Safety Assessment of Glycerin Ethoxylates as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	November 15, 2019
Panel Meeting Date:	December 9-10, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.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 CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Alice Akinsulie, former Scientific Writer/Analyst, and Preethi Raj, Senior Scientific Writer/Analyst.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Preethi S. Raj, Senior Scientific Analyst/Writer
Date: November 15, 2019
Subject: Draft Tentative Report on Glycerin Ethoxylates

Enclosed is the Draft Tentative Report on the Safety Assessment of 8 Glycerin Ethoxylates ingredients (identified as *glyeth122019rep* in the report package). This is the second time the Panel is reviewing this document. These ingredients were first reviewed at the June 2019 meeting, at which the Panel issued an insufficient data announcement for method of manufacture, impurities, and inhalation toxicity data.

According to 2019 VCRP survey data, Glycereth-26 has the highest frequency of use, with a total of 379 formulations. The Council provided updated concentration of use survey data (identified as *glyeth122019data1* and *glyeth122019data2*). The results of the concentration of use survey conducted in 2018 by the Council indicate that Glycereth-26 has the highest maximum concentration of use, and is used at up to 39.5% in skin cleansing products. A singular update from the 2019 concentration of use survey, includes the discontinuation of a potentially inhaled body and hand product containing 4% Glycereth-26, resulting in a 1% maximum reported concentration of use for potentially inhaled, possibly powder, Glycereth-26 products. The concentration reported for this rinse-off use product category is much higher than that reported for other product categories; the highest maximum leave-on use concentration reported is 6% Glycereth-26 in eye lotions.

The following unpublished data were received and have been incorporated into the document:

glyeth122019data3 – all pertaining to Glycereth-26

- Anonymous (2019). Certificate of Analysis
- Anonymous (2017). Safety testing summary (includes acute oral, ocular irritation, and dermal irritation studies)
- Anonymous (2007). Topical application EpiOcular™ ocular irritation assay

glyeth122019data4

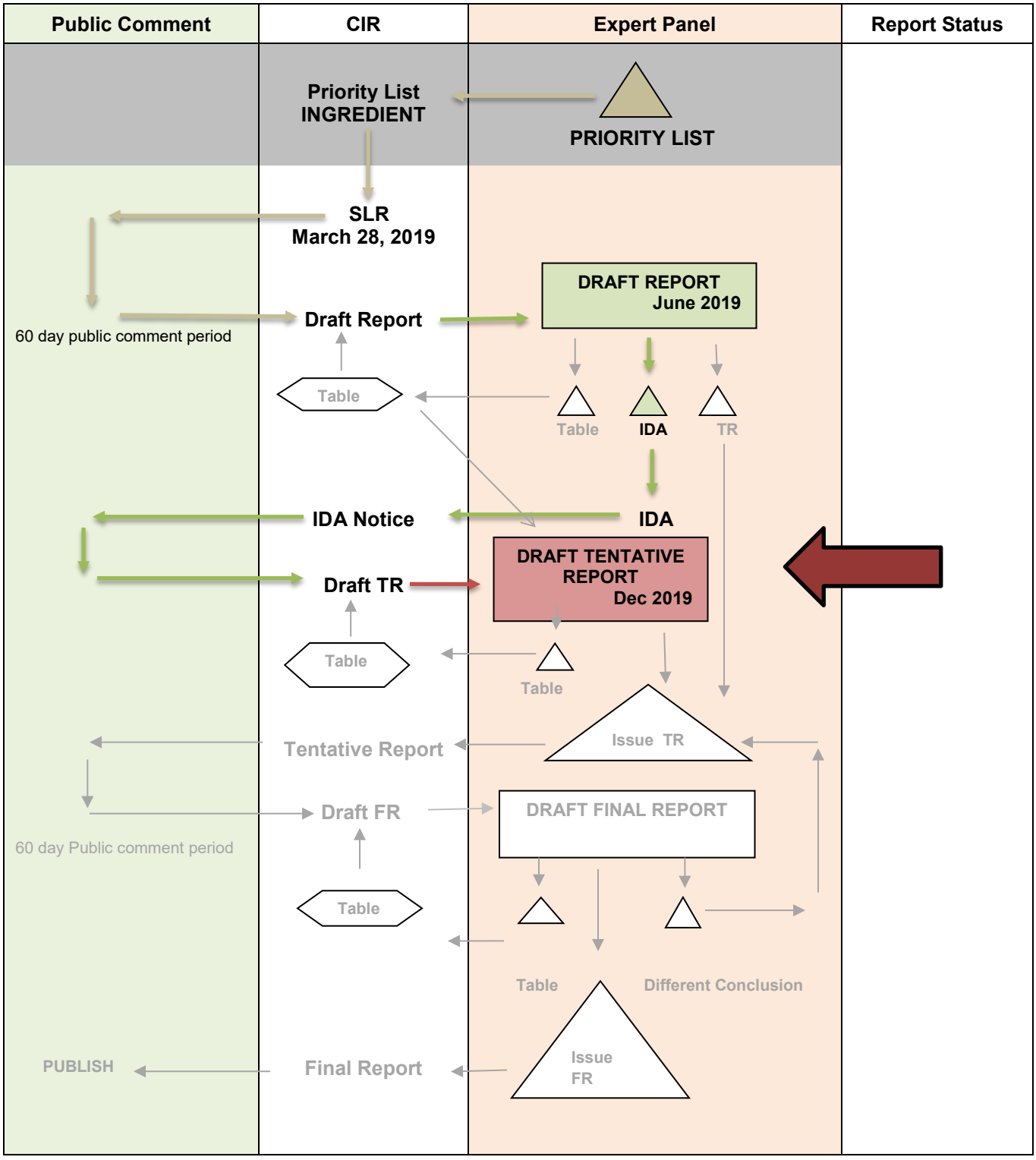
- Anonymous (2019). Summary of an HRIPT on product containing 0.68% Glycereth-7
- Anonymous ((2019). Summary of an HRIPT on product containing 3% Glycereth-26

The following are also included in this package for your review:

- *glyeth122019flow*: flow chart
- *glyeth122019hist*: history
- *glyeth122019min:* meeting minutes
- *glyeth122019prof*: data profile
- *glyeth122019strat*: search strategy
- *glyeth122019fda*: 2019 VCRP data (US FDA)

Comments on the Draft Report (*glyeth122019pcpc*) were received from the Council and have been addressed.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should identify matters to be addressed in the Discussion, and then issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion. If, however, the available data remain insufficient, the Panel should issue a Tentative Report with a conclusion of insufficient data, discussing the rationale therein.


Public Comment
CIR
Expert Panel
Report Status
Priority List
INGREDIENT
PRIORITY LIST
SLR
March 28, 2019
60 day public comment period
Draft Report
DRAFT REPORT
June 2019
Table
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IDA Notice
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DRAFT TENTATIVE
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Dec 2019
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60 day Public comment period
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CIR History of:

Glycerin Ethoxylates

A Scientific Literature Review (SLR) was issued: March 28, 2019

The CIR sought the following during the 60-day public comment period:

- Method of manufacture
- Impurities
- Dermal absorption
    - If absorbed, also requested systemic toxicity data

Data for two HRIPT studies and an in vitro ocular irritation assay were received from the Council and incorporated into the report.

A Draft Report was presented at the 151st Expert Panel Meeting: June 6-7, 2019
Upon initial review of this ingredient, the Panel found the data insufficient to determine safety. The results of a concentration of use survey conducted by the Council in 2018 indicated that Glycereth-26 is used at up to 1% in body and hand spray formulations, which may result in incidental inhalation exposure. The Panel discussed the issue of incidental inhalation exposure from aerosol spray moisturizers, and body and hand products. The Panel also asked to see data from similar alkoxylated ingredients for potential inference.

These observations resulted in the Panel issuing an Insufficient Data Announcement for the following:

- Method of manufacture
- Impurities
- Inhalation toxicity

The Panel noted that if sufficient manufacturing and impurities data are found, they may able to make a safety evaluation in the absence of inhalation data.

After the mail date for the 151st Expert Panel Meeting, CIR received Council comments, new concentration of use, and the following industry data to be incorporated in the upcoming report:

- Glycereth-26
    - 2019 HRIPT on product containing 3% Glycereth-26
    - 2019 Certificate of Analysis
    - 2017 Safety testing summary, including studies on the following:
        - Acute oral toxicity
        - Ocular irritation
        - Dermal irritation
    - 2007 ocular irritation assay summary
- Glycereth-7
    - 2019 HRIPT on product containing 0.68% Glycereth-7

A Draft Tentative Report is now presented at the 153rd Expert Panel meeting: December 9-10, 2019

Glycerin Ethoxylates Data Profile* – December 9-10, 2019 – Preethi Raj

				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	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
Glycereth-3				X			X	X	X						X					X						X	X		
Glycereth-7	X			X																	X								
Glycereth-8				X																									
Glycereth-12	X			X																	X					X			
Glycereth-18	X			X																									
Glycereth-20	X			X																									
Glycereth-26	X		X	X				X												X				X		X	X		
Glycereth-31				X																									
Read across ingredients																													
"Ethoxylated glycerols"		X	X				X	X	X						X				X										
Propoxylated nitrilotriethanol											X			X	X														
Propoxylated glycerol															X								X						

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

[Glycerin Ethoxylates]

Ingredient	CAS #(generic)	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Glycereth-3	31694-55-0	✓	0/9	0/674	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Glycereth-7	31694-55-0	✓	0/7	0/205	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Gycereth-8	31694-55-0	✓	0/1	0/173	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Glycereth-12	31694-55-0	✓	NR	0/79	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Glycereth-18	31694-55-0	✓	0/1	0/41	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Glycereth-20	31694-55-0	✓	1/3	0/93	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Glycereth-26	31694-55-0	✓	1/129	0/18	✓	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Glycereth-31	31694-55-0	✓	NR	0/26	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Glycerin Ethoxylate	31694-55-0	NR	1/225	0/7	NR	NR	NR	✓	NR	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	✓

***NR – No results were found; Check mark - Data available; 0/0 – relevant/hits**

Web Search

1,2,3-Propanetriol, ethoxylated
Ethoxylated glycerine
Ethoxylated glycerol
Glycereth-3; Glycereth-7; Glycereth-8; Glycereth-12; Glycereth-18; Glycereth-20; Glycereth-26; Glycereth-31
Glycerol poly(oxyethylene) ether
Glycerol polyoxyethylene ether
Glycerol, ethoxylated
Lupranol VP 9209
Alkoxylated alcohols
Acute inhalation toxicity → Glycereth-26
Propoxylated nitrilotriethanol toxicity; propoxylated glycerol toxicity; ethoxylated glycerol toxicity
Impurities of ethoxylated compounds
Ethoxylated compounds and lung toxicity
Case reports; Clinical reports
Composition of alkoxylated alcohols
PEG ethers of glycerin
Acute toxicity; Repeated dose toxicity; Subacute toxicity; Short-term toxicity; Subchronic toxicity; Chronic toxicity; Adverse health effects; Hypersensitivity; Sensitization; Carcinogenicity; Genotoxicity; Mutagenicity; Dermal absorption; Dermal penetration; Dermal irritation; Developmental toxicity; Reproductive toxicity; In vitro toxicity; Ocular effects; Oral exposure; Phototoxicity; Photosensitivity

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- additional terms will be used as appropriate

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

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;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- 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
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- 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/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- 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
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.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

JUNE 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

BELSITO TEAM – June 6, 2019

DR. BELSITO: Okay. And then Glycerin Ethoxylates. So we need manufacture and impurities, right?

DR. SNYDER: Yes.

DR. LIEBLER: Yep.

DR. BELSITO: We need absorption, distribution, metabolism?

DR. LIEBLER: Yes.

DR. BELSITO: Regarding the DART study, it says that concentration of test article -- this is page 11 in the PDF. "Concentration of test article and days of dosing were not specified." But it was performed according to the OECD guidelines, so the days of dosing would be specified by those guidelines. Right?

And then it says the doses of 0, 100, 300, and 1000 milligrams per kilogram bodyweight. We have the doses and we would know the days of application, of gavage, based on OECD. So, I think that sentence needs to go out.

Dan, we're using read across for ethoxylated glycerol?

DR. LIEBLER: Yeah. I thought that was fine.

DR. BELSITO: Okay.

DR. LIEBLER: It's fine. It kind of covers the lower mass range of these ingredients. But those are the ones, I think, where one might have more concern about possible toxicity because those could be absorbed to some extent dermally. They'd have more extensive absorption in the gut. So, safety with those on both dermal and oral endpoints, I think, is likely to be quite predictive for the whole group.

DR. BELSITO: What about sensitization?

DR. LIEBLER: I think it's appropriate for sensitization because the fundamental chemical feature of this is a polyethoxylated core piece.

None of the parts of this family of molecules has any real propensity for reaction with proteins, nor could any reasonable metabolites -- I mean, I suppose aldehydes produced from any of these alcohols could be protein reactive. But certainly, the parents aren't. Not all aldehydes are really good protein modifiers. Most of the aldehydes we look at, or RIFM for example, aren't sensitizers.

DR. BELSITO: Right. Okay.

DR. LIEBLER: So, I was very comfortable with it. In fact, I'd go further to say that the eco read across material, the propoxylated nitrilotriethanol, I think that was also reasonable as read across materials. It's a nitrogen-containing compound in the core, but the overall structure is very similar. It's a polyethoxylated molecule that presents a very similar overall structure, and it presents the polyethoxylated part of the molecule well.

In fact, while we're on the topic of read across and analogs, this is something I think I'd like to see us do more. But we've reviewed a lot of polyethoxylated ingredients with different core molecules that are polyethoxylated. And I think it would be helpful to cite the safety conclusions from some of those reports. Because, in general, these have been very safe. Even if the core part of the molecule isn't the same structure, essentially we're talking about very similar overall chemical presentations.

We could use them -- I think read-across isn't quite the word, but weight-of-evidence that we could cite somewhere in the report; a paragraph on -- maybe in the introduction -- that we've reviewed the following related families of chemicals. And then, in the discussion, the Panel noted that previous safety assessments containing structurally related polyethoxy, you know, materials have -- provide further weight-of-evidence support for the safety of these. I mean, these are low toxicity.

DR. BELSITO: Okay. So, then, that brings me back. Since the DART and genotox are okay, do we need absorption, distribution, and metabolism?

DR. SNYDER: No.

DR. LIEBLER: No.

DR. BELSITO: Okay. But we still need method of manufacturing and impurities?

DR. SNYDER: Yes. We got nothing there.

DR. BELSITO: So, that's the only insufficiency?

DR. SNYDER: Yep.

DR. BELSITO: We're going to add a paragraph in the introduction of the discussion about other polyethoxylated ingredients that we found safe.

DR. SNYDER: Right.

DR. BELSITO: And we're going to discuss that we don't need the ADME data because the DART and genotoxicities are fine.

DR. LIEBLER: We already have good --

DR. BELSITO: However, we need to know the manufacturing and impurities, and we're going insufficient just for that.

DR. LIEBLER: I do think the low molecular weight members of this family will be absorbed a little bit. Under 500 molecular weight, there will be a little dermal absorption. But we know, from the oral endpoints, that these have a very favorable safety profile. So, I'm not concerned about dermal absorption, systemic tox. And I don't think there's any mechanistic reason to be concerned about sensitization with these.

DR. BELSITO: Well, I mean, we have sensitization studies that are above -- I think at 0.35. And the max leave-on is 0.25.

DR. SNYDER: We actually have 0.5.

DR. LIEBLER: Yeah. So, I think once we have method of manufacture and impurities, we're on the way to the finish line with these. I think that'd be fine.

DR. BELSITO: Okay. Anything else on these?

MARKS TEAM – June 6, 2019

DR. MARKS: Next is glycerin ethoxylates. Let's see here. So this is a draft report on these eight glycerin ethoxylate ingredients. So this is the first review. They are a combination of polyethylene glycose PEGs -- PEG 4, et cetera -- plus glycerin, which has been reviewed previously and found to be safe.
Tom and Ron, and Ron the surrogate, are these eight ingredients okay, or is there any one that you feel shouldn't be included in this?

DR. SLAGA: I thought they all could be included.

DR. SHANK: I don't know why nitrilotriethanol is included in use for read across. I'm looking to see if Dr. Hill addresses that, and I don't see it. So I guess the chemists think that's okay.

DR. MARKS: So in the report, they use the safety of that as a read across. Is that what you're saying?

DR. SHANK: Yes.

DR. MARKS: And we don't have Bart here to say.

DR. SHANK: No.

DR. MARKS: What was your sense, Alice, why that was included?

MS. AKINSULIE: The ECHA dossier was prepared for ingredients on ethoxylated glycerol, but the test materials specifically were read across constituents.

DR. MARKS: So you're questioning whether it should even be in the report?

DR. SHANK: Right.

MS. FIUME: We also found it interesting when it was included. But it's in here because if ECHA gives it to us, we present it to you to weigh in on.

DR. SHANK: If the chemists can say it makes no difference, then I guess it didn't seem to fit for me. But we can discuss that tomorrow.

DR. MARKS: So do you want me to mention it, Ron? When Wilma asks for comments after, you'll just bring that up?

DR. SHANK: I'll be happy to, yes.

DR. MARKS: Great. I had the sensitization data were okay for these ingredients.
Tom, Ron, any needs?

DR. SLAGA: I didn't have any needs. Irritation is not a problem and genotoxicity not a problem.

DR. SHANK: Okay. I didn't think there was very much tox data here, so I have a 28-day dermal tox on glycereth-26 because that one has the greatest number of uses and the highest concentrations. Skin penetration -- and if it's absorbed, then we need genotox in DART. These are used in inhalable products, so we need inhalation tox data.

MS. FIUME: Any specific study time length on inhalation tox?

DR. SHANK: I'd have to look at the table --frequency of use table. Okay. So it's used in powders and sprays at 2 to 4 percent. That's glycereth-26. That's the only one.

MS. FIUME: So just a generic request for inhalation tox without any specific timeframe included?

DR. SHANK: I would do just an acute toxicity, because this would be an incidental spray with exposure a few seconds at a time.

MS. FIUME: Thank you.

DR. SHANK: So I don't see any long term tox needs.

DR. MARKS: And Ron, just to be clear, the previous reviews of the PEGs and glycerin you don't think could be used as a substitute for needing these -- the 28-day? Since they were safe, you don't think that could be used as a proxy for the safety of, if I heard you correctly, the glycereth-26 is the prototype. We want the 28-day dermal tox, the inhalation tox, and the skin penetration data and, if absorbed, genotox and DART.

DR. SHANK: Possibly DART, yes.

DR. MARKS: So I just want to be clear that you couldn't use those previous safety of the -- since this is a combination of PEGs and glycerin, that wouldn't substitute for the combined? I'm asking that from a point of –

DR. SHANK: I don't think so. Perhaps the chemists can convince me.

DR. MARKS: No, that's fine. I just want to clarify.

DR. SLAGA: I assumed that we could use it, but that's just me.

DR. SHANK: PEGs by themselves or glycerin by themselves, okay. But now, this is a much bigger molecule.

DR. MARKS: Okay. I'll put in there -- if that comes up tomorrow, I'll mention those. Do I have that correct, Ron? Needs are glycereth-26. That's the prototype -- 28-day dermal tox, the inhalation tox, and a skin penetration; if absorbed, then genotox and DART. And then we'll see where it goes from there.

DR. SHANK: Okay.

DR. SLAGA: The 26 Ron picked because of concentration of use?

DR. SHANK: Right.

DR. MARKS: It's the highest concentration, highest use. 379 uses and the highest leave-on is 6 percent.

DR. SLAGA: A lot of times we usually ask for the one that's lower, smaller.

DR. MARKS: Yes. I thought of that, too, Tom. I agree.

DR. SHANK: Do you want both?

DR. SLAGA: There's a 3, 12, 24, and 26.

DR. MARKS: Yeah. The 3 there are no uses. The 7 is 80 uses at 1 percent. But I like your approach to ask for 26. And we'll see. We'll see what the -- I like how you, Ron, defer to the chemists. If Dan feels we can use the PEGs and the glycerin individually as a read across, so to speak, for the combination, then maybe we'll go from there. But I'll bring this up so that it's a discussant point tomorrow, Ron, and let you weigh in.

DR. SLAGA: Okay.

DR. BERGFELD: Can you just clarify the situation here? This is reopened, is it not?

DR. MARKS: No, this is the first review.

DR. BERGFELD: The first -- but we looked at the components. Those are the propylene ethyl glycol PEGs in 2010. I see. So this is just another ingredient using some of the stem ingredients.

DR. MARKS: Exactly. Yeah. This is glycerin plus PEGs. And did I say that right? Ethoxylates?

DR. SHANK: Ethoxylates.

DR. MARKS: I guess it depends on whether you're from Boston or Philly. Okay. So I'm going to put second insufficient data announcement, and we'll see what the other team -- if they come to a different conclusion, we'll have a discussion and then resolve that. But for now, an ISA.
Does that sound good, Tom?

DR. SLAGA: Yeah.

DR. MARKS: It's fine with me. Okay. And we took into consideration Ron Hill's comments. Okay. So I will presumably second tomorrow an insufficient data announcement. And I mentioned the needs previously.

FULL PANEL – June 7, 2019

DR. BELSITO: Okay, so this is the first time we're looking at these glycerin ethoxylates. There was a good amount of data. It would appear that the low molecular weight members could be absorbed a bit. But there was good oral data, and the DART and genotoxicity data were good.

Dan felt that we should add in a paragraph in the introduction and discussion indicating that we've reviewed other polyethoxylated ingredients and found them safe as used. And, I suspect Ron Shank may object, we just thought we needed method of manufacture and impurities. But given the DART and genotox data, do we want to just say safe as used instead?

DR. BERGFELD: Dan, you want to respond?

DR. LIEBLER: Method of manufacture and impurities are insufficient. And I'm sure we can come up with something.

DR. BERGFELD: Ron Shank?

DR. MARKS: I'd like to hear, is this a motion for an insufficient data announcement?

DR. BELSITO: We said insufficient for method of manufacture and impurities.

DR. MARKS: Right. So, we second that insufficient data announcement. We have some other insufficiencies. But, Dan, go ahead. I wanted to be clear what the motion was.

DR. LIEBLER: Yeah. That was it.

DR. MARKS: Okay.

DR. BERGFELD: Ron Shank?

DR. SHANK: I'd like to ask Dr. Liebler, is propoxylated nitrilotriethanol a good proxy for these?

DR. LIEBLER: It is to the extent that it's essentially a relatively unreactive internal core that serves as a scaffold for these polyethoxylated chains. So, I would use it with some explanation in the discussion, why we were able to rely on it. There's also, although you didn't ask, the other read-across proposed in the report was the mixture of ethoxylated glycerols. And I thought that that was an appropriate read-across as well.

DR. SHANK: Okay. Thank you.

DR. LIEBLER: Just to the extent that these molecules are essentially a little core, in this case glycerol with these polyethoxylated antennas hanging off them. So, the other molecules that present that structure, I think, are an appropriate read-across in the right context.

DR. SHANK: Do you feel these will not be absorbed -- penetrate?

DR. LIEBLER: Oh, I think the lower molecular ones will be absorbed to some extent. The lower molecular ones are under 500 molecular weight, so that we'd probably have some modest absorption.

DR. SHANK: Okay, so, I thought we needed some toxicology data. Choosing glycereth-26 for the tox studies 28-day dermal, skin penetration if it's absorbed, and then if it is absorbed genotox and possibly DART. These compounds can be inhaled, so we'd need inhalation toxicology data.

DR. BELSITO: So, you're not buying the read-across?

DR. SHANK: I didn't, but I really have to defer to our chemist, so if he's happy that we can read across the tox data, then I will accept that. But I didn't accept it on my own.

DR. LIEBLER: Here's my thinking. For dermal application, so we'll set aside the respiratory for the moment, for the dermal application the low molecular weight compounds are more likely to be absorbed. We have tox data for glycereth-3, and then that ethoxylated glycerol. There were the acute tox studies, and these were very low toxicity. And then for the short-term we had the propoxylated nitrilotriethanol, that read across from the ECHA dossier that you just asked about. And my feeling is that this is essentially a surrogate for a polyethoxylated molecule. And those molecules were fine in both the DART and the short-term oral.

And then we've got a very much bigger body of data for other polyethoxylated molecules that we've absorbed, where we've got some pretty innocuous core decorated with these polyethoxy chains. And, I thought that those data could be brought into the report to provide weight of evidence to support the safety profile of these overall because they really look pretty non-toxic.

Now the respiratory, I haven't been thinking about that too much, if you wanted to elaborate on your concerns about that. I don't think we have too much to go on.

DR. SHANK: Just that they are used in products that could be inhaled, and they don't have inhalation toxicology data.

DR. LIEBLER: So we can leave that on the list of insufficiencies, see what we get, and then deal with that next time.

DR. SHANK: Okay. I would put it on the insufficient list, inhalation data.

DR. BERGFELD: Okay, are we going to do that? Paul, did you have something to say?

DR. SNYDER: No, I was just going to second Ron's concern. I had the same concern until our team meeting when Dan assured me that it was a good read-across. And it also gave me some comfort that both the DART study and the short-term study, there was no observed adverse effect level, with the highest dose tested at 1,000. So that gave me another level of comfort that there's probably no signal there.

DR. SHANK: Yes, right.

DR. BERGFELD: Curt?

DR. KLAASSEN: I agree.

DR. BERGFELD: You agree. So, where do we stand with this? We have the insufficient data announcement going out. And, would you please read what the insufficiencies are that you've got?

MS. AKINSULIE: Sure. So we have the 28-day dermal...

DR. BERGFELD: 28-day dermal?

DR. MARKS: No, I don't think so, because we're reassured, as Dan explained. Really it's method of manufacture, impurities, and then an inhalation is the three I've got.

DR. BERGFELD: Three things?

MS. AKINSULIE: Okay.

DR. BERGFELD: Okay.

DR. MARKS: Is that correct, Don?

DR. BELSITO: Yeah, I mean I just wanted to raise the point that we're now -- I mean, previously we were using the respiratory boilerplate when we didn't have inhalation. And now it looks like we've gotten rid of that boilerplate and we'll ask for inhalation.

DR. BERGFELD: Ron Shank, saying yes?

DR. SHANK: I say yes.

DR. BERGFELD: See what's out there?

DR. SNYDER: It's kind of a change in our strategy, I think.

DR. BELSITO: Yeah, I mean that's...

DR. BERGFELD: Paul, want to comment?

DR. SNYDER: Well, I mean it's -- it is a significant deviation from what we've done. Previously we used the boilerplate to obviate the inhalation issue. But, again, if we have composition impurities then we would know whether we felt there was any issue with inhalation.

DR. LIEBLER: The thing about the boilerplate was that it essentially gave us an out if you will that the particle sizes were not going to be respirable. And, now we basically have had discussions at the last several meetings where there's been ambiguity about that question. And we feel that we can't necessarily always just rely on that accretion.

So if we ask for respiratory data and we get back data indicating that the particles in any of the products that we would review would be not respirable, then we would have specific information to that effect and then we could bypass the inhalation tox study.

DR. SNYDER: I think in the instances that we're asking for it, is that we have either case studies or we have evidence that there's inhalation toxicity. And so therefore, that's a bigger driver then just using the template to get around that.

In this instance I don't see anything -- but I don't have the impurities or composition. So, if we get that and we don't see anything of concern, and then I think we should just go with our boilerplate like we have, less we'll be changing our strategy for aerosolized products.

DR. BELSITO: I think, in which case, we need another look at the respiratory boilerplate to decide where we're going to go with that.

DR. SHANK: We didn't do that with the polyaminopropyl biguanide.

DR. BELSITO: We didn't do that because there was a respiratory signal. That's what Paul is saying.

DR. SHANK: But you don't know with this, there are no data.

DR. KLAASSEN: But the other, there was data.

DR. SHANK: Inhalation data?

DR. KLAASSEN: Yeah.

DR. SHANK: Where?

DR. KLAASSEN: Well, we knew for the other compounds.

DR. SHANK: Oh, yes.

DR. KLAASSEN: We knew that there was a signal there.

DR. SHANK: Yes.

DR. KLAASSEN: And, I understand what you're saying. But it is a marked change in our philosophy.

DR. SHANK: Well we may end up using the boilerplate. But since it's going out for insufficient, I would like to add a request for inhalation data.

DR. KLAASSEN: Okay.

DR. BERGFELD: Appears okay.

DR. BELSITO: So method of manufacture, impurities, and inhalation.

DR. BERGFELD: And, you're seconding that?

DR. MARKS: Oh, yes.

DR. LIEBLER: Just to come back to the boilerplate issue, I mean, if we have a boilerplate and we sort of decide whether or not to use it. On a case-by-case basis we need to take a careful look at the boilerplate and think more about how we approach this.

Because you're right, Ron, to begin with here we have nothing. And I think we have greater doubts about whether we can assume that any particles that would contain this ingredient would not be respirable. And so, that leaves us with having to ask for the data. And then we may get data that satisfy -- we may get an inhalation tox study -- or we might get data that indicate

that we will not have respirable particles with this ingredient once we get more data. But I still think our boilerplate might need another look, and we kind of left that hanging.

DR. BERGFELD: Bart wishes to speak.

DR. HELDRETH: I mean, possibly the panel won't consider it sufficient, but there is some inhalation tox data in this report. Glycereth-3 has an inhalation study as does the read-across item, the ethoxylated glycerol; the PDF Page 11 of the report. Maybe it's not sufficient information, but there is some inhalation and tox information there.

DR. SNYDER: No, I don't see -- where?

DR. LIEBLER: To the top.

DR. SNYDER: Table 4 -- oh, there is on Table 4, yeah.

DR. LIEBLER: Yeah, and the top of the PDF 11, under ethoxylated glycerol, the last paragraph before short-term toxicity studies.

DR. SHANK: Yeah, there's something wrong with that study. The females gained -- let's see. In seven hours they gained -- went from 178 grams of body weight to 266. I don't think so.

DR. KLAASSEN: They bulked up.

DR. SHANK: Unless it's -- it's just not right.

DR. SNYDER: I didn't see that. That's buried underneath all that.

DR. LIEBLER: Yeah, that's like rat superheroes.

DR. BERGFELD: Are we able to move on? We have our insufficient list. And we have had a vote.

DR. SHANK: I think we can move on.

DR. BERGFELD: I want to make sure we have a vote. All those in favor of this insufficient data announcement? Thank you. Unanimous. All right, if there's anything to be added, certainly that can be added later, until Bart or Monice have added it.

Going on to the next ingredient, which is Dr. Marks, on BHT.

Safety Assessment of Glycerin Ethoxylates as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: November 15, 2019
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The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.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 CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Alice Akinsulie, former Scientific Writer/Analyst, and Preethi Raj, Senior Scientific Writer/Analyst.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 8 ethoxylated glycerin ingredients in cosmetic products. These ingredients primarily function as skin-conditioning agents, and viscosity-reducing agents. The Panel concluded [to be determined].

INTRODUCTION

This is a safety assessment of the following 8 glycerin ethoxylates as used in cosmetic formulations:

Glycereth-3	Glycereth-18
Glycereth-7	Glycereth-20
Glycereth-8	Glycereth-26
Glycereth-12	Glycereth-31

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all of these ingredients are reported to function in cosmetics as skin-conditioning agents, and most are reported to function as viscosity decreasing agents (Table 1).[1]

The rationale for this grouping of ingredients stems from the fact that these ingredients are structurally related as polyethylene glycol ethers of glycerin. The Panel has reviewed the safety of the components of these ingredients. In 2010, CIR issued a final report on the safety of polyethylene glycols (PEGs); the Panel concluded that the PEGs are safe in the present practices of use and concentration.[2] In 2015, the Panel issued a safety assessment on glycerin, with the conclusion that glycerin was safe as a cosmetic ingredient in the practices of use and concentration described in the safety assessment.[3] Additionally, CIR has issued safety assessment reports of structurally-related polyethoxylated compounds, such as alkyl polyethylene (PEG) ethers[4] and PEGs cocamine[5], which provide further weight of evidence to support the safety of these ingredients. In a previous safety assessment of laureths, a type of alkyl PEG ether, the Panel consensus was that in spite of dermal absorption, mild dermal irritation, and alkyl chain degradation (molecular weight)-dependent excretion, these ingredients exhibited low oral toxicity and sensitization, and were therefore considered safe as used, when formulated to be non-irritating. Similarly, although the PEGs cocamine ingredients showed potential for dermal and ocular irritation, and local gastrointestinal effects, no systemic, mutagenic, or developmental/reproductive toxicity outcomes were observed, and these ingredients were hence deemed safe, when formulated to be non-irritating.

These reports are available on the CIR website (https://www.cir-safety.org/ingredients).

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

Much of the data included in this safety assessment was obtained from robust summaries submitted to the European Chemicals Agency (ECHA) by companies as part of the REACH chemical registration process.[6] The REACH dossier was prepared for ingredients with the generic CAS No. 31694-55-0 (identified as glycerol, ethoxylated in the dossier) but the specific identities of the ingredients were not discerned; the identification of the test article in each study was provided as a trade name, and those trade names were not found in the *Dictionary*. Therefore, it is not known how the substances being tested in these studies compare to the cosmetic ingredients being reviewed in this assessment, because the test articles are of unknown or variable composition. However, because these data were included as part of the REACH dossier on "ethoxylated glycerols," they are included in this safety assessment as potential read-across. If it is known that a test substance is a cosmetic ingredient, then the INCI name is used; otherwise, a generic term that identifies that test substance (e.g., "ethoxylated glycerol") is used.

CHEMISTRY

Definition and Structure

These ingredients are polyethylene glycol ethers of glycerin, as depicted in Figure 1.

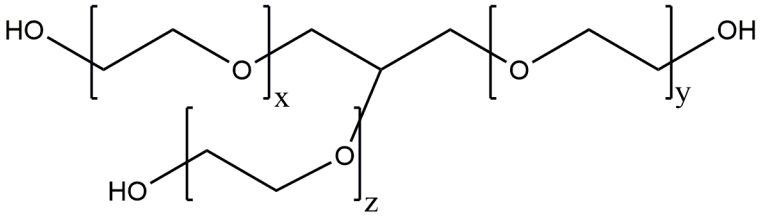

Figure 1. Glycerin ethoxylates, wherein the average ethoxylation value equals x + y + z (e.g., x + y + z = 3 in the case of Glycereth-3)

The definition of each ingredient, as given in the *Dictionary*, is provided in Table 1. For the data summarized herein as "ethoxylated glycerol," the REACH dossier describes the average ethoxylation value as between 1 and 6.5, inclusive of 1 and 6.5. Thus, the average ethoxylation value for "ethoxylated glycerol" may be described as $1.0 \leq x + y + z \leq 6.5$ for the test material evaluated in those summaries. Comparing this range of average ethoxylation values to those of the ingredients in this report, Glycereth-3 (i.e. x + y + z = 3) falls in that range.

Physical and Chemical Properties

Ethoxylated glycerin is a non-volatile (vapor pressure 0.0000389 hPa at 20ºC), slightly viscous liquid at room temperature, and it is fully miscible with water.[6] Physical and chemical properties of glycerin ethoxylates are presented in Table 2.

Method of Manufacture

These ingredients, in general, are the products resulting from the reaction of glycerin and ethylene oxide.[7] Alkaline catalysis is a common method of manufacturing ethoxylated glycerols, as seen in the manufacturing of alkyl PEG ethers.[4] The initiation of the alkaline catalyzed synthesis of ethoxylated glycerin consists of the addition of an alkoxide, such as ethylene oxide, to a dry solution of the appropriate alcohol (e.g., glycerin). The reaction continues to propagate (i.e. continues to add additional units of ethylene oxide to the alcohol) until the available ethylene oxide is consumed or the reaction is terminated by the addition of an acid. The finishing step consists of adding one or more oxidizing agents (e.g., hydrogen peroxide) or antioxidants/stabilizers (e.g., butylated hydroxytoluene (BHT) or α-tocopherol (vitamin E)).

Impurities

Glycerin ethoxylates belong to the chemical class of alkoxylated alcohols which are also polyether alcohols (specifically, polyethylene glycol ethers of glycerin). Polyether alcohols are often formed from the reaction of an alcohol with an alkylene oxide, such as ethylene or propylene oxide.[1] Since this reaction is driven by a 1:1 molecular ratio of reactants, it is possible for ethylene oxide to remain as a residual impurity. A previous CIR safety assessment of the chemically similar alkyl PEG ethers confirms that dioxane (1,4-dioxane) and ethylene oxide can be present as reaction by-products.[4]

Glycereth-26

In a certificate of analysis provided by a manufacturer, it was noted that Glycereth-26 contained < 0.0005% 1,4- dioxane, < 0.0001% ethylene dioxide, 0% free glycerin, and 0.05% water.[8] Additionally the aforementioned Glycereth-26 had an acid value of 0.2 mg potassium hydroxide/g, a hydroxyl value of 133.40 mg potassium hydroxide/g, a specific gravity of 1.134 at 25°C, and a pH of 6.6 in a 5% aqueous solution.

USE

Cosmetic

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

These ingredients are used in a variety of rinse-off and leave-on cosmetics products. According to 2019 VCRP survey data, Glycereth-26 is reported to be used in 379 formulations, and Glycereth-7 is reported to be used in 80 formulations (Table 3).[9] The three other in-use ingredients are reported to be used in 21 formulations or less. The results of the concentration of use survey conducted by the Council in 2018, and updated in 2019, indicate Glycereth-26 has the highest maximum concentration of use, at 39.5% in skin cleansing products.[10] The highest concentration of use reported for products resulting in leave-on dermal exposure is 6% Glycereth-26 in eye lotion formulations.

Uses were reported in the VCRP for Glycereth-20, but no concentration of use was reported for this ingredient in response to the industry survey. The ingredients not in use, according to the VCRP and industry survey, are Glycereth-3, 8, and 31.

A few of the glycerin ethoxylate ingredients could be used in products that may be incidentally ingested or come into contact with mucous membranes; for example, Glycereth-7 is reported to be in 67 lipstick formulations (concentration of use data were not reported for this category) and Glycereth-18 is reported to be used in bath soaps and detergents at a maximum concentration of 0.3%. Additionally, these ingredients have been reported to be used in products that may come into contact with the eyes; for example, Glycereth-26 is reported to be used at up to 6% in eye lotions. Moreover, these ingredients are reported to be used in spray products that could possibly be inhaled. Glycereth-26 was reported to be used at up to 1% in body and hand spray formulations. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[11,12] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[13,14]

The ingredients 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

"Ethoxylated glycerol" is used in a number of non-cosmetic applications such as modelling clay adhesives, sealants, polymer preparations and compounds, coatings, and paints.[6]

TOXICOKINETICS STUDIES

Toxicokinetics data (such as dermal penetration and absorption, distribution, metabolism, and excretion data) were not discovered in the published literature, and unpublished data were not submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute oral, dermal, and inhalation studies summarized below, are also described in Table 4.

No toxicity was observed when Glycereth-3, at concentrations of 1 - 50%, was given to rats orally at doses of 0.025 - 10 mL/kg body weight.[6] The oral LD_{50} of Glycereth-3 tested at concentrations of 1 - 50% was > 10 mL/kg in male and female rats.

In an an acute oral toxicity study of Glycereth-26, the LD_{50} was determined to be > 5000 mg/kg in male and female albino rats.[16]

In female Wistar rats, the oral LD_{50} of "ethoxylated glycerol" was > 2000 mg/kg.[6] In another oral toxicity study, the LD_{50} of "ethoxylated glycerol" in Sprague-Dawley rats was > 10,000 mg/kg.

The dermal LD_{50} of "ethoxylated glycerol" in male and female Wistar rats was > 5000 mg/kg.[6]

In an inhalation study, performed in accordance with Organisation for Economic Co-operation and Development test guidelines (OECD TG) 403, no mortality was observed when male and female rats were exposed (whole body) to an aerosol of 3.575 mg/L of Glycereth-3 for 8 h.[6] In an inhalation study of "ethoxylated glycerol", performed in accordance with OECD TG 403, in which rats were exposed to 0.178 mg/L of the test article for 7 h, no mortalities were observed.[6] Similarly, no mortalities were observed in rats following exposure (whole body) to 0.143 mg/L of the "ethoxylated glycerol" for 7 h as a vapor.

Short-Term Toxicity Studies

Oral

Propoxylated nitrilotriethanol (a read-across source for "ethoxylated glycerol," according to the ECHA dossier)

A pilot study was performed using 2 male and 2 female Wistar rats.[6] Animals were administered a propoxylated nitrilotriethanol (with molar equivalents of 3.2 propoxyl) at doses of 0, 65, 160, 400, and 1000 mg/kg for two weeks. No clinical findings or relevant effects on body weight development were observed.

In a short-term oral exposure study, a propoxylated nitrilotriethanol (MW ~ 340 g/mol) in water was administered once daily by gavage to Wistar rats (5 per sex) at doses of 0, 100, 300, and 1000 mg/kg for 31 days in accordance with OECD TG 407.[6] No mortality was observed in either sex. There was no effect observed upon hematological, clinical biochemistry, or macroscopic examination at any dose. The histopathological evaluation revealed slightly more pronounced hypertrophy of the follicular cell epithelium in the thyroid gland of females of the high dose. Biochemical analysis revealed significantly low plasma creatinine concentrations in males dosed with 1000 mg/kg and higher levels in all groups of treated females. Based on these results, the no-observable-adverse-effect-level (NOAEL) was considered to be 1000 mg/kg bw/day.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Propoxylated nitrilotriethanol (a read-across source for "ethoxylated glycerol," according to the ECHA dossier)

A reproductive/developmental toxicity screen test was performed in accordance with OECD TG 421.[6] Groups of 12 male and 12 female Wistar rats were administered a propoxylated nitrilotriethanol (average MW 280 g/mol) in water at doses of 0, 100, 300, and 1000 mg/kg bw, by gavage. Typically, in a study following this TG females are dosed throughout the study; however, that was not stated in the summary. The rats in each dose group were allowed to deliver. Body weights were determined daily during pregnancy, and dams were examined shortly after birth and on day 4 postpartum. Transient salivation was noted in both sexes of the parental rats dosed with 1000 mg/kg. Slight body weight loss occurred in females of the 1000 mg/kg dose group during lactation, and marginal body weight gains were noted during the premating period at all doses. Neither significant embryotoxic or teratogenic effects, nor abnormalities, were noted, and no effects on reproductive performance were observed. Four pups from the F_1 generation developed filiformed tip at 1000 mg/kg, compared to 3 pups in the control group. No adverse effect levels (NOELs) were determined to be 100 mg/kg in females and 300 mg/kg in males, based on increased incidence of salivation. Under the test conditions, the NOAEL was derived as 1000 mg/kg because reduction of body weight was observed with females at the highest dose group (1000 mg/kg bw/day). The mild weight loss was considered to be a non-adverse treatment-related effect, as it follows a statistically significant increased body weight gain compared to the control group in the premating phase.

GENOTOXICITY

In Vitro

"Ethoxylated glycerol" (a read-across source for Glycereth-3, according to the ECHA dossier)

The mutagenicity of "ethoxylated glycerol" was evaluated in an Ames test, performed in accordance with OECD TG 471.[6] *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100 and *Escherichia coli* WP2 were studied with and without metabolic activation. The test article, dissolved in water, was administered at concentrations of 0, 33, 100, 333, 1000, 2500, and 5000 µg/plate. Appropriate positive and negative controls were used. The test article did not produce any mutagenic effects.

Propoxylated glycerol (a read-across source for "ethoxylated glycerol," according to the ECHA dossier)

In a mammalian chromosomal aberration study performed in accordance with OECD TG 473, a propoxylated glycerol was considered to be non-clastogenic to human lymphocytes with or without metabolic activation.[6] (No other details were provided.)

Propoxylated nitrilotriethanol (a read-across for "ethoxylated glycerol," according to the ECHA dossier)

Chinese hamster lung fibroblasts (CHL) V79 cells were used in a mammalian cell gene mutation assay (hypoxanthine-guanine phosphoribosyl transferase (HGPRT) test) to evaluate the mutagenicity of a propoxylated nitrilotriethanol (average MW 265 g/mol) in ethanol.[6] Cells were treated with the test article at concentrations of 400, 800, 1200, 1600, 2000, 2400, and 2800 µg/ml without metabolic activation and 42, 84, 168, 336, 672, 1344, and 2688 µg/ml with metabolic activation. Appropriate positive and negative controls were used. The test article did not induce mutagenic effects in the presence or absence of metabolic activation.

CARCINOGENICITY STUDIES

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

DERMAL IRRITATION AND SENSITIZATION

Irritation

In Vitro

"Ethoxylated glycerol" (a read-across source for Glycereth-3, according to the ECHA dossier)

In an in vitro study performed in accordance with OECD TG 439, dermal irritation potential was assessed by a single topical application of 30 µL of "ethoxylated glycerol" applied undiluted to a reconstructed three-dimensional human epidermis model (EpiDerm™).[6] Sterile phosphate buffered saline (PBS; 30 µl) was used as negative control. The tissues were washed with sterile PBS 1 h after the application. The results predicted that the test substance is not expected to be irritating.

Animal

Glycereth-3

Skin irritation potential was evaluated using 2 Vienna white rabbits using a test method comparable to OECD TG 404.[6] Glycereth-3 (1 mL) was applied neat to shaved skin area of 2.5 cm x 2.5 cm by an occlusive dressing for 20 h, and the test

sites were observed at 24 h, 48 h, and 8 days. No edema and erythema findings were observed. The test article was considered to be non-irritant to rabbit skin.

Glycereth-26

Three male and three female rabbits had single applications of 0.5 mL of Glycereth-26 applied under an occlusive patch on both abraded and non-abraded sites.[16] The tested areas were observed at 24 and 72 h after application. The irritation score was 0.0, and the test article was deemed to have no irritation potential.

Sensitization

Animal

Propoxylated glycerol (a read-across source for "ethoxylated glycerol," according to the ECHA dossier)

The sensitization potential of a propoxylated glycerol (MW 300 g/mol) was evaluated with a Buehler test, according to OECD TG 406.[6] Dunkin Hartley guinea pigs (10 males and 10 females) were patched with 0.5 mL of the undiluted test article for the topical induction, using an occlusive dressing, for 6 h on days 1, 7, and 14. Challenge consisted of a topical application of 0.5 mL undiluted test article held in place by an occlusive dressing for a 6-h exposure period on day 28. Five males and 5 females served as the control group. The test article was not a sensitizer.

Human

Glycereth-7

An undiluted leave-on product containing 0.68% Glycereth-7 was tested in a human repeat insult patch test (HRIPT) in 199 subjects.[17] The test material was applied occlusively for 24 to 48 h via nine, 0.2 g induction applications, made over a 3-week induction period. After a 2-week rest period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored at 24, 48, 72, and 96 h after application. No participants withdrew due to adverse reactions; 3 subjects exhibited low-level reactions (a 0-1 score, on a 0-4 scoring scale) during induction. The test material did not induce dermal sensitization.

Glycereth-12

An HRIPT of a product containing 0.35% Glycereth-12 was performed in 100 subjects.[18] The test material (0.2 g) was applied with an occlusive, hypoallergenic patch to the infrascapular regions of the back for nine applications. After a 14-day rest period, the same concentration and amount of the test substance was used in the challenge phase; patches were applied to a previously untested site, and reactions were scored 24 and 48 h after application. There were no signs of irritation or sensitization.

Glycereth-26

A product containing 3% Glycereth-26 was tested in an HRIPT in 200 subjects.[17] The test material was applied occlusively for 48 to 72 h via nine, 20 µL induction applications, made over a 3-week induction period. After a 2-week rest period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored at 48 and 96 h after application. No participants withdrew due to adverse reactions; 8 subjects exhibited low-level reactions (0-1 score, on a 0-7 scale) during induction, and 1 subject exhibited a high-level reaction (score of 2 and above on a 0-7 scale) during induction. The researchers concluded that the test material did not induce significant dermal irritation or allergic contact sensitization.

A product containing 5% Glycereth-26 was tested in an HRIPT on 55 subjects.[18] The test material was applied to a 1 in^2 absorbent pad portion of an adhesive dressing and applied to the skin under semi-occlusion for 24 h. Nine induction applications were made. After a 2-week rest period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24 and 72 h after application. The test material did not demonstrate a potential for eliciting dermal irritation or allergic contact sensitization.

OCULAR IRRITATION STUDIES

In Vitro

Glycereth-12

In an EpiOcular™ assay, a 20% aqueous dilution of a product containing 0.35% Glycereth-12 was tested at 100 µL; the effective test concentration was 0.07% Glycereth-12.[18] Appropriate negative and positive controls were used. The estimated Draize ocular irritation score of the test material at 100% was predicted to be 0, and it was classified to be non-irritant.

Glycereth-26

The ocular irritation potential of undiluted Glycereth-26 (100 µL) was evaluated in vitro in an EpiOcular™ human cell assay.[19] The cell cultures were tested in duplicate, with exposure times of 0.33, 1, 2, and 4 h. Appropraite negative and

positive controls were used. The ET_{50} (time to reduce tissue viability as measured using MTT) was > 4 h for Glycereth-26; the researchers stated Glycereth-26 was not observed to reduce MTT directly in the absence of viable tissue.

"Ethoxylated glycerol" (a read-across source for Glycereth-3, according to the ECHA dossier)

The potential irritation of "ethoxylated glycerol" was studied in a Bovine Corneal Opacity and Permeability (BCOP) test conducted according to OECD TG 437.[6] "Ethoxylated glycerol" (750 µL) was applied directly to the epithelial surface of the cornea using a syringe (open chamber method) for 10 minutes. Highly deionized water was used as the negative control, and a 1% (w/v) solution of sodium hydroxide in highly de-ionized water served as the positive control (treatment group consisted of 3 corneas). The opacity and permeability assessments of the cornea were derived by an In Vitro Irritancy Score (IVIS), which is used to classify the irritancy level of the test article. The calculated mean IVIS was 3.0 ± 1.2, 2.6 ± 3.3, and 184.0 ± 20.9 in the test group, the negative control group, and the positive control group, respectively. It was concluded the test substance does not cause serious eye damage in the BCOP test.

The potential of the same "ethoxylated glycerol" to cause eye irritation was further evaluated in a second study, in accordance with OECD TG 405 and using an EpiOcular™ three-dimensional human cornea model.[6] Fifty µL of the undiluted test article was applied (2 tissue sample per treatment). The treated tissue was incubated for 30 minutes, washed out, and post-incubated under normal medium and culture conditions for 2 h. The negative control tissues received applications of 50 µL of highly de-ionized water. The test article was considered to be non-irritating.

Animal

Glycereth-3

Ocular irritation was evaluated in 2 Vienna white rabbits using a test method that is similar to OECD TG 405.[6] Undiluted Glycereth-3 (50 µL) was instilled into the conjunctival sac of the right eye of each animal without washing, and the eyes were observed for 8 days. The left eye of the animals remained untreated and served as a control. Slight conjunctivae redness was observed in both animals after 10 min, 1 h, and 3 h. These effects were fully reversible within 24 h. The test article was found to be non-irritating.

Glycereth-26

Six rabbits of mixed sex were administered a single 1.8 - 2.4 g, 0.1 mL, dose of Glycereth-26, without washing, for 24 h. Ocular irritation to eye mucosa, cornea, iris, and bulbar/palpebral conjunctivae was observed for 7 days.[16] The irritation score was 0.0, and the test article was deemed non-irritating under these test conditions.

"Ethoxylated glycerol" (a read-across source for Glycereth-3)

Two Vienna white rabbits were used to test for ocular irritation following a protocol similar to OECD TG 405.[6] Fifty µL of undiluted "ethoxylated glycerol" were instilled into the conjunctival sac of one eye of each animal. The saline-treated contralateral eye served as a control. The eyes were not washed out and were observed for a total of 8 days. Hyperemia was noted in the blood vessels of both animals. In one animal, this effect was not fully reversible within 8 days; however, a similar observation was noted in the control eye of this animal. The test article was considered non-irritating.

SUMMARY

This is a safety assessment of 8 glycerin ethoxylates as used in cosmetics. These ingredients are all polyethylene glycol ethers of glycerin. All of the ingredients in this report are reported to function as skin-conditioning agents, and most are reported to function as viscosity decreasing agents. Data on "ethoxylated glycerols," propoxylated nitrilotriethanol and propoxylated glycerol are included in this safety assessment as potential read-across, according to the ECHA dossier. Both reviewed and read-across ingredients are polyethylene glycol ethers of glycerin.

These ingredients are mostly in leave-on formulations. Glycereth-26 has the highest reported frequency of use (379 formulations), and Glycereth-7 has the second greatest reported number of uses (80). Glycereth-26 has the highest concentration of use, at 39.5% in skin cleansing products. The highest concentrations of use reported for products resulting in leave-on dermal exposure is 6% Glycereth-26 in eye lotions.

No toxicity was observed when Glycereth-3 was administered orally at concentrations ranging from 1 - 50% to male and female rats. The oral LD_{50} was determined to be > 10 mL/kg. In an acute oral toxicity study of Glycereth-26, the LD_{50} was determined to be > 5000 mg/kg dose.

No evidence of toxicity was observed in an acute oral toxicity study using female Wistar rats where the oral LD_{50} of "ethoxylated glycerol" was greater than 2000 mg/kg. Similary, no evidence of toxicity was reported when "ethoxylated glycerol" was administered orally to Sprague-Dawley rats and the LD_{50} was greater than 10,000 mg/kg.

The acute dermal LD_{50} of "ethoxylated glycerol" was calculated to be > 5000 mg/kg in rats.

Two studies were performed in accordance with OECD guidelines, in which rats were used to determine acute inhalation toxicity. Glycereth-3 at a concentration of 3.575 mg/L, was tested in rats as an aerosol/mist for 8 h. No mortality occurred. The acute inhalation toxicity of "ethoxylated glycerol" was evaluated in a study involving rats. Animals were exposed whole-body to 0.178 mg/L, for 7 h, and 0.143 mg/L in experiment 2, for 7 h each. No mortality occurred.

In a pilot study, 2 male and 2 female Wistar rats received a propoxylated nitrilotriethanol at doses of 0, 65, 160, 400, and 1000 mg/kg for 2 weeks; no clinical findings or relevant effects on body weight development were observed. In a repeated dose toxicity study, rats (5 per sex) were administered a propoxylated nitrilotriethanol (MW ~ 340 g/mol) in water at doses of 0, 100, 300, and 1000 mg/kg for 31 d. No mortality and no clinical effects were observed in either sex of all dose groups. The histopathological evaluation revealed slightly more pronounced hypertrophy of the follicular cell epithelium in the thyroid gland of females of the high dose. Based on these results, the NOAEL was considered to be 1000 mg/kg bw/day.

A reproductive/developmental toxicity screening test was performed with 12 male and 12 female Wistar rats. Animals were administered a propoxylated nitrilotriethanol (average MW 280 g/mol) in water at doses up to 1000 mg/kg. The rats in each dose group were allowed to deliver. Transient salivation was noted in both sexes of the parental rats dosed with 1000 mg/kg. Slight body weight loss occurred in females of the 1000 mg/kg dose group during lactation and marginal body weight gains were noted during the premating period at all doses. There were no effects on total body weights or viability of offspring, and no embryotoxic or teratogenic effects were reported. The NOAEL was > 1000 mg/kg bw/day.

"Ethoxylated glycerol" was not mutagenic in Ames tests at concentrations up to 5000 µg/plate, with or without metabolic activation, in S. *typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100, and *E. coli* WP2. In a mammalian chromosomal aberration study, a propoxylated glycerol was not clastogenic to human lymphocytes (concentrations not reported), with or without metabolic activation. A propoxylated nitrilotriethanol was evaluated for genotoxicity in a mammalian cell gene mutation assay with CHL fibroblasts at doses of 400, 800, 1200, 1600, 2000, 2400, and 2800 µg/ml (-S9), and 42, 84, 168, 336, 672, 1344, and 2688 µg/ml (+S9) in ethanol. The test article did not induce mutagenic effects in the presence or absence of a metabolic activation system.

Based on observations made following a single topical application of 30 µL of "ethoxylated glycerol" to a reconstructed three-dimensional human epidermis model, the test substance is not expected to be irritating. In a dermal irritation study, Glycereth-3 was applied for 20 h to a shaved skin area of 2.5 cm x 2.5 cm on 2 Vienna white rabbits using an occlusive dressing. The test article was considered to be non-irritant to the skin. In another study, 3 male and 3 female rabbits, had 0.5 mL of Glycereth-26 applied once under an occluded patch on both abraded and non-abraded sites, with no signs of irritation observed at 24 and 72 h after application. The test article was deemed to have no irritation potential.

The sensitization potential of a propoxylated glycerol (MW 300 g/mol) was evaluated in a Buehler test using 10 male and 10 female Dunkin Hartley guinea pigs. Six-h occlusive patches of undiluted test article were used for both induction (days 1, 7, and 14) and challenge. The test article was not a sensitizer.

A leave-on product containing 0.68% Glycereth-7 was tested for skin sensitization potential using in an HRIPT completed in 199 subjects. No participants withdrew due to adverse reactions; 3 subjects exhibited low-level reactions during induction. The test material did not induce dermal sensitization. A product containing 0.35% Glycereth-12 was evaluated for skin sensitization potential in an HRIPT using 100 subjects. Neither irritation nor sensitization were observed. A product containing 3% Glycereth-26 was tested in an HRIPT in 200 subjects. No participants withdrew due to adverse reactions; 8 subjects exhibited low-level reactions during induction, and 1 subject exhibited a high-level reaction during induction. The researchers concluded tht the test material did not induce significant dermal irritation and allergic contact sensitization. The skin sensitization potential of a product containing 5% Glycereth-26 was evaluated in a maximization test involving 55 subjects. No adverse reactions were observed, and there were no instances of dermal irritation or allergic contact sensitization.

In an EpiOcular™ assay, a 20% aqueous dilution of a product containing 0.35% Glycereth-12 was predicted to not be an ocular irritant, and in the same type of assay, undiluted Glycereth-26 was not observed to reduce MTT directly in the absence of viable tissue. The potential of "ethoxylated glycerol" to cause damage to the eyes was evaluated in vitro in a BCOP test and in an EpiOcular™ assay. The test article did not show ocular irritation potential under either the test condition.

The ocular irritation potential of Glycereth-3 was studied using rabbits. The test article (50 µL) was found to be non-irritating. In rabbits administered single instillations of 1.8 - 2.4g, 0.1 mL, Glycereth-26 for 24 h without washing, the ocular irritation score was 0.0, and the test article was deemed non-irritating under these test conditions. In another study in which 50 µL of undiluted "ethoxylated glycerol" was applied to the conjunctival sac of one eye of 2 white Vienna rabbits, hyperemia was noted in blood vessels of both animals. In one animal, this effect was not fully reversible within 8 days. The test article was determined to be non-irritating

DRAFT DISCUSSION

[The following discussion items are pending Panel approval and are, therefore, subject to change.]

The CIR Expert Panel noted gaps in the available data for this safety assessment of glycerin ethoxylates, with the most interest in data for Glycereth-26, the ingredient with the highest frequency of use (379) and leave-on concentration in eye

lotions (6%). Consequently, the Panel requested method of manufacture, impurities, and acute inhalation toxicity data to reflect incidental exposure to these ingredients in spray or powder formulations. The Panel proposed that their concerns about inhalation toxicity may be abated upon receiving adequate manufacturing and impurities data. Additional ADME data were not requested because the Panel deemed the presented oral toxicity, developmental toxicity, reproductive toxicity, and genotoxicity studies sufficient.

Similarly, the Expert Panel did not suspect any mechanistic basis for concerns with sensitization in these ingredients. The Panel reasoned that this family of polyether alcohols does not have the propensity to react with proteins, or to produce metabolites that would cause concern. Thus, the Expert Panel noted that although some aldehydes theoretically resulting from metabolism of alcohols can potentially be protein-reactive, not all aldehydes are effective protein modifiers or sensitizers.

The Panel noted that previous safety assessments containing structurally-related polyethoxylated compounds provide further weight of evidence support for the safety of these ingredients. Alkyl PEG ethers and PEGs cocamine are products of reactions with alcohols and ethylene oxide, and water and ethylene oxide (combined with a coconut oil fatty acid), respectively. In a previous safety assessment, although the ingredients showed potential for dermal and ocular irritation, sensitization, and local gastrointestinal effects, no systemic, mutagenic, or developmental/reproductive toxicity outcomes were observed, and these ingredients were hence deemed safe, when formulated to be non-irritating.

The Panel considered propoxylated nitrilotriethanol, propoxylated glycerol, and ethoxylated glycerol as suitable read-across sources for these ingredients due to their previous review of polyethoxylated ingredients. Propoxylated nitrilotriethanol comprises a relatively unreactive nitrogen-containing internal core which serves as a scaffold for polyethoxylated chains; comparatively, ethoxylated glycerol is a mixture of ethoxylated glycerols, comprising a similar structural core motif, sans nitrogen. Furthermore, the Panel deemed both read-across materials as representative of lower molecular weight glycerin ethoxylates.

The Panel was concerned with the possible presence of 1,4-dioxane and ethylene oxide as impurities, and therefore sought more data for clarity. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit 1,4-dioxane and ethylene oxide impurities from the ingredients before blending them into cosmetic formulations.

The Panel discussed the issue of incidental inhalation exposure from formulations that may be aerosolized (e.g., in hair sprays; concentration not reported). The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

To be determined.

TABLES

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

Ingredient CAS No.	Definition	Function(s)
Glycereth-3 31694-55-0 (generic)	Glycereth-3 is the polyethylene glycol ether of glycerin with an average ethoxylation value of 3. [The chemical structure of this ingredient conforms to that of Figure 1, wherein x + y + z = 3.]	Skin-Conditioning Agents - Emollient; Surfactants - Cleansing Agents; Surfactants - Emulsifying Agents
Glycereth-7 31694-55-0 (generic)	Glycereth-7 is the polyethylene glycol ether of glycerin with an average ethoxylation value of 7. [The chemical structure of this ingredient conforms to that of Figure 1, wherein x + y + z = 7.]	Skin-Conditioning Agents - Humectant; Viscosity Decreasing Agents
Glycereth-8 31694-55-0 (generic)	Glycereth-8 is the polyethylene glycol ether of glycerin with an average ethoxylation value of 8. [The chemical structure of this ingredient conforms to that of Figure 1, wherein x + y + z = 8.]	Skin-Conditioning Agents - Emollient; Skin-Conditioning Agents - Humectant; Viscosity Decreasing Agents
Glycereth-12 31694-55-0 (generic)	Glycereth-12 is the polyethylene glycol ether of glycerin with an average ethoxylation value of 12. [The chemical structure of this ingredient conforms to that of Figure 1, wherein x + y + z = 12.]	Skin-Conditioning Agents - Humectant; Viscosity Decreasing Agents
Glycereth-18 31694-55-0 (generic)	Glycereth-18 is a polyethylene glycol ether of glycerin containing an average of 18 moles of ethylene oxide. [The chemical structure of this ingredient conforms to that of Figure 1, wherein x + y + z = 18.]	Skin-Conditioning Agents - Humectant
Glycereth-20 31694-55-0 (generic)	Glycereth-20 is the polyethylene glycol ether of glycerin with an average ethoxylation value of 20. [The chemical structure of this ingredient conforms to that of Figure 1, wherein x + y + z = 20.]	Skin-Conditioning Agents - Humectant; Viscosity Decreasing Agents
Glycereth-26 31694-55-0 (generic)	Glycereth-26 is the polyethylene glycol ether of glycerin with an average ethoxylation value of 26. [The chemical structure of this ingredient conforms to that of Figure 1, wherein x + y + z = 26.]	Skin-Conditioning Agents - Humectant; Viscosity Decreasing Agents
Glycereth-31 31694-55-0 (generic)	Glycereth-31 is the polyethylene glycol ether of glycerin with an average ethoxylation value of 31. [The chemical structure of this ingredient conforms to that of Figure 1, wherein x + y + z = 31.]	Skin-Conditioning Agents - Humectant; Viscosity Decreasing Agents

Table 2. Physical and Chemical Properties

Property	Value	Reference
	"ethoxylated glycerol"	
Physical Form	clear liquid	[6]
Density/Specific Gravity (@ 20ºC)	1.163	[6]
Viscosity (@ 20 ºC)	399	[6]
Vapor pressure (@ 20ºC)	0.0000389	[6]
Melting Point (ºC)	-49.1	[6]
Boiling Point (ºC)	260	[6]
Water Solubility (g/L @ 20ºC)	1000	[6]
	Glycereth-3	
Molecular Weight (g/mol)	224.25	[20]
log P	-1.79 (estimated)	[20]
	Glycereth-7	
Physical Form	Yellow to amber color, mild odor	[21]
Molecular Weight (g/mol)	400.47	[20]
log P	-2.42 (estimated)	[20]
	Glycereth-8	
Molecular Weight (g/mol)	444.52	[20]
log P	-2.57 (estimated)	[20]
	Glycereth-12	
Molecular Weight (g/mol)	620.73	[20]
log P	-3.19 (estimated)	[20]
	Glycereth-18	
Molecular Weight (g/mol)	885.05	[20]
log K_{ow}	-7.19 (estimated)	[22]
	Glycereth-20	
Molecular Weight (g/mol)	972.57	[20]
log K_{ow}	-7.73 (estimated)	[22]
	Glycereth-26	
Physical Form	Yellow to amber color, mild odor	[23]
Molecular Weight (g/mol)	1237.47	[20]
log K_{ow}	-9.38 (estimated)	[22]
Presence of Impurities		
1,4-dioxane	< 0.0005%	[8]

Table 2. Physical and Chemical Properties

Property	Value	Reference
Ethylene dioxide	< 0.0001%	8
Free glycerin	0%	8
Water	0.05%	8
Acid value (mg KOH/g)	0.2	8
Hydroxyl value (mg KOH/g)	133.40	8
Ash content	0.04%	8
Specific gravity (at 25°C)	1.134	8
Dissociates in water (at pH, in 5% aq solution)	6.6	8
	Glycereth-31	
Molecular Weight (g/mol)	1457.74	20
log K_{ow}	-10.75 (estimated)	22

Table 3. Frequency (2019)[2] and concentration (2019)[3] of use data for glycerin ethoxylates

	# of Uses[2]	Max Conc of Use (%)[3]	# of Uses[2]	Max Conc of Use (%)[3]	# of Uses[2]	Max Conc of Use (%)[3]
	Glycereth-7		**Glycereth-12**		**Glycereth-18**	
Totals*	**80**	**1 - 2**	**6**	**0.09 - 0.35**	**21**	**0.019 - 0.32**
Duration of Use						
Leave-On	*76*	*1*	*6*	*0.21 - 0.35*	8	*0.019 - 0.3*
Rinse-Off	*4*	*2*	*NR*	*0.09*	13	*0.3 - 0.32*
Diluted for (Bath) Use	*0*	*NR*	*NR*	*NR*	NR	*NR*
Exposure Type						
Eye Area	NR	NR	3	0.09-0.35	NR	0.019-0.036
Incidental Ingestion	67	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	6[a]; 2[b]	NR	2[b]	NR	5[a]; 1[b]	NR
Incidental Inhalation-Powder	2[b]	NR	2[b]	NR	1[b]	0.3[c]
Dermal Contact	13	1- 2	4	0.09- 0.21	21	0.036-0.32
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	68	NR	NR	NR	9	0.3
Baby Products	NR	NR	NR	NR	NR	NR

	Glycereth-20		**Glycereth-26**		
Totals*	**2**	**NR**	**379**	**0.3 - 39.5**	
Duration of Use					
Leave-On	*2*	*NR*	286	*0.3 - 6*	
Rinse Off	*NR*	*NR*	93	*0.9 - 39.5*	
Diluted for (Bath) Use	*NR*	*NR*	NR	*NR*	
Exposure Type					
Eye Area	NR	NR	18	2-6	
Incidental Ingestion	NR	NR	NR	NR	
Incidental Inhalation-Spray	1[a]; 1[b]	NR	5; 116[a]; 104[b]	1; 0.3-2[a]	
Incidental Inhalation-Powder	1[b]	NR	104[b]	1[c]	
Dermal Contact	2	NR	328	1-39.5	
Deodorant (underarm)	NR	NR	NR	NR	
Hair - Non-Coloring	NR	NR	49	0.3-1	
Hair-Coloring	NR	NR	1	NR	
Nail	NR	NR	NR	NR	
Mucous Membrane	NR	NR	35	NR	
Baby Products	NR	NR	NR	NR	

NR = Not reported.

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

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

[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

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

Table 4. Acute toxicity studies

Test Article/ Concentration/ Vehicle	Animals	No./Group	Dose/Protocol	LD_{50}/Results	Reference
			Oral		
Glycereth-3; 1 – 50% (v/v) solution at doses of 0.025 - 10 mL/kg bw in Water	Fischer 344 rats	13 male and 11 females	Similar to OECD TG 401. Three females were administered 0.025 mL/kg of a 1% (v/v) solution another 3 female rats were administered 0.2 mL/kg of a 10% solution. Three male rats were administered 1.6 mL/kg of a 10% solution. Another 5 male rats were administered 3.2 mL/kg of a 50% solution. Five females were administered 6.4 mL/kg of a 50% solution and 5 males were administered 10 mL/kg of a 50% solution. Ten untreated animals were used as a negative control.	No mortality occurred and no abnormalities observed. The LD_{50} in male and female rats is > 10 mL/kg.	6
Glycereth-26; 5000 mg/kg bw	Albino rats	5/sex	Animals were dosed orally (route of administration not specified) with 5000 mg/kg bw and were observed for 14 days for toxicity endpoints.	No mortality occurred during the observation period and the LD_{50} was determined to be > 5000 mg/kg	16
"Ethoxylated glycerol;" 2000 mg/kg without vehicle	Wistar rats	2 groups of 3 females	According to OECD TG 423. Both groups of rats were administered test article at a maximum dosage-volume of 1.73 mL/kg.	No mortality occurred. No clinical signs were observed during the observation period. The mean body weight of the test groups increased throughout the study period within the normal range. LD_{50} is > 2000 mg/kg	6
"Ethoxylated glycerol," undiluted	Sprague-Dawley rats	5/sex	Similar to OECD TG 401. Five male rats were administered with 11,550 mg/kg bw and 5 female rats were exposed at a dose 10,000 mg/kg bw. Animals were observed for 14 days after administration.	No mortality occurred. Diarrhea was noted for a few hours after application; aggressiveness, convulsion and dirty fur were observed at days 3 and 4; animals fully recovered within 5 days. LD_{50} in male and female rat is > 10,000 mg/kg	6
			Dermal		
"Ethoxylated glycerol;" 5000 mg/kg without a vehicle	Wistar rats	5/sex	According to OECD TG 402. Rats were dermally administered test article; applied to a 40 cm^2 skin area and covered by a semi-occlusive dressing for 24 hours.	No mortality occurred. No systemic clinical signs were observed during clinical examination. No local effects were observed. LD_{50} is > 5000 mg/kg	6
			Inhalation		
Glycereth-3; 3.575 mg/L	"White, normal rats"	3/sex	Similar to OECD TG 403. Rats were exposed to test article in an aerosol/mist form for 8 hours and observed for 14 days.	No mortality or clinical signs of toxicity noted	6
'Ethoxylated glycerol;" 0.178 mg/L and 0.143 mg/L without vehicle	Rats	6 animals (males and females)/ experiment	Similar to OECD TG 403. Rats were exposed (whole body) to 0.178 mg/L in experiment 1 and 0.143 mg/L in experiment 2 as a vapor for 7 hours and observed for 14 days.	No mortality or clinical signs of toxicity noted.	6

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2019 VCRP Data

CATEGORY	MAINTERM	COUNT
07E - Lipstick	GLYCERETH-7	67
10E - Other Personal Cleanliness Products	GLYCERETH-7	1
12A - Cleansing	GLYCERETH-7	3
12D - Body and Hand (exc shave)	GLYCERETH-7	2
12F - Moisturizing	GLYCERETH-7	2
12I - Skin Fresheners	GLYCERETH-7	1
12J - Other Skin Care Preps	GLYCERETH-7	1
13B - Indoor Tanning Preparations	GLYCERETH-7	3
03F - Mascara	GLYCERETH-12	2
03G - Other Eye Makeup Preparations	GLYCERETH-12	1
07C - Foundations	GLYCERETH-12	1
12C - Face and Neck (exc shave)	GLYCERETH-12	2
07I - Other Makeup Preparations	GLYCERETH-18	1
10A - Bath Soaps and Detergents	GLYCERETH-18	9
12A - Cleansing	GLYCERETH-18	4
12C - Face and Neck (exc shave)	GLYCERETH-18	1
12F - Moisturizing	GLYCERETH-18	4
12G - Night	GLYCERETH-18	1
12J - Other Skin Care Preps	GLYCERETH-18	1
12C - Face and Neck (exc shave)	GLYCERETH-20	1
12F - Moisturizing	GLYCERETH-20	1
03A - Eyebrow Pencil	GLYCERETH-26	1
03D - Eye Lotion	GLYCERETH-26	12
03F - Mascara	GLYCERETH-26	1
03G - Other Eye Makeup Preparations	GLYCERETH-26	4
04A - Cologne and Toilet waters	GLYCERETH-26	3
04E - Other Fragrance Preparation	GLYCERETH-26	1
05A - Hair Conditioner	GLYCERETH-26	9
05B - Hair Spray (aerosol fixatives)	GLYCERETH-26	1
05E - Rinses (non-coloring)	GLYCERETH-26	1
05F - Shampoos (non-coloring)	GLYCERETH-26	26
05G - Tonics, Dressings, and Other Hair Grooming Aids	GLYCERETH-26	4
05I - Other Hair Preparations	GLYCERETH-26	8
06D - Hair Shampoos (coloring)	GLYCERETH-26	1
07C - Foundations	GLYCERETH-26	2
07F - Makeup Bases	GLYCERETH-26	1
07H - Makeup Fixatives	GLYCERETH-26	1
07I - Other Makeup Preparations	GLYCERETH-26	2
10A - Bath Soaps and Detergents	GLYCERETH-26	30

10E - Other Personal Cleanliness Products	GLYCERETH-26	5
11D - Preshave Lotions (all types)	GLYCERETH-26	1
11E - Shaving Cream	GLYCERETH-26	1
11G - Other Shaving Preparation Products	GLYCERETH-26	2
12A - Cleansing	GLYCERETH-26	12
12B - Depilatories	GLYCERETH-26	1
12C - Face and Neck (exc shave)	GLYCERETH-26	92
12D - Body and Hand (exc shave)	GLYCERETH-26	12
12F - Moisturizing	GLYCERETH-26	87
12G - Night	GLYCERETH-26	8
12H - Paste Masks (mud packs)	GLYCERETH-26	4
12I - Skin Fresheners	GLYCERETH-26	8
12J - Other Skin Care Preps	GLYCERETH-26	29
13B - Indoor Tanning Preparations	GLYCERETH-26	7
13C - Other Suntan Preparations	GLYCERETH-26	2

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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: May 9, 2019

SUBJECT: Updated Concentration of Use Information: Glycerin Ethoxylates

Concentration of Use by FDA Product Category – Glycerin Ethoxylates*

Glycereth-26
Glycereth-3
Glycereth-7
Glycereth-8
Glycereth-12
Glycereth-18
Glycereth-20
Glycereth-31

Ingredient	Product Category	Maximum Concentration of Use
Glycereth-26	Eye shadows	2%
Glycereth-26	Eye lotions	4-6%
Glycereth-26	Shampoos (noncoloring)	0.9-1%
Glycereth-26	Tonics, dressings and other hair grooming aids	0.3%
Glycereth-26	Foundations	3%
Glycereth-26	Shaving cream	9%
Glycereth-26	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	3-39.5%
Glycereth-26	Face and neck products Not spray	 3-3.5%
Glycereth-26	Body and hand products Not spray Spray	 1% 1%
Glycereth-26	Moisturizing products Not spray	 1%
Glycereth-26	Skin fresheners	2%
Glycereth-26	Other skin care preparations	3-5%
Glycereth-26	Other suntan products Not spray	 4%
Glycereth-7	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	2%
Glycereth-7	Moisturizing products Not spray	 1%
Glycereth-12	Eye makeup removers	0.09%
Glycereth-12	Mascaras	0.35%
Glycereth-12	Other eye makeup preparations	0.21%
Glycereth-18	Eyeliners	0.036%
Glycereth-18	Mascaras	0.019%
Glycereth-18	Bath soaps and detergents	0.3%
Glycereth-18	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.32%
Glycereth-18	Body and hand products Not spray	 0.3%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2018
Table prepared: June 26, 2018

Updated May 9, 2019: Body and hand product containing 4% Glycereth-26 deleted (discontinued product)

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Memorandum

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

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

DATE: June 11, 2019

SUBJECT: Glycereth-26

Anonymous. 2019. Certificate of analysis: Glycereth-26.

Anonymous. 2017. Safety testing summary: Glycereth-26.

Anonymous. 2007. Summary - Topical application ocular irritation screening assay using the EpiOcular™ human cell construct: Glycereth-26

Certificate of Analysis

Glycereth-26

5/24/19

Tests	Limits	Result
ACID VALUE	0.000 to 0.500	0.2 mg KOH/g
APHA COLOR	0 to 30	18 Pt-Co
APP@25C: CLEAR TO HAZY LIQUID	CLEAR LIQUID	CLEAR LIQUID
APP@40C, CLEAR LIQUID	PASS	PASS
ASH CONTENT	0.00 to 0.20	0.04 %
1,4 DIOXANE	< 5.0 PPM	< 5.0 PPM
ETHYLENE OXIDE	< 1.0 PPM	< 1.0 PPM
FREE GLYCERINE	0.00 to 0.70	0.00 %
WATER	0.00 to 0.50	0.05 %
HYDROXYL VALUE	128.00 to 138.00	133.40 mg KOH/g
ODOR, ODORLESS	ODORLESS	ODORLESS
pH, 5% AQUEOUS	5.5 to 7.0	6.6
SPECIFIC GRAVITY @ 25 C	>= 1.130	1.134

Glycereth-26

Safety Testing Summary:

Testing conducted in 1978

Acute oral toxicity:
10 albino rats, 5 male & 5 female, 180-300 gram, single dose orally of Glycereth-26 Subjects dosed according to body weight. Observation period was a total of fourteen days. LD-50: 5 g/kg dose.
Study score was 0 (zero), no animals died. Glycereth-26 was deemed a non-oral toxic material to rats under these test conditions.

Ocular irritation:
Six rabbits, mixed sex, 1.8 -2.4 kg, 0.1 ml single dose of Glycereth-26 administered, no wash for 24 hours and up to 7 day observations. Ocular irritation observations to eye mucosa, cornea, iris and bulbar/palpebral conjunctivae.
Study score was 0.0 and deemed not an ocular irritant to rabbits under these test conditions.

Primary dermal irritation:
Six rabbits, 3 male & 3 female, each abraded and non-abraded, had 0.5 ml single application of Glycereth-26 administered under occluded patch with 24 & 72 hour observations.
Study score was 0.0 and deemed no irritation potential.

Statement updated on May 9, 2017

Summary – Topical Application Ocular Irritation Screening Assay Using the EpiOcular™ Human Cell Construct

Test Article: Glycereth-26

Study completed: June 18, 2007

The test article was administered to the test system without dilution

The EpiOcular cultures were tested in duplicate with Glycereth-26 at four exposure times of 0.33, 1, 2 and 4 hours.

100 µl of Glycereth-26 was applied to the test system

Duplicate cultures of the negative control (100 µl of sterile deionized water) were exposed for 0.25, 4, 8 and 24 hours

Duplicate cultures of the positive control (100 µl 0.3% Triton-X-100) were exposed for 15 and 45 minutes

Results: The ET_{50} (time to reduce tissue viability as measured using MTT) was >4 hours for Glycereth-26 and 31.8 minutes for the positive control, 0.3% Triton-X-100. Glycereth-26 was not observed to reduce MTT directly in the absence of viable tissue.

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Memorandum

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

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

DATE: August 27, 2019

SUBJECT: Glycereth-7 and Glycereth-26

Anonymous. 2019. Summary of an HRIPT on a leave-on product containing 0.68% Glycereth-7.

Anonymous. 2019. Summary of an HRIPT on a leave-on product containing 3% Glycereth-26.

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Product Number	% Glycereth-7	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	0.68	LEAVE ON	YES	OCCLUSIVE	199	NO	3	0	0	0	PASS	Did not induce dermal sensitization in human subjects

	SCORING SYSTEM*:
0	No visible reaction
(+)	+ Faint, minimal erythema
1	Erythema
2	Intense erythema, induration
3	Intense erythema, induration, vesicles
4	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	Edema
DR	Dryness
^	Hyperpigmentation
ST	Staining
P	Peeling
C	Change of test site
(-)	No reading
N9R	No 9th reading
X	Discontinued

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24hrs, 48 hrs (Weekend Induction phase)	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
24hrs, 48 hrs, 72 hrs, 96 hrs	challenge readings
0.2gm	Amount of product applied
Test Material Concentration/Dilution	As is /Neat

Grading Scale interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Product Number	% Glycereth-26	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	3	LEAVE ON	YES	OCCLUSIVE	200	NO	8	1	0	0	PASS	Did not induce significant Dermal Irritation and Allergic Contact Sensitization in any of the subjects tested

Product Number 1	
Induction Phase Grading Scale	
Grade	Response
0	No evidence of irritation
1	Minimal erythema, barely percpetible
2	Defintely Erythema, readily visible;or minimal edema;or minimal papular response
3	Erythema and Papules
4	Definite Edema
5	Erythema, Edema and Papules
6	Vesicular Eruption
7	Strong reactions spreading beyond site
Effects on Superficial layer of Skin	
A	Slight gazed appearance
B	Marked glazing
C	Glazing wit peeling and cracking
D	Glazing with fissures
E	Film of dried serrous exudatecovering all or portion of patch site
F	Small petechial ersion or scabs

Challenge Phase Grading Scale	
Score	Interpretation
0	No Visible erythema
1	Mild erythema (faint pink to definite erythema)
2	Moderate erythema (definite redness)
3	Severe erythema (very intense redness)
E	Edema-Definite swelling
P	Papules-small, red, solid elevations; surface of reaction has granular feeling
V	Vesicles-small, circumscribed elevations having translucent surfaces so that fluid is visible (blister-like); vesicles are no larger than 0.5 cm in diameter
B	Bullae- vesicles with diameter >0.5cm; vesicles may coalesce to form one or a few large blisters that fill the patch size
Other Responses Characteristics	
S	Spreading- evidence of the reaction beyond the chamber area (does not include obvious signs of leakage of the test material away from chamber
W	Weeping-evidence of release of fluid from a vesicular or bullos reaction

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
48 to 72 hrs	patch duration
9	induction patches
3	weeks induction
14 Days	week rest period

Inducted/orginial and virgin site	challenge Patch
48 hrs and 96 hrs	challenge readings
20 uL	Amount of product applied
Test Material Concentration/Dilution	As is /NA

Grading Scale interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

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Memorandum

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

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

DATE: May 30, 2019

SUBJECT: Draft Report: Safety Assessment of Glycerin Ethoxylates as Used in Cosmetics (June meeting draft)

The Council respectfully submits the following comments on the draft report, Safety Assessment of Glycerin Ethoxylates as Used in Cosmetics.

Key Issue

As noted in the Chemistry section, the dossier submitted to ECHA associated with CAS No. 31694-55-0 has an ethoxylation value between 1 and 6.5; therefore, the Introduction should not say that the "specific identities of the ingredients were not discerned".

Additional Considerations

Cosmetic Use - Please revise: "A few of the glycerin ethoxylates have uses that may be incidentally ingested..." It is not clear how a "use" can be ingested. This should be revised to state that some of the ingredients may be used in products that may be ingested.

Acute, Ethoxylated Glycerol - The description of the inhalation study in Table 4 indicates that the animals were observed for 14 days after exposure, while the text stated that no mortalities were observed 7 hours after exposure. The text also needs to make it clear that there was a 14 day observation period. As young rats are used in this type of study, it is normal for them to gain weight during the study. The starting body weights and what appears to be ending body weights ("A marked gain in body weight was observed in females at 266 g and in males at 200 g.") do not need to be included in the text. If they are left in the text, the significance of 266 g and 200 g needs to be made clear.

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