 diisostearate?

DR. LIEBLER: Yep.

DR. BELSITO: Okay. Now, in our conclusion for the glyceryl diesters, we said, "safe as cosmetic ingredients provided that the content of 1,2-diester is not high enough to induce epidermal hyperplasia." Do we need this caveat on these ingredients?

DR. LIEBLER: No, they're chemically distinct enough that I don't think it's relevant. The ester is not on the glyceryl backbone. It's on the end of the PEGs. It's a really different structure.

DR. BELSITO: Okay.

DR. LIEBLER: It can't be metabolized. Even if it could be absorbed and metabolized, it couldn't be metabolized to those diacylglycerols.

DR. BELSITO: Okay. We're going insufficient for the concentration. Do we have any discussion points that we want to bring up at this point for the writer? The respiratory boilerplate is obviously --

DR. LIEBLER: The main point is the favorable safety profile reflects lack of absorption of these ingredients.

DR. BELSITO: Right. The inability to penetrate the stratum corneum obviated the need for DART and genotox data.

DR. LIEBLER: Yep.

DR. SNYDER: The only question I had, Don, was on Page 11 -- in addition to what we've already talked about -- under the non-cosmetic use. Where they said they've been studied for use as oral and topical drug carriers and/or solubilizers. So is there any data associated with those references that we could bring into this report regarding the topical drug carrier use?

DR. BELSITO: No.

DR. LIEBLER: Mainly, is there anything that suggests, contrary to our expectations, if there's any absorption?

DR. SNYDER: Yeah, exactly, because that seemed to be consistent with the statement above, "lack of absorption when it's used as a drug carrier for topical."

MS. BURNETT: I'd have to go back and review. But, from what I remember, they were investigating the efficacy of the drug that was part of the formulation as a whole. When they listed off what the other ingredients were, the nonactives, these came

up in the search, but they don't actually necessarily go into detail about them. I'd have to go back and check, but they were listed as inactive ingredients for the drug of interest.

DR. BELSITO: But couldn't you get a drug delivery system where the delivery just simply sits on the stratum corneum, and then the drug penetrates?

DR. SNYDER: Yeah. That's what I assumed is going on, but I don't know. Just to me -- it said a topical drug carrier, so.

DR. BELSITO: Yeah. Maybe some additional details if available. Otherwise, what do we do with it, Paul?

DR. SNYDER: I just want to make sure that there's not something that's going to say they used it as a penetration enhancer.

DR. BELSITO: Okay. I get your point.

DR. SNYDER: Yeah.

DR. BELSITO: Christina, could we look into that?

MS. BURNETT: Yes.

DR. BELSITO: Okay.

DR. SNYDER: And it's probably a moot point, but it just seems kind of odd that it was studied for use as an oral and topical drug carrier.

DR. BELSITO: Right. Paul, Curt, any other comments on this?

DR. SNYDER: The concentration, is that the 8/3 we're asking for?

DR. BELSITO: Yeah, PEG-3/8 diisostearate. It's the most used, and we have no concentration of use.

DR. SNYDER: Okay. Thank you.

DR. LIEBLER: I have nothing else to add. That's it.

Cohen Team – December 6, 2021

DR. COHEN: Okay. Let me just pull up the next one, fatty ester end-capped alkoxylates. All right.

MS. BURNETT: Say that fast five times.

DR. COHEN: So, Christina, this is yours, and it's a draft report. And it's our first time reviewing it. This assessment has 14 derived ingredients. They're used as surfactants in skin conditioning agents. We have frequency of use, the most common of which is the PEG/PPG-8/3-Diisostearate. Ten ingredients are not reported to be in use in the VCRP. And for PEG-12 glyceryl dimyristate we have a max concentration of 1.8 percent and no concentration on the diisostearate.

So, we have some method of manufacturing and some impurities. Molecular weights of the diisostearate are pretty big, 1,630. Looks like we need irritation and sensitization of PEG glyceryl dimyristate at the highest concentration. And there's a report about PEG 8/3 diisostearate sensitization and irritation, but I didn't see the concentration in that report anywhere.

MS. BURNETT: I think we closely looked at that in the other team and I think we determined that it was tested neat. It was (inaudible).

DR. COHEN: Oh.

MS. BURNETT: And the way the description is --let me -- on PDF page --

DR. COHEN: Let me open in PDF form.

MS. BURNETT: -- PDF page 31 -- as it's described -- it's like middle of the page -- 5.00 study product.

DR. COHEN: Clear yellow oil.

MS. BURNETT: It was tested as supplied and it's describing it as solely -- as the ingredient.

DR. COHEN: So, as supplied. And where is the description of what supplied is again?

MS. BURNETT: It just type of product -- based on what we can see here it's the PEG --

DR. COHEN: Yeah.

MS. BURNETT: -- PPG-8/3 Diisostearate. If there is something else in it, they don't describe it at all.

DR. COHEN: Okay. Lisa, what do you think?

DR. PETERSON: Well --

DR. COHEN: Can we read across this?

DR. PETERSON: I don't know. I thought we should ask for methods of manufacturing and impurities on all of them and we -- for all of them that we don't have. So that's all of them except the diisostearate.

DR. COHEN: That's to try to get some sense whether you feel comfortable reading across the whole list, right?

DR. PETERSON: Yeah.

DR. COHEN: Same with impurities?

DR. PETERSON: Yeah. And then I also thought we don't have concentration of use for the PEG -- the Diisostearate. So, I thought it was -- actually we don't have it for the glyceryl dimyristate either, the PEG-3 glyceryl. I thought we should ask for those -- for sure the diisostearate because there's 155 uses and no concentration of use.

DR. COHEN: Yeah.

DR. BERGFELD: Does the molecular weight mean anything to you for this particular?

DR. PETERSON: I think it does. I mean, they're all going to be large, but I think it would be useful to get the molecular weights on the ones we don't have. But they're all going to be pretty big. Why not ask while we're asking?

DR. COHEN: Tom?

DR. SLAGA: I don't see any other data needs. They're very large molecules. I don't think we need genotox here.

DR. COHEN: Do you agree with Lisa's ask? I mean, are you coming out with a different conclusion?

DR. SLAGA: No. I agree with what she has.

DR. COHEN: And Ron?

DR. SHANK: We've reviewed a lot of similar ingredients in the past. Can we use any of that -- those old reports, reviews for read across purposes? One is glyceryl diesters, triethylene glycol, polyethylene glycols, polypropylene glycols, polyethylene glycol diesters -- I think five or six old reports.

MS. BURNETT: It's Table 2 if you want to look at them all with the conclusions.

DR. SHANK: Thank you, I couldn't find it. Table 2?

MS. BURNETT: Yes.

DR. SHANK: Thank you.

DR. COHEN: What PDF is that on?

MS. BURNETT: 19.

DR. COHEN: It's interesting, though. A number of those have safe when formulated to be non-irritating.

DR. PETERSON: Yeah, and they're all the PEG ones, you know.

DR. BERGFELD: They're also mostly rinse offs.

DR. SLAGA: Yeah.

DR. PETERSON: Oh, I see. Most of the ones in the class we're looking at are rinse offs, so we don't worry quite so much because they're not staying on.

DR. COHEN: Well, yeah. The dimyristate reports a leave-on concentration of 1.8 percent in two products -- up to in two products. So, we're going with an insufficient data announcement on this. We want method of manufacturing for all of them except the diisostearate as well as impurities. And we'd like the concentration of use of the diisostearate. If we can get clarification, just corroboration that the PEG diisostearate sensitization and irritation study is neat material, that would be pretty helpful. And Lisa, if you feel comfortable with the method of manufacturing and the impurities then we could read across the next time.

DR. SLAGA: Right.

DR. COHEN: Did I get that right?

DR. PETERSON: Yeah.

DR. COHEN: Any other comments on this? Ron.

DR. SHANK: No.

DR. SLAGA: Just what Ron brought up, if there can be read across from some of the past ones, this could go to safe.

DR. COHEN: I think there's a few pathways for safe on it. It's Ron's comments which could be more immediate or Lisa's on looking at impurities and method of manufacturing.

DR. SLAGA: Right, agree.

DR. COHEN: All right. Are we okay with moving on from there with that information? Christina, is this enough for now?

MS. BURNETT: I'm good.

DR. SLAGA: Okay.

DR. COHEN: Okay.

DR. BERGFELD: I'd like to make a comment. In the discussion we need to have some reminders. And that would be that the high molecular weight would have a normal penetration. I think that's the note I have to myself. I wanted to make sure that got in there. And it was in rinse off products. Those two things.

DR. COHEN: Lisa, we have the molecular weight of the diisostearate.

DR. PETERSON: Yeah.

DR. COHEN: Would you expect any of the others to be substantially smaller?

DR. PETERSON: Hang on a second.

DR. COHEN: It's the PEG 8/3.

DR. PETERSON: I just closed the file. I mean, the only one that -- if I'm understanding right, the four and the three would be smaller, right, if I'm understanding how these -- it's three polyglycerides. So, there are a couple that are smaller than that, I think -- the PEG-3 glycerol diisostearate, the PEG-4 glycerol diisostearate. But they're still gonna be pretty big -- PEG-4 polyglycerol-2 diisostearate. But they're gonna be smaller than that, but they'll still be pretty big.

DR. COHEN: Okay.

DR. PETERSON: You know, if they said tomorrow that we think everything's safe, I would not disagree with that necessarily.

DR. COHEN: No, I'm staying flexible on this. I'm listening to our concerns.

DR. PETERSON: But I do feel like a few pieces more of information would be just helpful. I mean, I'm not totally -- I mean, the only other thing I would say is that, you know, that other class -- using the other one's that were done, you know, they -- the one's with PEG all said to be formulated to be non-irritating.

DR. COHEN: Yeah.

DR. PETERSON: So I would have concerns that the PEG moiety is -- you know, and we don't have much data to go off of because there's only one compound. But, you know, maybe there's an irritability thing here, too. So, that's my only -- you know, I guess we have the one piece of data for the one compound in this group and that said that it was non-irritating, right?

DR. COHEN: Yeah. And we don't have the max use concentration of the diisostearate, but the dimyristate is 1.8 percent. That's pretty low.

DR. PETERSON: Yeah, but the other ones we don't --

DR. COHEN: We don't know. We don't know. Okay. We can discuss that tomorrow. All right. We'll move on again. All right.

Full Panel – December 7, 2021

DR. BELSITO: Yeah. So this is the first time that we're looking at this group of 14 cosmetic ingredients. We've got lots and lots of data. Interestingly we found that the data by and large supported the safety as used, except that the material that has the most frequent use which is PEG/PPG3/8-diisostearate. We have no concentration of use for. So we're going insufficient for the use concentration of that specific ingredient, but otherwise we felt our data needs were met.

DR. BERGFELD: Dr. Cohen?

DR. COHEN: Yeah. Before I second that, Don, we came -- that's one of our highest concerns, so we agree with you on concentration of use. We thought we might ask for method of manufacturing and impurities on all of them except the 8/3-diisostearate since we had it. And did you conclude that the HRIPT on 8/3-diisostearate -- was that neat material? I could not figure out what concentration that was done.

DR. BELSITO: Yes, we looked at it, and we felt that it was neat material.

DR. COHEN: So we would second your motion and ask that the additional -- the impurities and method of manufacturing be put into the ask since we're so early in the phase of this review.

DR. BELSITO: I don't think we have any problems. Dan did not feel we needed it, but you can load on what you want at this point. It's insufficient.

DR. LIEBLER: Yeah. Exactly.

DR. BERGFELD: So this particular ingredient would be going out as a tentative and insufficient; is that correct?

DR. BELSITO: And insufficient data announcement, yes.

DR. BERGFELD: It's insufficient data announcement, not going to final? Just an insufficient data announcement?

DR. BELSITO: No. This is the first time we're looking at it.

DR. BERGFELD: I know. It's going for draft, so I'm asking that question. Okay. So IDA again. All right. Any other discussion before I call the question? Okay. Anyone opposing? Abstaining? Unanimous to move on as an insufficient data announcement with those listed needs. Do we need to repeat those, Christina, the needs, or are you understanding what they are?

MS. BURNETT: I believe I have them. It's concentration of use for the lead ingredient, method of manufacturing and impurities for the other ingredients. Yesterday, Dr. Peterson mentioned asking for molecular weights too. Do you still want that or not so much?

DR. PETERSON: I think they're all large, so I just thought as long as we're asking, we might as well ask for them.

DR. LIEBLER: Lisa, I noted that the one -- the PEG/PPG-8/3 diisostearate is 1630 Dalton, and that's one of the small ones.

DR. PETERSON: Okay. That's fine. I was just gathering information. I always feel more is better, and I didn't understand why somebody couldn't supply it. So I wasn't going to trust the internet on this one.

DR. COHEN: Dan, that conversation came up, and we asked Lisa are there going to be smaller ones? And there may be some smaller ones in that group thought; right?

DR. PETERSON: I would trust Dan more. I'm not a polymer person.

DR. COHEN: I thought there might have been.

DR. LIEBLER: That's the lower bound, that 8/3. That's the lower bound. That's why I figured okay. We're covered. So anyway, that's why I said that.

DR. PETERSON: Okay. So I will leave that off the list.

DR. BERGFELD: Okay. All right.

JUNE 2022 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – June 16, 2022

Dr. Belsito - OK. So then we're moving on to the Fatty Ester End-Capped Alkoxylates. And here in December of 2021, we issued an IDA for use concentration for PEG/PPG – 8/3 Diisostearate and method of manufacturing of all ingredients except for that diisostearate above and composition impurities data for all the ingredients again except for the diisostearate.

And since that time, we've gotten maximum concentration of use data on the PEG/PPG – 8/3 Diisostearate. Up to 5% in the leave on hair conditioner, was previously reported to be used at 59.9% in face and mud pack that those are no longer in production. And another supplier reported the concentration range from one to 10%. And the use table has been updated.

So based upon that I thought that we could go with a safe as used conclusion for the PEG/PPG – 8/3 Diisostearate but all the others remained insufficient for manufacturer impurities and composition. No comment team?

Dr. Snyder - I'm fine with that.

Dr. Belsito – Paul, I couldn't hear what you said, I'm sorry.

Dr. Snyder - I'm fine with that.

Dr. Belsito - OK. Dan?

Dr. Liebler - Yeah.

Dr. Belsito - Curt.

Dr. Rettie - Yep.

Dr. Klaassen - Yes

Dr. Belsito - OK and. Anyone want to add anything to Christina's discussion?

Christina Burnett (CIR) - I'm just going to point out that there's lack of, uh, data for genotoxicity, carcinogenicity, but because of the size of the molecule, the panel believes it wouldn't absorb.

Dr. Liebler - That's correct.

Dr. Belsito - Yeah, I mean, that's already in there – Right? It's that paragraph it says the panel noted lack of DART and genotoxicity studies for these ingredients. However, the panel also noted there are large molecules not likely to absorb gradually through the skin, backed up the with a favorable safety profile mark of structural features associated with genotox. So no need for DART or genotox. So I thought it was well covered.

Christina Burnett (CIR) - Yeah. OK, so nothing, nothing in addition? I'll be on that then, OK.

Dr. Belsito - Yeah. And just the respiratory boilerplate, right? Which is there. OK, very good.

Cohen Team – June 16, 2022

Minutes not captured.

Full Panel – June 17, 2022

Dr. Bergfeld - Moving on then, from that safe conclusion to the Fatty Ester End-Capped Alkoxylates. Dr Cohen?

Dr. Cohen - Yeah. So we might have a deja vu moment here. So in December 2021, the panel issued an IDA for 14 Fatty Ester End-Capped Alkoxylates with several data needs. For PEG/PPG – 8/3 Diisostearate we received data that it is used at 5% in the leave on hair conditioner. In the past it had been used at almost 60% in a face and mud mask, but these are no longer in production and through a Council survey the suppliers recommending one to 10%. We have sensitization and irritation at neat and we were going to go out with the safe as used for PEG/PPG – 8/3 Diisostearate but insufficient for impurities and method of manufacturing for the others. And we specifically are welcoming the Belsito team's discussion on this.

Dr. Belsito - We agree with you. The only other thing we added to manufacturing, impurities was composition.

Dr. Cohen - Yes, agree. We agree.

Dr. Bergfeld - So we've had a motion and a second. With some added tidbits. Doctor Cohen, can you restate your motion with the thing that's been added?

Dr. Cohen - Yeah. Sure, our motion is, safe as used for PEG/PPG – 8/3 Diisostearate. Insufficient for the remaining 13 derived ingredients for impurities, method of manufacturing and composition.

Dr. Bergfeld - Yeah, that's a second. I'm going to call the question then. All those opposed. Abstaining. Unanimously approved. A split decision on this ingredient, OK.

Safety Assessment of Fatty Ester End-Capped Alkoxylates as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: September 1, 2022
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Lisa A. Peterson, Ph.D. and Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer, CIR.

ABBREVIATIONS

CIR = Cosmetic Ingredient Review

Council = Personal Care Products Council

CPSC = Consumer Product Safety Commission

DART = developmental and reproductive toxicity

ET₅₀ = exposure time that induces a 50% reduction in viability

FDA = Food and Drug Administration

Panel = Expert Panel for Cosmetic Ingredient Safety

PEG = polyethylene glycol

PPG = polypropylene glycol

VCRP = Voluntary Cosmetic Registration Program

wINCI *Dictionary* = web-based *International Cosmetic Ingredient Dictionary and Handbook*

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 14 fatty ester end-capped alkoxyates as used in cosmetics. These ingredients are reported to function mainly as surfactants – emulsifying agents and skin-conditioning agents in cosmetic formulations. The Panel reviewed the available data to determine the safety of these ingredients. The Panel concluded that PEG/PPG-8/3 Diisostearate is safe in cosmetics in the present practices of use and concentration described in this safety assessment. However, the Panel also concluded that the available data are insufficient to make a determination of safety for the remaining 13 fatty ester end-capped alkoxyated ingredients under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This assessment reviews the safety of the following 14 fatty ester end-capped alkoxyates as used in cosmetic formulations:

PEG/PPG-8/3 Diisostearate	PEG-12 Glyceryl Dimyristate
PEG-15 Butylene Glycol Diisostearate	PEG-12 Glyceryl Dioleate
PEG-10 Glyceryl Diisostearate	PEG-3 Glyceryl Distearate
PEG-15 Glyceryl Diisostearate	PEG-4 Glyceryl Distearate
PEG-20 Glyceryl Diisostearate	PEG-12 Glyceryl Distearate
PEG-30 Glyceryl Diisostearate	PEG-23 Glyceryl Distearate
PEG-60 Glyceryl Diisostearate	PEG-4 Polyglyceryl-2 Distearate

Most of the fatty ester end-capped alkoxyates presented in this safety assessment are glyceryl or polyglyceryl di-fatty acid esters with ethylene glycol repeat units. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients function mainly as surfactants – emulsifying agents, skin-conditioning agents – emollients, and skin-conditioning agents – miscellaneous in cosmetic formulations (Table 1).¹ At the time this safety assessment was written, PEG-3 Glyceryl Distearate was not listed in the *Dictionary*, but it has reported uses in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database.

The Expert Panel for Cosmetic Ingredient Safety (Panel) has reviewed numerous related ingredients, including glyceryl diesters, triethylene glycol and polyethylene glycols (PEGs) > 4, PEG diesters, PEGylated oils, and monoglyceryl monoesters, and concluded these ingredients are safe or safe with qualifications.²⁻⁷ A full listing of the related report families, specific related ingredients, and the conclusions of safety determined by the Panel for these ingredients are provided in Table 2.

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

CHEMISTRY

Definition and Structure

The definitions and idealized structures of the fatty ester end-capped alkoxyate ingredients included in this review are provided in Table 1. Most of the fatty ester end-capped alkoxyates presented in this safety assessment comprise a glycerin core, which is PEGylated (i.e., substituted with multiple ethylene glycol repeat units) and end-capped with fatty acid esters on 2 of the 3 termini (i.e., glycerin is tridentate (a triol), wherein all 3 alcohol functional groups are PEGylated ending in a terminal that may be esterified). Two of the 3 alcohols of glycerin are primary (i.e., the carbon the alcohol is attached to is only attached to 1 other carbon) and the remaining 1 is secondary (i.e., the carbon the alcohol is attached to is attached to 2 other carbons). The resulting PEG chains on those 2 primary alcohol functional groups, are the ones to be esterified. The number of units (e.g., “10” in PEG-Glyceryl Diisostearate) is representative of an average number of ethylene glycol repeat units (i.e., PEG-10 Glyceryl Diisostearate contains some PEG-9 and PEG-11 glyceryl diisostearate, in addition to PEG-10). For example, PEG-20 Glyceryl Diisostearate comprises a glycerin core that is PEGylated across those 3 alcohol functional groups and esterified on two of the resulting PEG chains with isostearic acid (Figure 1).

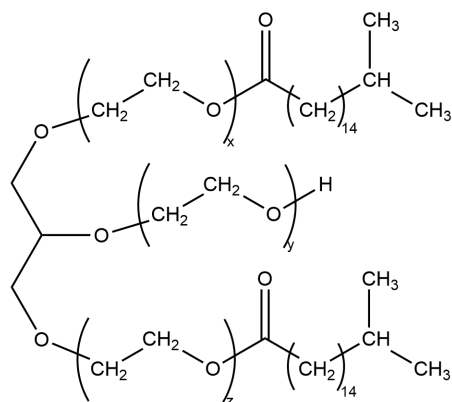


Figure 1. PEG-20 Glyceryl Diisostearate, wherein $x + y + z = 20$

For PEG/PPG-8/3 Diisostearate, in addition to the ethylene glycol repeat units, it also has polypropylene glycol (PPG) repeat units.

Most of the alkoxylate end-caps are stearates (i.e., 18-carbon alkyl chains). However, one ingredient is end-capped with 14-carbon alkyl chains (i.e., myristate) and one ingredient is end-capped with 18-carbon *alkenyl* chains (i.e., oleate).

Chemical Properties

A supplier reported that the molecular weight of PEG/PPG-8/3 Diisostearate is 1630 Da.⁸ At room temperature, PEG-12 Glyceryl Dioleate is reported to be a liquid, while PEG-12 Glyceryl Distearate is reported to be a waxy solid.⁹

No further chemical properties data were found in the published literature, nor were additional unpublished data submitted.

Method of Manufacture

Most of the ingredients in this report comprise a glycerin core, and are manufactured rather differently. Ingredients with structures such as these are typically synthesized from the appropriate glyceryl diester (i.e. not PEGylated).⁶ In such methods, the PEGylation effectually results in transesterification, or direct insertion of the PEG chain between the glycerin molecule and the fatty acid. For example, PEG-20 Glyceryl Diisostearate could be synthesized by PEGylation of Glyceryl Diisostearate. The 20 equivalents of ethylene oxide (the “20” in “PEG-20”) are thus distributed across the 3 termini: some at the free alcohol functional group of the glycerin core, and the rest inserted in the 2 isostearic esters.

PEG/PPG-8/3 Diisostearate

A supplier has reported that PEG/PPG-8/3 Diisostearate is produced through the condensation of fatty acids (i.e., isostearic acid) with alcohols (i.e., polyethylene glycol/polypropylene glycol).¹⁰ The esterification is acid-catalyzed. The by-product, water, is removed with the aid of heat and vacuum. No solvents are used in the manufacturing process.

PEG-15 Butylene Glycol Diisostearate

A supplier has reported that PEG-15 Butylene Glycol Diisostearate is produced through addition polymerization of ethylene oxide to 1,3-butylene glycol, followed by diesterification with isostearic acid.¹¹ No further details were provided.

PEG-10 Glyceryl Diisostearate, PEG-20 Glyceryl Diisostearate, PEG-30 Glyceryl Diisostearate, PEG-60 Glyceryl

Diisostearate

A supplier has reported that PEG-10 Glyceryl Diisostearate, PEG-20 Glyceryl Diisostearate, PEG-30 Glyceryl Diisostearate, and PEG-60 Glyceryl Diisostearate are produced through addition polymerization of ethylene oxide to glycerin, followed by diesterification with isostearic acid.¹¹ No further details were provided.

PEG-4 Glyceryl Distearate

A supplier has reported that PEG-4 Glyceryl Distearate is produced through addition polymerization of ethylene oxide to glycerin, followed by diesterification with stearic acid.¹¹ No further details were provided.

Impurities

PEG/PPG-8/3 Diisostearate

A supplier has reported that the purity of PEG/PPG-8/3 Diisostearate is > 95%.⁸ An expected impurity is isostearic acid (< 0.5%).

PEG-15 Butylene Glycol Diisostearate

A supplier has reported that the purity of PEG-15 Butylene Glycol Diisostearate is 100%.¹¹ Impurities may include isostearic acid ($\leq 5\%$) and ethylene oxide (≤ 1 ppm).

PEG-10 Glyceryl Diisostearate, PEG-20 Glyceryl Diisostearate, PEG-30 Glyceryl Diisostearate, PEG-60 Glyceryl Diisostearate

A supplier has reported that the purity of PEG-10 Glyceryl Diisostearate, PEG-20 Glyceryl Diisostearate, PEG-30 Glyceryl Diisostearate, and PEG-60 Glyceryl Diisostearate is 100%.¹¹ Impurities may include isostearic acid ($\leq 4\%$) and ethylene oxide (≤ 1 ppm).

PEG-4 Glyceryl Distearate

A supplier has reported that the purity of PEG-4 Glyceryl Distearate is 100%.¹¹ Impurities may include stearic acid ($\leq 2\%$) and ethylene oxide (≤ 1 ppm).

USE**Cosmetic**

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US 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 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.

According to 2022 VCRP survey data, PEG/PPG-8/3 Diisostearate is reported to be used in 98 formulations, with most of them being in bath soaps and detergents (Table 3).¹² The other 3 in-use ingredients in the VCRP are reported to be used in one or two formulations. The results of the concentration of use surveys conducted by the Council in 2019-2022 indicate PEG/PPG-8/3 Diisostearate has the highest concentration of use in a leave-on formulation; it is used at 5% in a leave-on hair conditioner.¹³ PEG-12 Glyceryl Dimyristate has the next highest concentration of use in a leave-on formulation; it is used at up to 1.8% in body and hand products.¹⁴ The 10 ingredients not in use according to the VCRP and industry survey are listed in Table 4.

Fatty ester end-capped alkoxylates may be used in cosmetic formulations that may be used near the eye or come into contact with mucous membranes. For example, PEG-12 Glyceryl Dimyristate is reported to be used in an eye lotion at 0.7% and PEG/PPG-8/3 Diisostearate is reported to be used in bubble baths and bath soaps and detergents (concentrations not reported).¹²⁻¹⁴ Additionally, some of the fatty ester end-capped alkoxylates are used in cosmetic sprays and could possibly be inhaled; for example, PEG-12 Glyceryl Dimyristate is reported to be used at 1% in hair sprays.¹⁴ 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.

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.

All of the fatty ester end-capped alkoxylates named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.¹⁵

Non-Cosmetic

PEG-12 Glyceryl Dioleate and PEG-12 Glyceryl Distearate, have been studied for use as liposomal drug carriers (encapsulation) and/or solubilizers in oral and intravenous pharmaceutical and nutraceutical products.^{9,16} PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate have been used as part of an inactive cream formulation used to study topically applied drugs for wound healing.¹⁷ PEG-12 Glyceryl Dimyristate was studied for use in controlled-release liposomal drug carriers for use in topical ophthalmic therapies to the back of the eye as a replacement for intravitreal injections.^{18,19}

TOXICOKINETIC STUDIES

Dermal Penetration

A supplier stated that, due to its molecular weight, PPG/PPG-8/3 Diisostearate is not expected to penetrate the skin or be bioavailable.⁸

Toxicokinetics studies were not found in the published literature, and additional unpublished data were not submitted for the remaining fatty ester end-capped alkoxyates described in this safety assessment.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

PEG/PPG-8/3 Diisostearate

A supplier reported that the LD₅₀ for PEG/PPG-8/3 Diisostearate in an acute oral rat study was greater than 2000 mg/kg.²⁰ Data was from initial reacted materials. No further details were provided.

Short-Term Toxicity Studies

Dermal

PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate

PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate were used in a base cream that was used as a placebo and as part of a pharmaceutical test compound in a dermal efficacy study in groups of 7 female Wistar rats.¹⁷ The placebo and test compounds were applied to damaged skin twice daily for up to 15 d. The amount of PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate in the base cream was not reported. No mortalities were observed during the testing period in either the placebo or treatment groups.

Oral

PEG-12 Glyceryl Dioleate and PEG-12 Glyceryl Distearate

In a 28-d oral toxicity study, groups of 5 male and 5 female Sprague-Dawley rats received 0, 250, 500, or 1000 mg/kg PEG-12 Glyceryl Dioleate or PEG-12 Glyceryl Distearate in a volume of 5 ml/kg via gavage.⁹ The vehicle was corn oil. Observations for clinical signs of toxicity were made at 10, 30, 60, and 120 min and at 4 and 6 h post-dosing starting on day 1 and daily for 28 d. Animals were observed twice daily for mortality. Body weight gains were recorded on day 0 and at weekly intervals throughout the study. Feed consumption by test groups was recorded weekly, and feed consumption per rat was calculated. Urinalysis was performed after the dosing period concluded. Hematological and plasma parameters were also measured after the dosing period concluded. The rats were killed and necropsied. Histopathological examinations of the liver and kidneys were made in the control and high dose groups.

No mortalities or clinical signs of toxicity were reported during the 28-d dosing period. Body weight gains and feed consumption in the treated animals were comparable to the controls. No statistically significant changes were noted in hematological or plasma parameters. No significant findings were reported in urinalyses. There were no abnormalities reported following necropsy and histopathological examination. The authors of this study concluded that PEG-12 Glyceryl Dioleate and PEG-12 Glyceryl Distearate was non-toxic in rats.⁹

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity (DART) data were not found in the published literature, and unpublished data were not submitted.

GENOTOXICITY STUDIES

Genotoxicity data were not found in the published literature, and unpublished data were not submitted.

CARCINOGENICITY STUDIES

Carcinogenicity data were not found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION

Human

PEG/PPG-8/3 Diisostearate

The dermal irritation and sensitization potential of a material identified as PEG/PPG-8/3 Diisostearate was studied in 114 subjects.²¹ The subjects were induced with four 24-h applications of the test material (150 µl, neat) per week for 3 wk on the left upper back, followed by a week hiatus prior to four, 24-h challenge patches on naïve sites. Patches were occlusive

devices with a 2 cm² absorbent pad centered on the adhesive-coated surface of a 4 cm² water-impermeable plastic film. No clinically significant adverse effects were detected during the induction or challenge phases. The test material, when tested neat, was determined to be non-irritating and non-sensitizing.

OCULAR IRRITATION STUDIES

In Vitro

PEG/PPG-8/3 Diisostearate

A supplier has reported that PEG/PPG-8/3 Diisostearate in 10% corn oil was non-irritating in an EpiOcular™ tissue model.²⁰ The exposure time that induces a 50% reduction in viability (ET₅₀) was greater than 256 min, and the estimated Draize score was 0. No further details were provided.

Animal

PEG-12 Glyceryl Dimyristate

The ocular irritation potential of a topical drug formulation containing PEG-12 Glyceryl Dimyristate (100 mg; 10% w/v) was assessed in 32 male New Zealand White rabbits.¹⁹ The rabbits received 1 drop (50 µl) of the test formulation in the right eye, every 2 h, 6 times/d (number of treatment days not reported). Control eyes received a saline balanced placebo solution. Clinical eye evaluations were then carried out under anesthesia at 10, 30, and 60 min, 6, 12, and 24 h, and 7 and 14 d post treatment. Four rabbits were killed after each clinical evaluation to obtain ocular tissue and fluids. No major findings or adverse effects were reported during the study. A Draize score of 1 was reported 30 min post-dosing, which resolved by the end of the 14-d observation period. No details regarding the scoring parameter that achieved this score at this observation point were provided. No increase in intraocular pressure was observed in any of the animals.

CLINICAL STUDIES

Ocular

PEG-12 Glyceryl Dimyristate

The tolerability, safety, and efficacy of a topical formulation containing PEG-12 Glyceryl Dimyristate (100 mg; 10% w/v) was evaluated in one eye of 12 patients with refractory pseudophakic cystoid macular edema.¹⁸ The patients received one drop of the test material every 2 h for 90 d or until best-corrected visual acuity was achieved. No ocular surface abnormalities or adverse events were observed.

In another safety and tolerability study of the same formulation containing PEG-12 Glyceryl Dimyristate, 20 healthy male and female subjects received topical doses (one drop) in one eye 6 times/d for 2 wk, followed by 1 wk of monitoring.¹⁹ No systemic adverse effects were reported. Mild burning and dryness of the eye (n = 6), moderate discharge (n = 2), mild tearing (n = 3), and mild blurred vision (n = 2) were reported after the end of the treatment period (day 14) and at the end of the monitoring period (day 21). No pain or discomfort were reported. No eyelid redness, conjunctival hyperemia, or edema were observed on day 21.

The same formulation containing PEG-12 Glyceryl Dimyristate was also used to assess biologic activity in 4 patients with diabetic macular edema.¹⁹ The patients received topical doses (1 drop) in one eye 6 times/d for 6 mo. Follow-up ophthalmic clinical evaluations were performed monthly. No systemic or severe adverse effects were reported. None of the patients showed intraocular hypertension.

SUMMARY

Most of the fatty ester end-capped alkoxylates presented in this safety assessment are glyceryl fatty acid esters with ethylene glycol repeat units. According to the *Dictionary*, these ingredients function mainly as surfactants – emulsifying agents, skin-conditioning agents – emollients, and skin-conditioning agents – miscellaneous in cosmetic formulations. At the time this safety assessment was written, PEG-3 Glyceryl Distearate was not listed in the *Dictionary*, but it has reported uses in the FDA VCRP database.

A supplier has reported that PEG/PPG-8/3 Diisostearate is produced through the condensation of fatty acids (i.e., isostearic acid) with alcohols (i.e., polyethylene glycol/polypropylene glycol). The esterification is acid-catalyzed. PEG-15 Butylene Glycol Diisostearate is produced through addition polymerization of ethylene oxide to 1,3-butylene glycol, followed by diesterification with isostearic acid. PEG-10 Glyceryl Diisostearate, PEG-20 Glyceryl Diisostearate, PEG-30 Glyceryl Diisostearate, and PEG-60 Glyceryl Diisostearate are produced through addition polymerization of ethylene oxide to glycerin, followed by diesterification with isostearic acid. PEG-4 Glyceryl Distearate is produced through addition polymerization of ethylene oxide to glycerin, followed by diesterification with stearic acid.

A supplier has reported that the purity of PEG/PPG-8/3 Diisostearate is > 95%. PEG-15 Butylene Glycol Diisostearate, PEG-10 Glyceryl Diisostearate, PEG-20 Glyceryl Diisostearate, PEG-30 Glyceryl Diisostearate, and PEG-60 Glyceryl

Diisostearate, and PEG-4 Glyceryl Distearate were reported to be 100% pure. Impurities may include isostearic acid, ethylene oxide, and/or stearic acid.

According to 2022 VCRP survey data, PEG/PPG-8/3 Diisostearate is reported to be used in 98 formulations, with most of them being in bath soaps and detergents. All other in-use ingredients in the VCRP (n = 3) are reported to be used in one or two formulations. The results of the concentration of use survey conducted by the Council indicate PEG/PPG-8/3 Diisostearate has the highest concentration of use in a leave-on formulation; it is used at 5% in a leave-on hair conditioner. PEG-12 Glyceryl Dimyristate has the next highest concentration of use in a leave-on formulation; it is used at up to 1.8% in body and hand products.

A supplier reported that the LD₅₀ for PEG/PPG-8/3 Diisostearate in an acute oral rat study was greater than 2000 mg/kg. In a short-term toxicity study, PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate, used in a base cream for pharmaceutical efficacy testing, caused no mortalities in female rats when applied twice daily for up to 15 d. PEG-12 Glyceryl Dioleate and PEG-12 Glyceryl Distearate at up to 1000 mg/kg in corn oil caused no mortalities or clinical signs of toxicity in a 28-d oral toxicity study in male and female rats. No abnormalities were observed at necropsy or in histopathological examination.

In a repeated insult patch test in 114 subjects, PEG/PPG-8/3-Diisostearate tested neat was non-irritating and non-sensitizing. PEG/PPG-8/3-Diisostearate in corn oil was determined to be non-irritating in an in vitro ocular study. In male rabbits, PEG-12 Glyceryl Dimyristate (100 mg; 10% w/v) was not an ocular irritant in a topical drug formulation where the rabbits were treated 6 times/d for several days. The same formulation was tested for tolerability, safety, and efficacy in healthy human volunteers and in patients with macular edema: no abnormalities or adverse events were observed.

Minimal data on chemical properties and impurities were made available via unpublished data submissions and no data were found in the published literature. The information on chemical and physical properties indicate that dermal penetration would be minimal. No toxicokinetic studies, DART studies, genotoxicity studies, or carcinogenicity studies were found in the published literature; and unpublished data were not submitted.

DISCUSSION

The Panel reviewed the safety of 14 fatty ester end-capped alkoxyates, which are reported to function mainly as surfactants and skin-conditioning agents in cosmetic products. Most of these ingredients are glyceryl fatty acid esters with ethylene glycol repeat units. The Panel concluded that the available data are sufficient for determining safety of PEG/PPG-8/3 Diisostearate as reportedly used in cosmetics. The Panel noted the lack of DART and genotoxicity studies for fatty ester end-capped alkoxyated ingredients. However, the Panel also noted these ingredients are large molecules (>1600 Da) and are not likely to absorb readily through the skin. This finding, coupled with the favorable safety profile and lack of structural features associated with genotoxicity, obviated the need for DART and genotoxicity data.

However, the Panel also concluded that the available data are insufficient to determine safety for the remaining 13 fatty ester end-capped alkoxyated ingredients. The Panel felt that there may be differences in the methods of manufacturing, compositions, and impurities for the other ingredients in this report, as compared to PEG/PPG-8/3 Diisostearate; thus, it was unclear if inferences from such data on PEG/PPG-8/3 Diisostearate could be applied to these other ingredients. Accordingly, the additional data needed to determine the safety of these ingredients in cosmetics are:

- Method of manufacturing
- Composition and impurities

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients. (For example, PEG-12 Glyceryl Dimyristate is reported to be used at 1% in hair sprays.) Inhalation toxicity data were not available on any of the fatty ester end-capped alkoxyated ingredients in this safety assessment. However, the Panel noted that in aerosol products, the majority of the 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 the ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <https://www.cir-safety.org/cir-findings>.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that PEG/PPG-8/3 Diisostearate is safe in cosmetics in the present practices of use and concentration described in this safety assessment. However, the Panel also concluded that the available data are insufficient to make a determination of safety for the following 13 fatty ester end-capped alkoxylated ingredients under the intended conditions of use in cosmetic formulations.

PEG-15 Butylene Glycol Diisostearate*
PEG-10 Glyceryl Diisostearate*
PEG-15 Glyceryl Diisostearate*
PEG-20 Glyceryl Diisostearate*
PEG-30 Glyceryl Diisostearate*
PEG-60 Glyceryl Diisostearate*
PEG-12 Glyceryl Dimyristate

PEG-12 Glyceryl Dioleate*
PEG-3 Glyceryl Distearate
PEG-4 Glyceryl Distearate*
PEG-12 Glyceryl Distearate
PEG-23 Glyceryl Distearate*
PEG-4 Polyglyceryl-2 Distearate*

**Not reported to be in current use.*

TABLES**Table 1.** Definitions, reported functions, and idealized structures of the ingredients in this safety assessment¹, CIR Staff

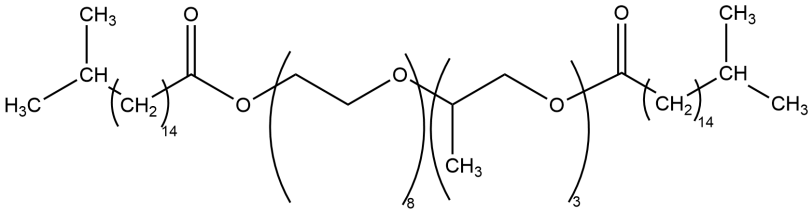
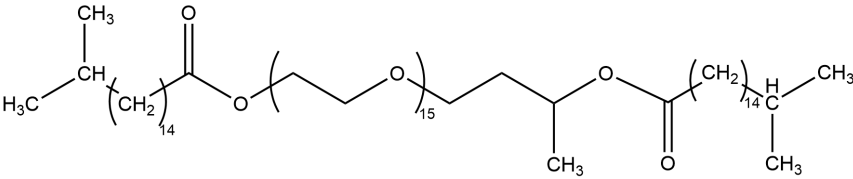
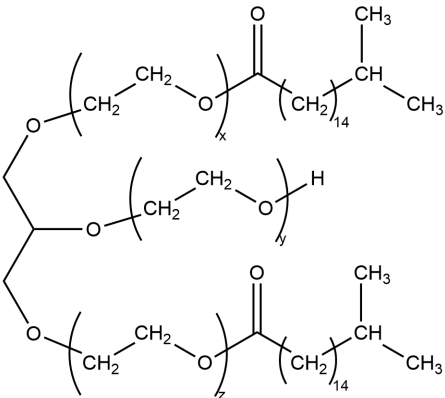
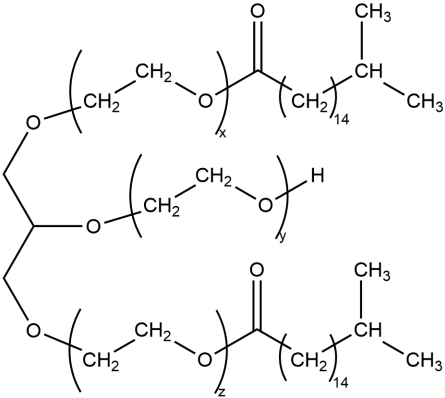
Ingredient & CAS No.	Definition	Function(s)
PEG/PPG-8/3 Diisostearate	PEG/PPG-8/3 Diisostearate is the polyethylene glycol ether of the propoxylated diester of isostearic acid containing an average ethoxylation value of 8 and propoxylation value of 3. <i>(Drawn block-style; connectivity may be different.)</i>	Surfactant – Emulsifying Agent
		
PEG-15 Butylene Glycol Diisostearate	PEG-15 Butylene Glycol Diisostearate is the polyethylene glycol derivative of the diester of 1,3-butylene glycol and isostearic acid containing an average of 15 moles of ethylene oxide. <i>(Drawn block-style; connectivity may be different.)</i>	Surfactant – Emulsifying Agent
		
PEG-10 Glyceryl Diisostearate	PEG-10 Glyceryl Diisostearate is the polyethylene glycol ether of glyceryl diisostearate that conforms generally to the structure:	Surfactant – Emulsifying Agent
	 where x+y+z has an average value of 10.	
PEG-15 Glyceryl Diisostearate	PEG-15 Glyceryl Diisostearate is the polyethylene glycol ether of glyceryl diisostearate that conforms generally to the structure:	Surfactant – Emulsifying Agent
	 where x+y+z has an average value of 15.	

Table 1. Definitions, reported functions, and idealized structures of the ingredients in this safety assessment¹, CIR Staff

Ingredient & CAS No.	Definition	Function(s)
PEG-20 Glyceryl Diisostearate	PEG-20 Glyceryl Diisostearate is the polyethylene glycol ether of glyceryl diisostearate that conforms generally to the structure: where $x+y+z$ has an average value of 20.	Surfactant – Emulsifying Agent
PEG-30 Glyceryl Diisostearate	PEG-30 Glyceryl Diisostearate is the polyethylene glycol ether of glyceryl diisostearate that conforms generally to the structure: where $x+y+z$ has an average value of 30.	Surfactant – Emulsifying Agent
PEG-60 Glyceryl Diisostearate	PEG-60 Glyceryl Diisostearate is the polyethylene glycol ether of glyceryl diisostearate that conforms generally to the structure: where $x+y+z$ has an average value of 60.	Surfactant – Emulsifying Agent

Table 1. Definitions, reported functions, and idealized structures of the ingredients in this safety assessment¹, CIR Staff

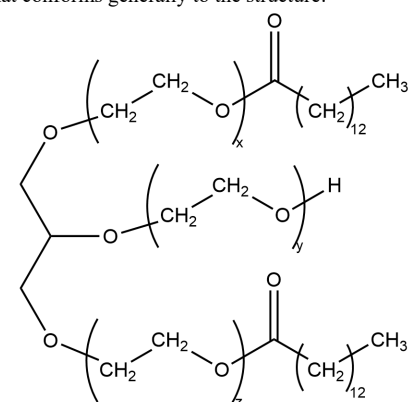
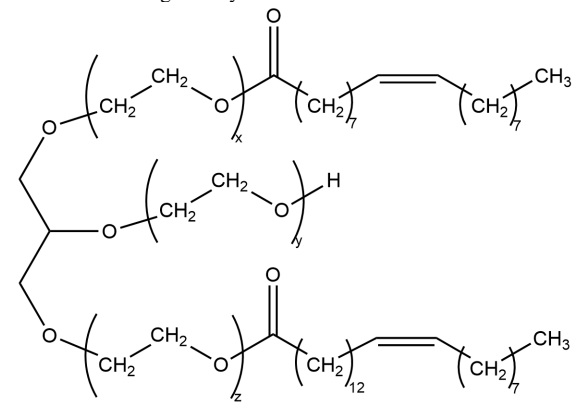
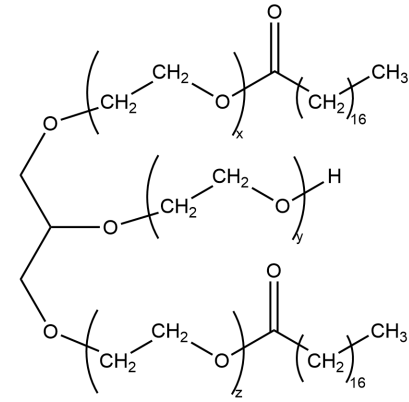
Ingredient & CAS No.	Definition	Function(s)
PEG-12 Glyceryl Dimyristate	PEG-12 Glyceryl Dimyristate is the polyethylene glycol ether of glyceryl dimyristate that conforms generally to the structure:  where x+y+z has an average value of 12.	Skin-Conditioning Agent – Misc.
PEG-12 Glyceryl Dioleate	PEG-12 Glyceryl Dioleate is the polyethylene glycol ether of glyceryl dioleate that conforms generally to the structure:  where x+y+z has an average value of 12.	Skin-Conditioning Agent – Emollient; Surfactant – Emulsifying Agent
PEG-3 Glyceryl Distearate	Not found in the <i>Dictionary</i>. (Structure based on other PEG glyceryl diesters)  where x+y+z has an average value of 3.	Not found in the <i>Dictionary</i> .

Table 1. Definitions, reported functions, and idealized structures of the ingredients in this safety assessment¹, CIR Staff

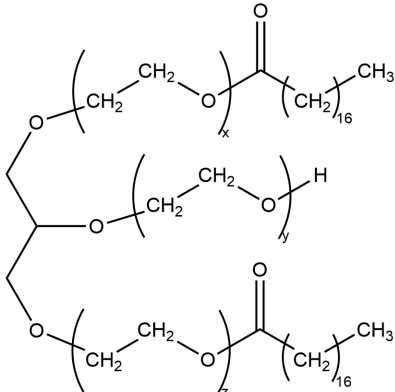
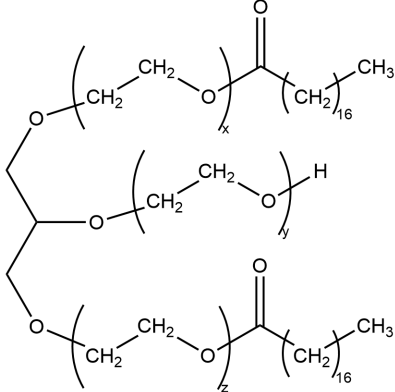
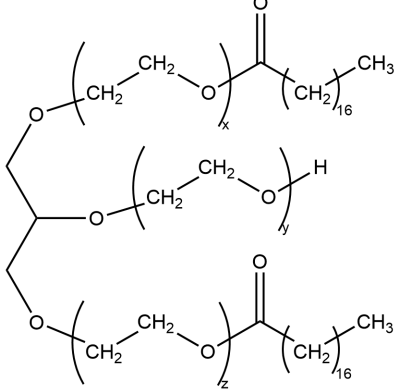
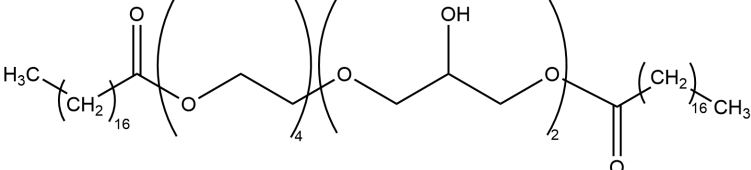
Ingredient & CAS No.	Definition	Function(s)
PEG-4 Glyceryl Distearate	PEG-4 Glyceryl Distearate is the polyethylene glycol ether of glyceryl distearate that conforms generally to the structure:  where x+y+z has an average value of 4.	Skin-Conditioning Agent – Emollient
PEG-12 Glyceryl Distearate	PEG-12 Glyceryl Distearate is the polyethylene glycol ether of glyceryl distearate that conforms generally to the structure:  where x+y+z has an average value of 12.	Skin-Conditioning Agent - Emollient
PEG-23 Glyceryl Distearate	PEG-23 Glyceryl Distearate is the polyethylene glycol ether of glyceryl distearate that conforms generally to the structure:  where x+y+z has an average value of 23.	Skin-Conditioning Agent – Misc.
PEG-4 Polyglyceryl-2 Distearate 72828-11-6	PEG-4 Polyglyceryl-2 Distearate is the polyethylene glycol ether of polyglyceryl-2 distearate with an average ethoxylation value of 4. (<i>Drawn block-style; connectivity may be different.</i>) 	Surfactant – Emulsifying Agent

Table 2. Relevant related safety assessments and Panel conclusions.

Report Family	Specific Related Ingredients	Conclusion	Reference
Glyceryl Diesters	glyceryl diisostearate, glyceryl dimyristate, glyceryl dioleate, glyceryl distearate	Safe as cosmetic ingredients provided that the content of 1,2-diester is not high enough to induce epidermal hyperplasia	²
Triethylene Glycol and PEGs ≥ 4	triethylene glycol, PEG-4, PEG-8, PEG-10, PEG-12, PEG-20, PEG-60	Safe as used	³
PPGs	PPG-3	Safe when formulated to be nonirritating	⁴
PEG Diesters	PEG-8 diisostearate and PEG-12 dioleate	Safe when formulated to be nonirritating	⁵
PEGylated Oils	several PEG-3, PEG-4, PEG-8, PEG-10, PEG-15, PEG-20, PEG-30, PEG-60 oils and oil esters	Safe when formulated to be nonirritating	⁶
Monoglyceryl Monoesters	glyceryl isostearate, glyceryl oleate, glyceryl stearate	Safe as used	⁷

Table 3. Frequency (2022)¹² and concentration (2019-2022)^{13,14} of use according to duration and exposure.

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	PEG/PPG-8/3 Diisostearate		PEG-3 Glyceryl Distearate	
Totals*	98	5	2	NR
Duration of Use				
Leave-On	NR	5	1	NR
Rinse Off	98	NR	1	NR
Diluted for (Bath) Use	3	NR	NR	NR
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1 ^a	NR
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	97	NR	1	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	1	5	1	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	96	NR	NR	NR
Baby Products	NR	NR	NR	NR
	PEG-12 Glyceryl Dimyristate		PEG-12 Glyceryl Distearate	
Totals*	1	0.7-1.8	1	1
Duration of Use				
Leave-On	1	0.7-1.8	1	1
Rinse-Off	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR
Exposure Type				
Eye Area	NR	0.7	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	1 ^a	1	NR	NR
Incidental Inhalation-Powder	NR	1.8 ^b	NR	NR
Dermal Contact	NR	0.7-1.8	1	1
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	1	1	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

*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 these products are sprays, but it is not specified whether the reported uses are sprays.

^b It is possible these products are powders, but it is not specified whether the reported uses are powders

NR – not reported

Table 4. Ingredients not reported in use.¹²⁻¹⁴

PEG-15 Butylene Glycol Diisostearate
 PEG-10 Glyceryl Diisostearate
 PEG-20 Glyceryl Diisostearate
 PEG-30 Glyceryl Diisostearate
 PEG-60 Glyceryl Diisostearate

PEG-12 Glyceryl Dioleate
 PEG-4 Glyceryl Distearate
 PEG-23 Glyceryl Distearate
 PEG-4 Polyglyceryl-2 Distearate
 PEG-15 Glyceryl Diisostearate

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Memorandum

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

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

DATE: July 19, 2022

SUBJECT: Fatty Acid End-Capped Ethoxylates

Anonymous. 2022. Method of Manufacture, Composition, and Impurities - Fatty Acid End-Capped Alkoxylates.

July 2022

Method of Manufacture, Composition, and Impurities – Fatty Acid End-Capped Alkoxylates

INCI Name/Composition	Method of Manufacture	Impurities
PEG-15 Butylene Glycol Diisostearate/100%	After addition polymerization of ethylene oxide to 1,3-butylene glycol, diesterification with isostearic acid	Isostearic Acid $\leq 5\%$; Ethylene Oxide ≤ 1 ppm
PEG-10 Glyceryl Diisostearate/100%	After addition polymerization of ethylene oxide to glycerin, diesterification with isostearic acid	Isostearic Acid $\leq 4\%$; Ethylene Oxide ≤ 1 ppm
PEG-20 Glyceryl Diisostearate/100%	After addition polymerization of ethylene oxide to glycerin, diesterification with isostearic acid	Isostearic Acid $\leq 4\%$; Ethylene Oxide ≤ 1 ppm
PEG-30 Glyceryl Diisostearate/100%	After addition polymerization of ethylene oxide to glycerin, diesterification with isostearic acid	Isostearic Acid $\leq 4\%$; Ethylene Oxide ≤ 1 ppm
PEG-60 Glyceryl Diisostearate/100%	After addition polymerization of ethylene oxide to glycerin, diesterification with isostearic acid	Isostearic Acid $\leq 4\%$; Ethylene Oxide ≤ 1 ppm
PEG-4 Glyceryl Distearate/100%	After addition polymerization of ethylene oxide to glycerin, diesterification with stearic acid	Stearic Acid $\leq 2\%$; Ethylene Oxide ≤ 1 ppm

2022 FDA VCRP Raw Data

PEG/PPG-8/3 DIISOSTEARATE	02B	Bubble Baths	3
PEG/PPG-8/3 DIISOSTEARATE	05F	Shampoos (non-coloring)	1
PEG/PPG-8/3 DIISOSTEARATE	10A	Bath Soaps and Detergents	93
PEG/PPG-8/3 DIISOSTEARATE	12A	Cleansing	1
PEG-12 GLYCERYL DIMYRISTATE	05G	Tonics, Dressings, and Other Hair Grooming Aids	1
PEG-12 GLYCERYL DISTEARATE	12J	Other Skin Care Preps	1
PEG-3 GLYCERYL DISTEARATE	05F	Shampoos (non-coloring)	1
PEG-3 GLYCERYL DISTEARATE	12F	Moisturizing	1