Safety Assessment of Glycerin Ethoxylates as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	May 15, 2020
Panel Meeting Date:	June 8-9, 2020

The Expert Panel for Cosmetic Ingredient Safety 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 Cosmetic Ingredient Review (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, CIR.

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Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Safety Members and Liaisons
From: Preethi S. Raj, Senior Scientific Analyst/Writer, CIR
Date: May 15, 2020
Subject: Draft Tentative Report on Glycerin Ethoxylates

Enclosed is the second Draft Tentative Report on the Safety Assessment of 8 Glycerin Ethoxylates ingredients (identified as *glyeth062020rep* in the report package). This is the third time the Panel is reviewing this document. These ingredients were first reviewed at the June 2019 meeting, during which the Panel issued an insufficient data announcement (IDA) for method of manufacture, impurities, and inhalation toxicity data. Shortly before the December 2019 meeting, Wave 2 HRIPT summary data were received and presented to the Panel for review. Although prior data insufficiencies were met, the Panel deemed that the available HRIPT summaries provided insufficient information, especially in instances of low-level reactions during induction. Thus, the Panel issued a second IDA for full experimental details for each of these summaries, or, newly completed HRIPT experimental data, at or above maximum concentrations of use, with n ≥ 100 participants. The Panel was especially interested in receiving complete experimental data for an HRIPT done with the maximum reported concentration of use for the ingredient with the highest reported use, namely, 6% Glycereth-26.

In response to the IDA, the following data were submitted and have been incorporated (and are highlighted in yellow in the report):

1. Details for two previously reviewed Glycereth-12 and -26 HRIPTS (*glyeth062020data1*)
    a. Summary of results for an HRIPT on a product containing 0.35% Glycereth-12 (AMA Laboratories Inc, 2014)
    b. Individual results for an HRIPT on a product containing 5% Glycereth-26 (Consumer Product Testing Co., 2016)
2. HRIPT on a 10% aqueous solution of Glycereth-26 (new data Food and Drug Research Labs, 1973; *glyeth062020data2)*

Comments received from Council prior to the December meeting have been addressed (*glyeth062020pcpc*). Updated (2020) FDA VCRP data have been received and incorporated into the report (*glyeth062020FDA*), showing modest increases in reported use of Glycereth-20 and Glycereth-26 in face and neck, body and hand, and moisturizing products.

Also included in this package for your review:

- *glyeth062020flow*: flow chart
- *glyeth062020hist*: history
- *glyeth062020min:* meeting minutes
- *glyeth062020prof*: data profile
- *glyeth062020strat*: search strategy

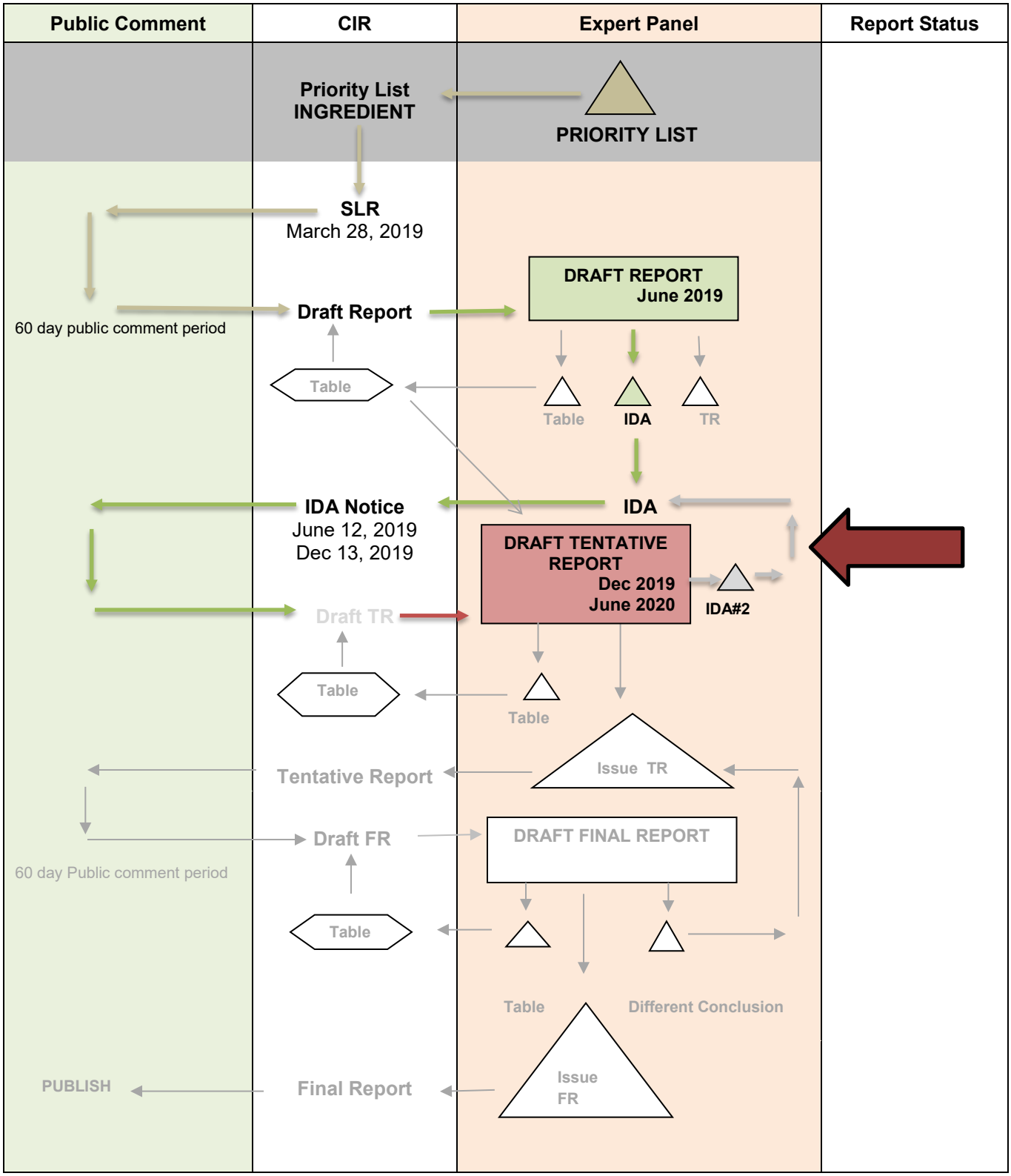
After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should identify matters to be addressed in the Discussion and then issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion. If, however, the available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

Distributed for Comment Only -- Do Not Cite or Quote

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Glycerin Ethoxylates

MEETING June 2020



CIR History of:

Glycerin Ethoxylates

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.

Draft Report was presented at the 151st 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 Panel Meeting, Council comments, new concentration of use, and the following industry data to be incorporated in the upcoming report were received:

- 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

Draft Tentative Report was presented at the 153rd Panel meeting: December 9-10, 2019

The Panel deemed that their previous data insufficiency requests were satisfied because:

- the described method of manufacture addressed the family of ingredients,
- the Glycereth-26 certificate of analysis confirmed minimal impurity levels,
- and the revised Glycereth-3 inhalation toxicity study reassured respiratory safety.

However, the Panel found the available HRIPT summaries to provide insufficient information. Thus, the Panel requested full experimental details (issued a second insufficient data announcement) for each of these summaries, or, newly completed HRIPT experimental data, at or above maximum concentrations of use, with $n \geq 100$ participants.

The Panel was especially interested in receiving complete experimental data for an HRIPT done with the maximum reported concentration of use for the ingredient with the highest reported use, namely, 6% Glycereth-26.

After the mail date, for the 153rd Panel Meeting, Council comments, new 2020 FDA frequency of use data, and the following industry data to be incorporated into the upcoming report were received:

- Wave 2, Glycereth-7 and Glycereth-26
    - 2019: 2 HRIPT summaries on products containing 1% and 2% Glycereth-7
    - 2019: 2 HRIPT summaries on products containing 3% Glycereth-26
- Individual-level data for 2 existing HRIPTs for Glycereth-12 and -26
    - 2014: HRIPT on product containing 0.35% Glycereth-12
    - 2016: HRIPT on product containing 5% Glycereth-26
- 1973 HRIPT summary on product containing 10% Glycereth-26, in 200 subjects

A (2nd) Draft Tentative Report is being presented at the June 8-9, 2020 Panel meeting

Glycerin Ethoxylates Data Profile* – June 8-9, 2020 – 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
Impurities of ethoxylated compounds
Ethoxylated compounds and lung toxicity
Case 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.

DECEMBER 2019 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – December 9, 2019

DR. BELSITO: Okay. Glycerin ethoxylates. Preethi.

At the last meeting, we, again, issued an IDA for glycereth-26. We wanted a certificate of analysis, safety testing summary, topical application for ocular irritancy. Oh, our IDA was for manufacturing, impurities and inhalation. And we received certificate of analysis. We received an EpiOcular study. We received an HRIPT.

DR. SNYDER: Six of them.

DR. BELSITO: We did not receive anything on inhalation toxicity. And for glycereth-7, we also got an HRIPT at 0.68.

DR. SNYDER: There were four additional HRIPTs in Wave 2.

DR. BELSITO: Right.

DR. LIEBLER: So, we have inhalation tox acute for glycereth-3 on PDF 19. It's not yellow highlighted as new data. And let's see, is glycereth-3 one of the ingredients in our list?

DR. SNYDER: No.

PREETHI RAJ: It is.

DR. LIEBLER: Oh, it's not -- oh, it is, yeah. Glycereth-3, -7, -8, -12, et cetera.

So it's not highlighted as new data, but I don't -- was this in here last time?

MS. RAJ: It was. I think it was just misinterpreted in the sense that -- do I have to turn this on?

DR. LIEBLER: Yeah.

DR. BELSITO: Yeah.

MS. RAJ: Thanks. I think it was just misinterpreted in that like for the acute inhalation exposure, the rat's weight increased dramatically, but that was because there was a 14-day observation period.

DR. LIEBLER: Oh, because they grew, too.

MS. RAJ: Yeah.

DR. LIEBLER: Okay. And my logic for this is that if you're going to have inhalation tox on any of them, this is the one to have because it's the lowest molecular weight, and the highest likelihood of producing an inhalation tox effect.

MS. RAJ: Okay. And I think when you all had put the IDA out last time, you had said that you had wanted method of manufacture, impurities, and inhalation tox data. But if you got method of manufacture and impurities, that you would probably waive the need for inhalation tox data is what you had said.

DR. LIEBLER: Well, we've got the method of manufacture -- well, we already kind of had method of manufacture for the family, which is, I think, is okay.

And then we had the description of the new data for glycereth-26. It's at about PDF 18 with the yellow highlight. This satisfies any concern I would have about defining the composition and impurities. So, I think we're --

MS. RAJ: Okay.

DR. LIEBLER: That data need is met as far as I'm concerned.

MS. RAJ: You mean the --

DR. BELSITO: So, the certificate of analysis was good enough for you?

DR. LIEBLER: Yes.

MS. RAJ: For method of manufacturer?

DR. LIEBLER: Well, the method of manufacturer above is a general description for this family, which I think is adequate.

MS. RAJ: Okay.

DR. BELSITO: So, the fact that we were assured about dioxin and methylene oxide levels, and the certificate of analysis is what you was concerned about?

DR. LIEBLER: Yeah. Right. That's exactly what I was looking for.

DR. BELSITO: Okay. So it's used at --

DR. SNYDER: 39.5 percent rinse-off, 6 percent leave-on.

DR. BELSITO: Right. And we have three percent HRIPT in Wave 2. And we don't have anything that approaches 6 percent. We have a five percent in 55.

I was okay with it, but we don't have six percent in a leave-on. We have five percent in 55 subjects. But I've never seen these sensitized. And I'm not concerned, I'm just pointing that out. And rinse-offs are usually like a one to ten dilution so that, I think, we're covered for the rinse-offs.

DR. LIEBLER: And we'll have the discussion.

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah.

MS. RAJ: How did you feel about the HRIPT where there were 38 low-level reactions, but they called it a non-sensitizer?

DR. BELSITO: This was in Wave 2?

MS. RAJ: Yes.

DR. BELSITO: Let me go to Wave 2 data.

MS. FIUME: PDF Page 11.

DR. LIEBLER: One of these summaries.

DR. BELSITO: Yeah.

MS. FIUME: And then for glycereth-7, the reactions were also seen in a different study during challenge. There were low-level reactions during challenge in 11 subjects out of 211.

DR. BELSITO: Okay. So for the glycereth, the HRIPT for the 26 at 3 percent. The low-level reactions occurred in the rinse-off product. The leave-on product under occlusion resulted in no low-level reaction. So, I interpret those as irritant from the vehicle, a matrix effect.

MS. FIUME: Okay.

DR. BELSITO: So, it didn't bother me.

MS. FIUME: Okay.

DR. BELSITO: I mean, because there were no reactions at all with the -- well, wait a minute. It said, number of subjects exhibiting low-level reactions during induction, there were 38.

MS. FIUME: Um hmm.

DR. BELSITO: Oh, I missed that. Number of subjects exhibiting a high level, zero. Number of subjects in low level at challenge, zero. Yeah. Okay. I wish they would define a low-level reaction.

DR. LIEBLER: Well, that just underscores the problem with these summaries.

DR. BELSITO: Low level. Okay, grading scale interpretation, low-level reactions, zero or one, which is really weird because zero is nothing. So, how can you include a low-level reaction as zero, when the zero is no reaction? It makes no sense.

So it has to be -- because otherwise, everyone would have a low-level reaction, right, if they have either a zero or a one?

DR. LIEBLER: I think this is Russian disinformation.

DR. BELSITO: Yeah. I think this is -- yeah. So, you have to assume low-level reactions are one, which is minimal erythema, barely perceptible.

DR. SNYDER: All on induction.

DR. BELSITO: What?

DR. SNYDER: All on induction.

DR. BELSITO: Yeah. I mean, that's just irritation. So, I don't see that as sensitization.

MS. FIUME: What about on PDF Page 12?

DR. BELSITO: Of Wave 2?

MS. FIUME: Of Wave 2. In the first study, the way it is written, I actually --

DR. BELSITO: Wait. I need to figure out how to rotate this, counterclockwise.

MS. FIUME: View. If you go to view.

DR. BELSITO: Yeah, I know, I'm just being funny. Okay. This is glycereth-7 now.

MS. FIUME: The way the comments were written, it was unclear if there was no primary dermic irritation potential, but there was potential and sensitization potential observed. Or if that was all included within the same. There was no -- because there is a semicolon.

So, it would almost read as the cumulative irritation and sensitization potential was observed, being that a semicolon was used. But there were 11 subjects with low-level reactions during the challenge.

So, I wasn't sure on the comments how to interpret the conclusion.

MR. GREMILLION: It says that there's 11 that exhibited low level, but then it says there was no irritation. Is that the question, to kind of reconcile this?

DR. BELSITO: Well again, this is a rinse-off product and now its occlusive testing.

DR. BERGFELD: Oh, occlusive didn't have anything.

DR. BELSITO: And the funny thing is that -- this is sort of counterintuitive. Because with a rinse-off, occlusive, they had two subjects with low-level reactions during induction; and with the leave-on they had four. And then during challenge, they had none with the leave-on, and 11 with the rinse-off.

DR. SNYDER: All irritation?

DR. BELSITO: That's all irritation; but again, I think that -- I've never seen problems with glycereths in terms of sensitization or, in fact, really irritation.

But the question is, do we stand our ground and say that we're not accepting data like this, where we don't have individual data supplements and know who the company is that did the testing? Which is what we --

DR. SNYDER: I mean, we can clearly see that some of the ones that had the irritation and induction, were also some of the ones that had irritation at challenge. That was the useful information, wasn't it?

DR. BELSITO: Yeah, but the quirky thing here is that, again, the leave-on product, you would expect to see more low-level reactions during induction, where you're putting it on, taking it off, putting it on, taking it off, with a wash-off; and they saw two. And with the leave-on, they saw four.

And then at the challenge -- so now they've gone two weeks, and nothing's been put on their back, you get 11 in the rinse-off product, and none in the leave-on. Which I can believe is irritation, but I mean, it just -- it's quirky.

I would just like to see, you know, who -- what were the numbers for each subject. Like was there one particular person that kept popping up, or was this 11 different people --

DR. BERGFELD: Well, you only had two, though, that had induction problems. So, the rest would assume that they didn't have that.

DR. BELSITO: No, I understand. But it would be nice to see if it was the same person who had the four different -- you know, like, one panelist out of 199 had a little bit of erythema at each of the induction patches.

DR. BERGFELD: We have nine new people.

DR. BELSITO: Well, nine new people -- but you know what I mean? I just can't believe someone would test a rinse-off product, in an HRIPT, under occlusion. I mean, we don't do use tests in rinse-off products. You do a use test or ROAT in a leave-on product.

MS. DEWAN: If you do a patch test on a wash-off product, then what's the purpose? It wouldn't really --

DR. BELSITO: Well, we do a patch test. We don't do an HRIPT. So, we used to dilute them to try and read through irritation. We'd do like one to two, one to five, one to ten, and we would occlude them.

An Goossens, a decade, ago looked at doing what was called semi-occlusive patching to rinse-off products but as-is. The purpose behind that is, is that a lot of the sensitizers are things like fragrances and preservatives. And when you start diluting them, you dilute them down beyond their ability to induce a positive patch test. So, a negative patch test is meaningless to a product as is.

And even when you test a leave-on as is, a negative reaction does not rule out the potential for an allergic reaction to the product, when it's used someplace repeatedly other than the back.

But we don't put it on, take it off, put it on, take it off, put it on, take it off.

MS. DEWAN: Thank you.

DR. BELSITO: I don't know. I mean, expert opinion that it's not an issue for sensitization. But how do we -- I mean, I guess we're already making our comment back to industry on other ingredients that we're looking at, that this type of report of sensitization, irritation is not sufficient for us.

So, maybe we don't need to make that point for this one. We have another one that will get through to industry. Will that be a general industry comment across the board, or will it just be back to whatever company was involved with the report we looked at this morning?

MS. EISENMANN: Well, we'll get back to the company that provided these reports, yeah.

DR. SNYDER: But going forward, we definitely want to see the data like we had previously.

DR. BELSITO: Right.

DR. LIEBLER: I think in the last incidence --which ingredient was it that we first pointed this out with this morning?

DR. SNYDER: Pomegranate.

MS. FIUME: Christina, it was pomegranate?

DR. SNYDER: Pomegranate?

MS. FIUME: The summary data?

DR. LIEBLER: Was it a pomegranate summary?

MS. BURNETT: Oh, it was coconut.

DR. LIEBLER: Oh, coconut. Okay. So, the coconut suppliers are going to get notice that we need better documentation, right? But not everybody else who supplies ingredients in this space. So, I don't think one is much notice to anybody except the manufacturers of the ingredient that we cited. So I think we may need to simply notify everybody who gives us these, starting now, and when we get them --

DR. BELSITO: Okay, so they --

DR. LIEBLER: -- notify them right away, that the panel's not going to take this.

DR. BELSITO: Carol, can we let whoever supplied this data know that it really didn't suffice, completely, our needs for sensitization?

DR. LIEBLER: And this isn't really --

DR. BELSITO: And that this was one that went through expert judgment more than the data they provided.

DR. LIEBLER: Right. And this is a really good example of why that summary is inadequate.

DR. BELSITO: Yeah.

DR. LIEBLER: Because there are things that we're forced to speculate about, about the data that we need to know about.

DR. BELSITO: Yeah. And it's very helpful. You know, when you see, like, four reactions and it's all in this same person out of 199, that's easy to discount. There was something going on with that individual.

DR. SNYDER: What about the fact that it's max concentration of use is 6 percent, and we only have data at 3 percent; and we got quirky results at three percent?

DR. LIEBLER: All the more reason.

DR. BELSITO: So, do you want to go insufficient for sensitization and irritation? I don't have a problem.

DR. LIEBLER: I mean, if we go insufficient then that's going to force them to respond substantively. And word can go back to them that they can respond substantively by providing us better quality data in support of the --

DR. BELSITO: So, sensitization and irritation for glycereth-26 and -7 at concentration of use?

DR. LIEBLER: Yeah.

DR. BELSITO: And not just summary data?

DR. LIEBLER: Right.

DR. HELDRETH: Alternatively, I can make a point of it in the post-meeting announcement to put it out there for anybody interested. And certainly all the companies that submit information to the panel see this that an HRIPT study is something that the panel finds quite useful but a summary like this often has its drawbacks.

DR. BELSITO: Yes.

DR. HELDRETH: And then it gets to everyone.

DR. LIEBLER: I think that would be helpful, but it still may not reach -- I think, it may not reach everybody we need it to reach. And in this case, we have a specific need for this ingredient family.

DR. KLAASSEN: It's a good time to start.

DR. LIEBLER: Right.

DR. BELSITO: Okay. So, insufficient for sensitization.

MS. RAJ: And would this be for just glycereth-26 or, I guess, whichever ingredients you're able to get?

DR. BELSITO: Glycereth-26 is the maximum concentration of use, so glycereth 26 at 6 percent maximum concentration of use in a leave-on.

DR. BERGFELD: Unless they can come back and demonstrate the details of that study. Is that a comment that can be made in the minutes?

DR. KLAASSEN: I mean they have the data, most likely.

DR. BELSITO: Of course they have the data.

MS. EISENMANN: See, for something that's large like glycereth-26 they're not testing the -- these are -- a lot of it is finished product testing and not ingredient testing. Because it's large, they're not going to test the ingredient on its own.

So, I'm not sure you're going to get -- I mean, you've got glycereth-26 at what, 3 percent?

DR. BELSITO: Three.

MS. EISENMANN: And well, there's a small study at 5 percent on 55 subjects. I don't know if you're going to get -- I don't know the molecular weight, at what point glycereth-7 would be absorbed or 3 or --

DR. LIEBLER: Yeah, I mean, I think the smaller ones might be absorbed a little bit just into the stratum -- or just through the stratum corneum enough that you couldn't exclude a possibility of any sensitization.

MS. EISENMANN: But they're not used as much.

DR. LIEBLER: The thing is, I think that they could have satisfied us with a clear report on the study that was done, so that we could interpret this. Right now, we're speculating about what the report is because all we have is the summary. If we had the report, we'd probably be on to the next ingredient right now.

MS. EISENMANN: But do -- well, that is the summary --

DR. BELSITO: We have the 5 percent, 55 subjects for glycereth-26. Again, just a summary, we don't see the actual details. And it says, the test material did not demonstrate a potential for eliciting dermal irritation or allergic contact sensitization. That's PDF Page 21.

DR. LIEBLER: I mean, it's a draft tentative report. We can go back out and get the reports.

DR. HELDRETH: Yeah, procedurally, since the panel asked for manufacture, impurities, and inhalation last time in an IDA, this is a new data request. So, essentially, if you were going to go insufficient here, instead of coming out with a tentative conclusion with that, it would be a second IDA.

DR. LIEBLER: Yeah, that's what we need. Because the data they submitted, even though we didn't ask for it, raised new questions.

DR. BELSITO: Well, we asked for summary of an HRIPT on product containing 3 percent, and for the 26th. And the summary for the glycereth-7 at 0.68. And, I guess, what we got was a summary. And what we thought we were going to get was the study.

DR. LIEBLER: And the thing is, the summary indicates that there have to be study data, it's just not being shared with us.

DR. BELSITO: I understand, but we didn't ask for the study data, we asked for the summary, and that's what they gave us. So, I don't know, procedurally, what we do here, but it puts us on notice that we don't ask for summaries anymore.

DR. LIEBLER: Right. But from here on, we do the right thing, which is get the data we need to be confident in our conclusions.

DR. BELSITO: So, what are we doing with this?

DR. SNYDER: I think it's more your call. Do you think the 5 percent and a 55 is sufficient for 6 percent max use? I'm okay with it, but I'll go with what the dermatologists on the panel think.

DR. BELSITO: Yeah, I think it's fine. But again, I'm just concerned because, you know, we're going back to the coconut people and saying, we want the hard data; and we're not going back to these people and doing the same thing.

DR. LIEBLER: I think we issue an IDA and we communicate back to them here's how -- easily how you can address it.

DR. BELSITO: So, we don't need the inhalation anymore?

DR. LIEBLER: No.

DR. BELSITO: So then the IDA is at 6 percent or -- which would be the maximum concentration for glycereth-26. Or is it the experimental results for the HRIPT on the 26 at 3 and the 7 at 0.68?

DR. SNYDER: The HRIPT at 6 percent will easily clear. We could clear it if we have the data to understand the quirky results and the other test, where we tried to decipher whether it was irritation and not sensitization. So we have a comfort level there; is that not right?

DR. BELSITO: Yeah.

DR. SNYDER: So, it'd be either/or.

DR. BELSITO: So, insufficient for sensitization of glycereth 26 at a maximum concentration of 6 percent, or the experimental details for the HRIPT performed on the three percent material, right? And the experimental details for the 7 performed on the 0.68.

DR. SNYDER: For all HRIPT studies in the report?

DR. BELSITO: Well, we don't have the details for the five percent. I mean, we don't have the actual experimental details, we just have the summary saying that there was no evidence. Rather than in the other one where we're told that there was low level --

DR. LIEBLER: Right. So, we have to get away from those.

DR. BELSITO: So basically, if you look at the sensitization and irritation data we had, it just said a product containing five percent glycereth-26 was done in 55 subjects, and the test material did not demonstrate a potential for eliciting dermal irritation or allergic contact sensitization.

It doesn't say anything about reactions or anything. And that was the conclusion of the other study, too. But they just happened to say that there were these low-level reactions, eight subjects. The researchers concluded the test material did not induce significant dermal irritation or allergic contact sensitization.

If we hadn't had that sentence put in about low-level reactions, we would have never asked for it. We don't know whether there were low-level reactions in the 5 percent. We just know the conclusion.

DR. SNYDER: Well, I think we just ask, and then go from there and see what we get, and we'll hear what the other team says and then --

DR. BELSITO: Okay. So -- and if that was the same for asking for the details for the -7, it's -- they stated there were some low-level reactions.

So, if we're going to ask for the experimental details for the 7 and the 26 at three percent, do we want the details for the 12 and the 26 at five percent?

DR. SNYDER: Well, the 12 I'm not worried about, because that was a very low level, like 0.68 or something like that percent or something, very low.

DR. BELSITO: 7 was 0.68, 12 was 0.35.

DR. SNYDER: Yeah, I mean, the 55 at 5 I'd like to know.

DR. BELSITO: Okay.

DR. SNYDER: If that was super -- if that was -- there were no induction reactions, and that was under all the right (inaudible) conditions --

DR. BELSITO: But it was only 55 subjects.

DR. SNYDER: Well, I know, but -- and then --

DR. BELSITO: Normally, you ask for a hundred at least.

DR. SNYDER: Right. I don't remember seeing so many HRIPTs that had these low-level reactions before. Usually they're just clean.

DR. BERGFELD: Occasionally, we've had them in the beginning but not in the end.

DR. BELSITO: Well, often times we weren't told that data. We just had a summary statement that said, boom, there was no evidence of irritation or sensitization just as we have for the five percent.

MS. EISENMANN: I think it depends on what company is doing the study. Some companies report low-level reactions more carefully than other companies, is what I think. And I also think that location of where the study is done makes a difference too. If it's done it Texas where it's nice and hot during the summer, they might have more low-level reactions, than if it's done in New Jersey in the winter.

DR. BELSITO: When your skin is dry and irritated and cracked.

MS. EISENMANN: Well, maybe in the winter, fall, spring, you know what I mean. You understand.

DR. SNYDER: Well, I mean, maybe we're over-interpreting the data. We should just go with the summary that says it was negative.

DR. LIEBLER: We're over-interpreting a summary of the data.

DR. SNYDER: Right.

DR. LIEBLER: That's the problem.

DR. SNYDER: Right.

DR. LIEBLER: We have a summary of the data that doesn't tell us enough. So we're forced to over-interpret it because there are uncertainties that suggest there might be a problem.

DR. BELSITO: And it's not tested at the maximum concentration of use. But clinically, glycereths have not been a problem.

DR. SNYDER: Well, I think that our insufficient data announcement should be very specific that we -- the preference would be to have an HRIPT done at maximum concentration of use and minimum of n equals 100, right?

DR. BELSITO: I'm fine with whatever you guys want to do. So, you want an HRIPT, n of 100), glycereth-26 at six percent. And you want to see the hard data of what goes with that study.

DR. SNYDER: Well, I think it's an either/or. If they give us new data at the highest concentration of use, with adequate numbers of subjects, then I'm clear. If we get data at the -- experimental data that we then can make valid interpretation of these low-level reactions, then we might clear it also.

DR. BELSITO: So, you no longer are requesting the individual data for glycereth-7? You just want insufficient for sensitization of glycereth-26 at maximum concentration of six percent in an HRIPT of a hundred. Or you want the experimental data for the HRIPT on the three percent; is that right? Isn't that what you just said?

DR. SNYDER: Yeah, I mean, otherwise if we don't ask for that then we have to say it's sufficient right now. It's either sufficient right now as it stands, 55 subjects at seven percen,t glycereth-26. And some other ones at the 7 and three percent level, or --

DR. BELSITO: 26, glycereth-26 was 55 at five percent --

DR. SNYDER: Right.

DR. BELSITO: -- and 102 at --

DR. SNYDER: Three.

DR. BELSITO: -- three percent.

DR. SNYDER: So we have to make a decision of what we're comfortable with. If we're comfortable with that data, which is quite a bit of sensitization data with very little --

DR. BELSITO: I told you that I'm comfortable.

DR. SNYDER: Okay.

DR. BELSITO: The question is, do we set a precedent and let this company sneak by when we're not doing it for the coconut people?

DR. BERGFELD: Well, you're really asking for them to give you the details on the three percent and giving them an option to do a new study.

DR. BELSITO: What we're really asking for, going forward, is, yes, those kind of details. For this material because of other things that surround it, we're not as concerned by the abbreviated study data. However, for other materials, we could be, but in general we find it insufficient to get a study like this, an HRIPT, when we've asked for data without the actual data to back it up.

Although in retrospect, I don't know how often we've looked at actual data. We've often times relied on summaries just like what we're getting for the five percent. You know, there was -- it was tested.

DR. BERGFELD: But you didn't have a question of the results. This is a question of the results that were recorded.

DR. BELSITO: I know, but typically we've seen individual data only when we specifically said, okay, it's insufficient for this endpoint, and give us the data. We haven't seen them with the original reports. We've just -- with the first SLR, you don't send us all of that data. It's only when we turn around and say, oh, we want this data. So very frequently we have passed on sensitization with the type of information that we got for the five percent without asking to see the individual data.

MS. FIUME: Having done quite a few of these reports, I think historically we did receive the entire studies. Because our data submission size would be very hard, because there would be a table that included --

DR. BELSITO: So, you would get it all, but we would just --

MS. FIUME: Every single --

DR. BELSITO: -- see the summary?

MS. FIUME: Well, and often you would get all of them too because sometimes we would question the summary that was in the write up --

DR. BELSITO: Right.

MS. FIUME: -- didn't match the --

DR. BELSITO: If there were reactions, yeah.

MS. FIUME: Yes.

DR. BELSITO: Okay. You're right. Okay. So then my assumption was not totally correct. If your writers looked at it and had concerns, they would send all of the data together in the package we saw, yeah. Because sometimes we do get full studies and sometimes we don't.

MS. FIUME: Right.

MR. GREMILLION: Okay. I just wanted to ask if you -- you'll say this is sufficient, but then say in general it's not sufficient to have this kind of data. Would that really send a message that you --

DR. BELSITO: No, that's what I'm saying.

MR. GREMILLION: Yeah.

DR. LIEBLER: Yeah, that's what worried me about doing. Look, I'm where I was all along on this. We have data that suggests that there might be a problem. That the summary of the data is -- does not enable us to interpret it. We should get the actual report of the study. If we have to issue an IDA to do that, then we have to issue an IDA to do that.

DR. BELSITO: Okay.

DR. LIEBLER: So, let's just do it.

DR. BELSITO: So, it's insufficient for sensitization of glycereth-26 at maximum concentration of six percent, or the experimental details for each subject for the HRIPT on the three percent.

And do we want similarly for the glycereth-7, even though it was a lower concentration, now that's more penetrable that also gave quirky data?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay. So, then we want experimental details for the glycereth-7 at 0.68. Okay?

DR. KLAASSEN: You need to make clear --

DR. BELSITO: Capisce?

DR. KLAASSEN: -- that the experimental details needs a results. I mean, some people can --

DR. BELSITO: Well, we did say summary. Okay.

DR. KLAASSEN: Exactly.

DR. BELSITO: Are we done? Anything more on glycereth?

MS. RAJ: Well, since you all, you know, obviously want more details, maybe this is a little premature. But I just wanted to get your feedback on what I presented so far, in the discussion, as far as bringing in some language from previous reports.

Because I know you had said that you wanted weight of evidence from previously reviewed ingredients. So, I just wanted to make sure, you know, I'm in line with your thinking. And if you have anything to add, please do share.

DR. BELSITO: I thought it was fine.

DR. LIEBLER: Yeah, I added a sentence in your discussion section, basically saying that just to state that the panel felt that other families of structurally analogous ingredients, previously reviewed, could be used to provide read-across and weight of evidence support for the safety assessment. And I indicate exactly where that goes in my edited copy.

MS. RAJ: Okay. Thank you.

DR. BELSITO: That's it? Okay.

Marks Team – December 9, 2019

DR. MARKS: At any rate, we're here for reviewing a draft tentative report on glycerin ethoxylates. At the June meeting, the panel issued an insufficient data announcement for method of manufacture, impurities, and inhalation tox data on these. And they are listed in Preethi -- am I saying that correctly?

MS. RAJ: Preethi.

DR. MARKS: Pree-three.

MS. RAJ: No, Preethi. My friend says is like pretty with a lisp.

DR. MARKS: These are your friends?

MS. RAJ: I don't -- no, no, she's a lady. And I'm fine with ladies saying that; men I am not. But you're fine. It's okay.

DR. MARKS: Preethi. I'm not a linguist, so it'll take me a while. Please excuse me.

MS. RAJ: No worries.

DR. MARKS: Okay. So are we going to -- so we're at a point of issuing a tentative report that -- let me see? I didn't see where we had gotten any of this.

MS. RAJ: No.

DR. MARKS: And that's oftentimes in the memo, helpful, no new data.

DR. SLAGA: In Wave 2, didn't we get some --

DR. SHANK: HRIPT.

DR. MARKS: Yeah. But not the method of manufacture or the impurities. We didn't get that, did --?

MS. RAJ: There was a certificate of analysis for glycereth-26, which I was wondering if you all thought that qualified as some sort of method of manufacturing data.

DR. PETERSON: Say that again.

MS. RAJ: So, for glycereth-26, in the -- well not Wave 2, but prior, like an interim data from the council -- or industry, I guess. There was a certificate of analysis for glycereth-26, which kind of listed some, I guess, various values, which I wasn't sure would qualify as method of manufacturing in some capacity.

DR. HELDRETH: It's really --

DR. MARKS: What page is this?

DR. HELDRETH: So, this is -- the actual submitted information is PDF Page 36. It's really a property information, so chemical-physical properties. I don't think there's any methodologies there. So you have things like acid value, hydroxyl value.

DR. SLAGA: Would that serve for the impurities?

MS. RAJ: Oh, yeah.

DR. PETERSON: But not the method of analysis, not the method of manufacturer, but the impurities.

DR. ANSELL: But isn't the reason we need a method is to identify what are the potential impurities? The manufacturing in and of itself is not of interest. It's whether --

MS. RAJ: There are impurities?

DR. ANSELL: Yeah.

MS. RAJ: But Bart, the council, remember, their comments that we got right before the meeting, they said that they felt that that information fit in the, I think, chemical and physical properties, not in the impurities, which was interesting, I thought.

DR. HELDRETH: It's up to the panel how they want to use it.

DR. MARKS: So Ron, Tom, Lisa, move forward with still insufficient for method of manufacture and impurities versus safe? Ron, you had comments the last time about that, which is on page 14 in the minutes.

Do you want to reiterate those for Lisa? I think it'd be helpful.

DR. SHANK: Well, my position was this is a -- these are single chemicals. And if there were impurities that had significant toxicity, that would have been indicated in the toxicology studies. So I felt it wasn't necessary to have the impurity data.

But the other team felt very strongly that, if you don't know what the impurities are, we're missing significant data. So, we see it differently. And if they want the impurity data, I won't object.

DR. MARKS: Okay. Good.

DR. ANSELL: And the impurity data that's most of concern, with ethoxylates, is the presence of dioxane. So, that we monitor very closely, and you now have the dioxane levels.

DR. PETERSON: Dioxane? Or ethylene dioxide.

DR. ANSELL: And EO. Although, EO is so reactive you don't really see EO per se. But you do see the 1,4-dioxane, which is something we manage very carefully and have recommended, as a Council, that it be controlled to less than ten PPM.

MS. LORETZ: Recommended under the international ICCR. It's far beyond us, actually.

DR. ANSELL: Right. Canadian, Brazilian, European, U.S., and --

DR. SHANK: Japan.

DR. ANSELL: Do I have five? And Japan.

DR. HELDRETH: It's a rather volatile chemical. Isn't that correct? They're easy to get rid of if you make an effort to --

DR. ANSELL: It is volatile, and it can be managed. I'm not sure easy is the right word.

DR. HELDRETH: Okay. There's no methodologies.

DR. ANSELL: Yeah. Yeah. And it's something we've been tracking for decades with FDA. And ten PPM in the final product is what we manage, and this was less than five an in a raw material, which is then diluted itself.

DR. MARKS: So tomorrow -- I'm sorry.

DR. ANSELL: No, I was just going to finish. So, we feel that we've address the manufacturing, impurity issue.

DR. SHANK: At the September meeting, I raised a concern about the inhalation data for --

DR. MARKS: Yeah. I'm going to get to that. So are we going to -- we're seconding it, the tentative report? But are we -- I gather, Ron --

DR. SHANK: I'll remain silent.

DR. MARKS: Yeah. If the Belsito team says insufficient for method of manufacture and impurities, we're going to go ahead and second that. Jay, even though you bring up a very important point -- did we capture that either in the discussion at all, this issue with the dioxanes?

MS. RAJ: There's some boilerplate language. Let me see, that is on Page 24. But you'll see it's pretty short mention there.

DR. HELDRETH: Yeah. We usually say -- since there are no methodologies to get rid of it and industry is well aware that this is an issue. We usually put in a statement to the effect of industry should continue to use, you know, basically good manufacturing procedures to --

DR. MARKS: That's under the draft -- which paragraph is that under?

MS. RAJ: The second to last of the discussion.

DR. MARKS: Oh, yeah. Dioxane and ethylene oxide impurities -- yeah. Okay. Super. So we'll see how that runs out.

And actually, Preethi brought up -- she wanted us to also comment about the discussion, since I don't know if this is the first one you've written --

DR. HELDRETH: Yeah.

DR. MARKS: -- but close to it.

MS. RAJ: Yes.

DR. MARKS: So, we'll get to overall comments on the discussion in a minute. Ron, thank you for bringing up the respiratory because that was my next point I wanted to bring up, is the potential respiratory toxicity.

MS. RAJ: Yes. And since you just finished talking about the method of manufacture and impurities, I just wanted to remind you that you had said that if you found sufficient method of manufacture and impurities, you would, I guess, waive the need for inhalation data. That's what you had said before, so just reminding you all.

DR. SHANK: Well, we have inhalation data. It was just misinterpreted the first time.

MS. RAJ: Yeah.

DR. MARKS: Oh, okay.

DR. SHANK: It said that the rats gained half their bodyweight in seven hours or something like that. And I said I didn't think that was correct. And it wasn't.

MS. RAJ: But now you're satisfied?

DR. SHANK: I'm fine.

DR. MARKS: So, all we do is use the inhalation tox resource document is that --

DR. SHANK: Yes.

DR. MARKS: We include that. Okay.

DR. SHANK: With that dioxane and ethylene oxide paragraph, why do we say, "Therefore more data are required for clarity?"

MS. RAJ: Where are you looking?

DR. SHANK: What more data do we want? It's the second to the last paragraph in the discussion.

MS. RAJ: Yes, I see that. I think that's, I guess, going along with what I just explained. Because I had understood that until you felt satisfied with the method of manufacture, and impurities, that you would want inhalation data.

DR. HELDRETH: So now that we have --

DR. SHANK: But this is on the impurities.

MS. RAJ: Yeah. Well, the post-meeting announcement last time, there were three IDA requirements. There was method of manufacture, impurities and inhalation data.

DR. SHANK: Yes. Right.

DR. PETERSON: And you got the impurity information, but not the manufacturers, right?

DR. SLAGA: Right.

DR. SHANK: But we don't need more -- we don't need clarity, do we, on the --

DR. ANSELL: I think the method of manufacture is requested to determine whether there's a potential for unreactive materials or reaction products, which would be of concern. We feel that, for ethoxylated products, the chemistry is well-known, and the ingredients of concern are the potential for the formation of 1,4-Dioxane.

We have established international standards for what are appropriate residuals. And these materials, even unformulated, would fall below the concern level for the international standards set for 1,4-Dioxane. So we believe that that responds to the concern of residuals and method of manufacture.

DR. SHANK: Okay. But we don't need more data for clarity on 1,4-Dioxane?

DR. ANSELL: No, no -- that's --

DR. SHANK: That's what it says.

DR. ANSELL: I think those two sentences are --

DR. SHANK: The other impurities maybe, but --

MS. RAJ: We can modify that.

DR. SHANK: Okay.

MS. RAJ: So, how would you like that worded?

DR. SHANK: Just say more data are sought on other impurities for clarity.

MS. RAJ: Okay. Thank you.

DR. ANSELL: Well, no. This is very specific to the 1,4-dioxane. I would suggest that the modification is -- rather than saying the Panel was concerned with the possible presence, that the Panel is aware of the possible presence and, therefore, recommends that we continue to use all the necessary procedures to limit the 1,4-dioxane impurities.

MS. RAJ: Okay. Thanks.

DR. ANSELL: Yeah. So, first sentence and then the second sentence align.

DR. SHANK: Yeah. Right.

DR. PETERSON: And then you have the report on the certificate of analysis for the --

MS. RAJ: Glycereth-26.

DR. PETERSON: Yup. That says that it's really low.

MS. RAJ: When you say "it" you mean impurities?

DR. PETERSON: Yeah. The 1,4-dioxane was less than 0.0001 percent.

MS. RAJ: Yeah. Okay.

DR. MARKS: So Ron, you would be -- you would be okay going on with a safe conclusion?

DR. SHANK: I would.

DR. MARKS: Yeah. And Tom?

DR. SLAGA: I would, too.

DR. SHANK: They'll want impurities.

DR. SLAGA: Well, we -- we had -- that's what we wanted when we said flag for the time before, wasn't it?

DR. SHANK: Well, we had the concern about the inhalation.

DR. SLAGA: Inhalation, right.

DR. SHANK: These rats gained a whole lot of weight really fast.

DR. MARKS: Well, we'll see what the Belsito team moves tomorrow. And if they still want the insufficient for method of manufacture, we will not dispute it. We've had that long discussion before.

I wanted to comment about Wave 2, W2. So we didn't discuss -- we talked about method of manufacture, the impurities and inhalation.

But the new data on Wave 2 were sensitization data. So, the 2 percent glycereth-7 was HRIPT. And the 3 percent glycereth-26, both were fine. However, in one of the HRIPTs, with the glycereth-26, 38 subjects had a, quote/unquote, low level reaction with induction but not with challenge.

When I compare it with the other HRIPTs, 3 percent and 5 percent, which had been done previously, they were okay. So, I don't know if this was a leave-on product they had there, that those 38 reactions were just a mild irritant reaction to that particular formula in leave-on.

To me, it didn't create a big alert. And again, the formatting was fine. I was able to take a look and see.

MS. RAJ: Is this something you would allude to in the discussion?

DR. MARKS: No, I don't feel compelled to allude to it.

DR. SHANK: Well, they concluded -- I found it very confusing.

DR. MARKS: Yeah.

DR. SHANK: One concentration was negative, and another concentration even lower, potential sensitizer. And I didn't know how to interpret that.

DR. MARKS: They didn't -- in the end, they didn't categorize this as a potential sensitizer. They didn't call it a sensitizer. Correct?

MS. RAJ: Yes, correct.

DR. MARKS: So, I think they interpreted it as just being mild irritation. That's what I suspect with it.

DR. SHANK: Okay.

DR. MARKS: I mean, we could mention it in the discussion if you think that would be helpful. But with two other studies and the other ingredients being negative as far as sensitization, and with this not being -- with the lab that did this interpreting it as a non-sensitizer, then I was fine as a non-sensitizer.

DR. SHANK: Okay. Good.

DR. MARKS: And I didn't think we needed to have some sort of caveat, formulate to be non-irritating, either.

DR. SHANK: Good.

MS. RAJ: Okay.

DR. MARKS: So is that okay, Ron?

DR. SHANK: Yes.

MS. RAJ: So, would you say something to the effect that there was a study, a sensitization study, where you saw some low-level reactions? You weren't sure of the nature of the product, like if it was leave-on?

DR. MARKS: It was a leave-on.

MS. RAJ: Okay. It was a leave-on.

DR. MARKS: Because they had one that was -- the other one that was in there was not a leave-on.

MS. RAJ: Right. But that basically the lab did not classify it as a sensitizer, so that's why you're not concerned?

DR. MARKS: Correct. That and the other ones with the same ingredient, the glycereth-26, the other HRIPTs which were negative.

So, I think with those others that were negative, even though -- you're right, Ron, one was the same concentration, 3 percent. But then there was a 5 percent, higher concentration, which was okay. That was from the original data.

We always put in the data we have. I don't know that we have to speculate that, perhaps, this was a mild irritant in the induction phase or not.

DR. SHANK: Okay.

MS. RAJ: Okay.

DR. MARKS: But I think the investigator is saying it's non-sensitizing, that's important.

DR. SHANK: Yeah.

DR. MARKS: Because otherwise then we're trying to explain -- and they didn't -- and what I saw, they didn't try to explain what the reactions were. It came to the conclusion non-sensitizing.

MS. RAJ: Yeah.

DR. MARKS: Okay. Any other comments?

MS. RAJ: I was hoping, if you had anything you'd like to add in the discussion about the nature of previous reports, which Dr. Liebler had said he wants to use as weight of evidence for safety of these ingredients.

Because, again, me being very new here, I looked at, I guess, all these -- there were about like 20 reports referenced from before -- and it seems to be practice to usually draw on, or kind of use, the safety of similar ingredients from the past as, like, a substantiation for, like, the presently reviewed ingredients being safe. So, do you have any language for that?

DR. SHANK: I didn't go back and look at those earlier reports.

MS. RAJ: I do have -- I mean, I'm not -- obviously, it's has to be coming from you. But to jog your memory, I was looking at there were laurates, stearates, cetates, PEG, cetyl alcohol, oleates, laneth-10 acetate. So, they kind of had a nice paragraph here.

It said, the alcohol ethoxylates -- this is paraphrased. There PEG metabolites are noncarcinogenic and relatively innocuous when given orally. Various alcohol ethoxylate preparation are nontoxic when inhaled, and do not inhibit ciliary movement in vitro. Ingredients are relatively innocuous when administered orally, acutely, and subchronically. They are not mucosal irritants.

Some are slight to moderate skin irritants, but are not sensitizers. Negative for teratological, multiple generation, and mutagenic potential. So, is that kind of what gives you -- ?

DR. SHANK: Okay. I guess that would be helpful.

DR. MARKS: It's long-winded. I didn't like "relatively." I guess it depends. That to me is a little bit --

MS. RAJ: Okay.

DR. HELDRETH: I think Preethi already has something to this effect in her draft discussion. If you look on PDF Page 24, the second full paragraph. "The Panel noted." That may be sufficient. It's up to the panel if you think we should expand upon that or not.

MS. RAJ: Yeah. That I took from Dr. Liebler's comments. But I'd love to see if you have anything to add to that.

DR. MARKS: See, I like that, because you kind of --

MS. RAJ: I feel like there's quite a bit of language across these reports, about how it's -- because of the chemical structure.

But again, me not being a chemist and kind of knowing everything, it kind of feels a little vague in that, okay, it's because of the chemical structure. But what is so safe about this chemical structure? So, should there be more explanation there? I'm not sure.

DR. PETERSON: I actually, like -- I mean, I like how that paragraph reads.

MS. RAJ: Okay.

DR. PETERSON: Because the difference is this methyl group or change in the --

DR. MARKS: And in my mind, even though we -- it's helpful we have these read across or related -- the chemistry, it's these ingredients stand on their own with the data we have in this report.

DR. SHANK: I thought so.

DR. MARKS: So, this is nice background, but the ingredients themselves stand. If we had the method of manufacture, it would be easy. It'd be a safe.

MS. RAJ: Okay. And there was some language on previous reports about how the toxicity is inversely proportional to the length of alkyl chains. Or I guess maybe in this case, you could say the ethoxylation values, like, just the size of the molecule.

Also the fact that glycereth-26 is the one that's, I guess, the most used, does that maybe also maybe provide some assurance for the panel?

DR. ANSELL: They're all useful to model and extrapolate, but in the presence of actual data, I don't think we need to spend a lot of time talking about how we might have derived the data were it not --

MS. RAJ: Okay.

DR. ANSELL: But I do think those concepts are foundational in terms of the safety assessment of cosmetics, the ability to rely on materials that are --

MS. RAJ: Do you think the inverse line, though, about the size of the molecule and toxicity is worth putting in the discussion?

DR. ANSELL: It's really not toxicity. It's, I mean, there's certain surface-active properties that may affect irritation.

DR. SHANK: I don't think it's necessary to have that.

DR. PETERSON: I agree. It reads pretty well, pretty clear.

DR. MARKS: Okay. Any other comments, Preethi?

MS. RAJ: Yes. Let's see. That's mostly what I wanted to ask you. You seemed to have addressed everything.

DR. MARKS: Good. Any other comments, Ron and Lisa? So, tomorrow, our team will be seconding a tentative report motion, and we'll see what the conclusion is. It's going to be either insufficient or safe, and we'll see. Okay. Let me go ahead and close this.

Full Panel – December 10, 2019

DR. BELSITO: Okay, so at the June 2019 meeting we issued an IDA for method of manufacture, impurities, inhalation toxicity. And we received a certificate of analysis. We received some safety testing, an EpiOcular irritation assay, and some summaries of HRIPTs on a product containing 3 percent. We also received a summary of a HRIPT on a product containing 0.68 percent for glycereth-7.

We felt that these were still insufficient. We were not happy with the summary statements of the HRIPT; perhaps this was our fault for asking for a summary. But, there is some quirky data where there were low-level reactions during the induction phase. And, it's not clear to us if those were occurring in just one of the subjects, which you could easily discount, or whether it was occurring in different subjects which would raise other issues.

And so, going forward, when we ask for HRIPTs, we would like to see the individual data. And going forward means starting with these ingredients.

So, we are happy with the certificate of analysis and the ocular irritation, but we felt that it was insufficient. We would like to see the individual data on the actual HRIPT studies that were performed. Or, since glycereth-26 is used at a maximum concentration of six percent in leave-ons, a new HRIPT at six percent for glycereth-26.

We recognize that expert opinion would say these are not sensitizers; however, expert opinion is sometimes wrong as we've discussed previously in this meeting. And so, we would actually like to see the data, particularly, given that twinkling that's going on in these studies.

DR. BERGFELD: Again, this is at issue the validation of the abbreviated summaries of the testing that we've been discussing. Jim, do you have a comment?

DR. MARKS: Yeah, we concur that a tentative report should be issued with an insufficient data. And I wondered what happened with the method of manufacture and impurities. Did I over --?

DR. BELSITO: Dan felt that the certificate of analysis that we received was adequate. Well, I'll let him address that.

DR. LIEBLER: Yeah, with this, you know, it's a typical polymer situation. And with these we're worried about -- with this type of polymer we're worried about dyoxane and ethylene oxide. And they provided this data, very low for glycereth-26, which I think is probably reasonably representative of the group. So, I felt that our data need on that was met.

DR. MARKS: Interesting. So, our team would concur since the last meeting we thought we could move forward with a safe conclusion, so. We had that discussion about method of manufacture and impurities.

Concerning the sensitization, Don, I think the study you're talking about was a three percent glycereth-26, which the investigators concluded in this one HRIPT where they had 38 subjects had low-level reaction with induction of a leave-on. But in the end, on challenge, had no reactions and concluded that this was not a sensitizer.

We had two other HRIPTs at three percent, and then another one at five percent, and acknowledge that the five percent is not at the use concentration of six percent. But those were okay.

I was wondering, I agree, we don't have the details whether the leave-on was a mild irritant in the induction phase, and that's why they saw these low-level reactions. But certainly to be safe, I'm fine with moving forward with an insufficient -- we actually are concurring, going forward without a method of manufacture and impurities. But now we just do insufficient, forgetting the details of that study.

DR. BELSITO: Yeah, I mean, we also discussed the fact that the 5 percent was said to be non-sensitizing, but again we didn't have individual data for that one either.

And, you know, had this been a surfactant, or you know, something that we know has a tendency to irritation, like iodopropynyl butylcarbamate or methyldibromo glutaronitrile, I might easily dismiss these quirky reactions, even if they were occurring in five separate individuals, or how many. But, you know, the glycereths typically aren't irritants. You know, they're very well tolerated. So, I just wasn't certain -- you know, the tests that were done on the rinse-offs I had no problems with.

DR. MARKS: Exactly.

DR. BELSITO: You know, but it was the leave-ons that bother me. And, in fact --

DR. MARKS: Yes, it was that one leave-on.

DR. BELSITO: Yeah. For glycereth-26, I think there were more, you know, low-level reactions in the leave-on product then there was in the rinse-off product.

DR. MARKS: Yes, which you would expect perhaps the opposite way.

DR. BELSITO: Exactly the opposite. So, you know, I just --

DR. MARKS: No, I'm concurring, Don, insufficient and a tentative report. In this case the only insufficient is clarifying the HRIPTs.

DR. BELSITO: Right.

DR. MARKS: And I don't know if "quirky" is a scientific word, but I like it.

DR. BERGFELD: Any other discussion?

DR. HELDRETH: Yeah, so procedurally, since the panel put out an insufficient data announcement on this report for three issues that are now resolved, and we're making a new data request, this should actually go out as a second IDA, instead of a tentative report.

DR. BERGFELD: Okay.

DR. BELSITO: That's fine.

DR. HELDRETH: And then it'll come back as a tentative report again at the next meeting.

DR. MARKS: Yeah, and did we mention that the inhalation tox data, did you mention that that we got that and that was okay?

DR. BELSITO: Right. Yes.

DR. MARKS: Because that was one of the insufficient data needs in the last go round with these ingredients. Okay.

DR. BERGFELD: All right? Seeing no other questions, I'll call the vote on that then, a tentative IDA again going out. All those in favor, please indicate yes. Consensus is met, unanimous.

Moving on to the next ingredient, Methicones, Dr. Marks.

Safety Assessment of Glycerin Ethoxylates as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: May 15, 2020
Panel Meeting Date: June 8-9, 2020

The Expert Panel for Cosmetic Ingredient Safety 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 Cosmetic Ingredient Review (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, CIR.

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ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (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 considered the available data and 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, the Panel 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, the Panel has issued safety assessment reports of structurally-related polyethoxylated compounds, such as alkyl PEG ethers and PEGs cocamine, in which it was concluded that these ingredients are safe in the present practices of use and concentration.[4,5] These reports are available on the Cosmetic Ingredient Review (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 the Panel 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.

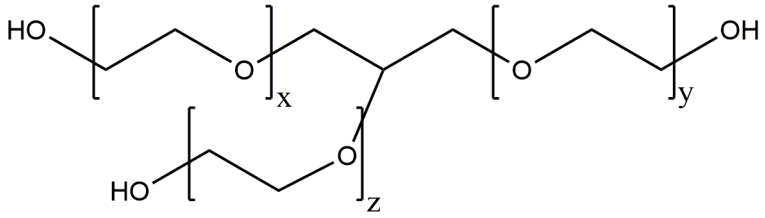

Figure 1. Glycerin ethoxylates, wherein the average ethoxylation value equals x + y + z (e.g., x + y + z = 3 in the case of Glycereth-3)

The definition of each ingredient, as given in the *Dictionary*, is provided in Table 1. This group of ethoxylated glycerin ingredients is identified by the CAS No. 31694-55-0.[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] 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 the ether formed from the reaction of one molecule of an alcohol with one molecule of the alkylene oxide is also an alcohol, the reaction with the alkylene oxide can continue until the latter is consumed.

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

A previous Panel 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 2020 VCRP survey data, Glycereth-26 is reported to be used in 437 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 three ingredients not reported to be in use by both 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 described in Table 4.

The oral LD_{50} of Glycereth-3 tested at concentrations of 1 - 50% was > 10 mL/kg in male and female rats.[6] In 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 acute inhalation toxicity study, performed in accordance with Organisation for Economic Co-operation and Development test guideline (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")

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 2 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")

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)

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")

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")

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)

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-irritating 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")

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.

A leave-on product containing 1% Glycereth-7 was tested in an HRIPT in 199 subjects.[18] The test material was applied occlusively for 24 to 48 h via 9 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 24, 48, 72, and 96 h after application. Four subjects exhibited low-level reactions (0 - 1 score, on a 0 - 4 scale) during induction; no other responses were noted during induction, or during challenge. The researchers concluded that the test material did not induce dermal sensitization.

A rinse-off product containing 2% Glycereth-7 was tested in a similar occlusive HRIPT in 211 subjects.[18] The test material was diluted to 1% v/v with tap water (effective test concentration, 0.02%). Two subjects exhibited low-level reactions during induction, and 11 subjects exhibited low-level reactions during challenge. The researchers concluded that although there was no primary dermal irritation potential, cumulative dermal irritation and sensitization potential were observed.

Glycereth-12

An HRIPT of a mascara formulation containing 0.35% Glycereth-12 was performed in 100 subjects.[19] The test material (0.2 g) was applied with an occlusive, hypoallergenic patch to the infrascapular regions of the back for 9 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. Of the 103 initial study participants, only 3 did not complete the study; discontinuation was not due to adverse reactions. There were no signs of irritation or sensitization in those who completed the study.

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 rinse-off product containing 3% Glycereth-26 was tested as received in a semi-occlusive HRIPT in 103 subjects.[20] One participant withdrew due to an adverse reaction; 4 subjects exhibited low-level reactions during induction, and 1 subject exhibited a low-level reaction during challenge. The researchers concluded that although there was no primary dermal irritation, cumulative dermal irritation and sensitization potential was observed.

A leave-on product containing 3% Glycereth-26 was tested as received in an occlusive HRIPT in 208 subjects.[20] No participants withdrew due to adverse reactions; 38 subjects exhibited low-level reactions during induction, no subjects exhibited any reactions during challenge. The researchers concluded that the test material did not induce dermal sensitization.

A product containing 5% Glycereth-26 was tested in an HRIPT on 55 subjects.[21] 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 non-treatment 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.

An HRIPT of a product containing 10% Glycereth-26 was performed in 200 subjects.[22] Discs of lintine paper were moistened with the test material (amount not specified) and secured to a site on the upper arm for 24 h. After 24 h, the patch was removed and the contact site was rested for 24 h. Repeated 24-h patch applications were applied 3 times/wk , for 5 wks, for a total of 15 applications. After a 2-wk non-treatment period, the challenge patch was applied on the same contact sites with the test material (amount not specified) for 24 h under occlusion. No visible skin changes occurred upon challenge, and test substance was deemed a non-sensitizer.

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.[23] 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.[24] The cell cultures were tested in duplicate, with exposure times of 0.33, 1, 2, and 4 h. Appropriate negative and positive controls were used. The ET_{50} (time to reduce tissue viability as measured using MTT) was > 4 h for Glycereth-26; this was predicted to be non-irritating.

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

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 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 read-across sources for these ingredients.

These ingredients are mostly used in leave-on formulations. Glycereth-26 has the highest reported frequency of use (437 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 acute 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 > 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 > 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, or *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.

According to the results of an EpiDerm™ assay, "ethoxylated glycerol" 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-irritating 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 undiluted for skin sensitization potential using in an HRIPT completed in 199 subjects. Three subjects exhibited low-level reactions during induction; the test material did not induce dermal sensitization. A 1% leave-on, and 2 % rinse-off Glycereth–7 product was tested for skin sensitization potential via occlusive HRIPT, in up to 211 subjects. Four subjects exhibited low level reactions during induction for the leave-on product. Two subjects exhibited low-level reactions during induction, and eleven subjects during challenge, for the rinse-off product. The test materials were deemed non-sensitizing. A mascara formulation 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 evaluated in an HRIPT in 200 subjects. Eight subjects exhibited low-level reactions during induction, and 1 subject exhibited a high-level reaction during induction; the researchers concluded that the test material did not induce significant dermal irritation and allergic contact sensitization. A rinse-off product containing 3% Glycereth-26 was tested undiluted in a semi-occlusive HRIPT in 103 subjects; one participant withdrew due to an adverse reaction, and low-level reactions during induction and challenge supported the potential for cumulative dermal irritation potential. A leave-on product containing 3% Glycereth-26 was tested undiluted in an occlusive HRIPT in 208 subjects; 38 subjects exhibited low-level reactions during induction; the test material did not induce dermal 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. An HRIPT was performed in 200 subjects on a product containing 10% Glycereth-26; induction patches were applied for 24 h, 3 times/wk for 5 weeks, and the challenge patch was applied following a 2-wk non-treatment period. No changes in skin or signs of sensitization were observed during the induction or challenge applications.

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 predicted to be non-irritating. 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 was found to be non-irritating. In rabbits administered single instillations of 1.8 - 2.4 g, 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 however, a similar observation was made in the control eye;. 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 ingredients reviewed in this document are structurally related as polyethylene glycol ethers of glycerin. The Panel has previously reviewed components of these ingredients, such as alkyl PEG ethers and PEGs cocamine, which were determined to be safe in the present practices of use and concentration, when formulated to be non-irritating.

Similarly, the 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.

Additonally, the Panel considered propoxlylated nitrilotriethanol, propoxylated glycerol, and ethoxylated glycerol as suitable read-across sources for these ingredients due to their previous review of polyethoxylated ingredients. Furthermore, the Panel deemed both read-across materials as representative of lower molecular weight glycerin ethoxylates.

The 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 (437) and leave-on concentration in eye lotions (6%). At the December 2019 meeting, the Panel felt that their data requests for method of manufacture and impurities data were met, and, therefore, acute inhalation toxicity data, were no longer required.

The Panel discussed the issue of incidental inhalation exposure from formulations which are aerosolized, such as the body and hand spray formulations containing 1% Glycereth-26. 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; results from an acute inhalation study of rats with Glycereth-3, the smallest and most volatile of these ingredients, produced no mortality, or clinical and gross pathology. 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 (mPa·s @ 20 ºC)	399	6
Vapor pressure (hPa @ 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	25
log P	-1.79 (estimated)	25
	Glycereth-7	
Physical Form	Yellow to amber color, mild odor	26
Molecular Weight (g/mol)	400.47	25
log P	-2.42 (estimated)	25
	Glycereth-8	
Molecular Weight (g/mol)	444.52	25
log P	-2.57 (estimated)	25
	Glycereth-12	
Molecular Weight (g/mol)	620.73	25
log P	-3.19 (estimated)	25
	Glycereth-18	
Molecular Weight (g/mol)	885.05	25
log K_{ow}	-7.19 (estimated)	27
	Glycereth-20	
Molecular Weight (g/mol)	972.57	25
log K_{ow}	-7.73 (estimated)	27
	Glycereth-26	
Physical Form	Yellow to amber color, mild odor	28
Molecular Weight (g/mol)	1237.47	25
log K_{ow}	-9.38 (estimated)	27
Acid value (mg KOH/g)	0.2	8
Hydroxyl value (mg KOH/g)	133.40	8

Property	Value	Reference
Ash content (following pyrolyzation)	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	[25]
log K_{ow}	-10.75 (estimated)	[27]

Table 3. Frequency (2020)[9] and concentration (2019)[10] 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*	**3**	**NR**	**437**	**0.3 - 39.5**	
Duration of Use					
Leave-On	*3*	*NR*	338	*0.3 - 6*	
Rinse Off	*NR*	*NR*	99	*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	2[a]; 1[b]	NR	5; 128[a]; 138[b]	1; 0.3-2[a]	
Incidental Inhalation-Powder	1[b]	NR	138[b]	1[c]	
Dermal Contact	2	NR	385	1-39.5	
Deodorant (underarm)	NR	NR	NR	NR	
Hair - Non-Coloring	NR	NR	50	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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2020 Glycerin Ethoxylates VCRP Data

CATEGORY	MAINTERM	COUNT
Glycereth-7; Total: 80		
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
Glycereth-12; Total: 6		
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
Glycereth-18; Total: 21		
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
Glycereth-20; Total: 3		
12C - Face and Neck (exc shave)	GLYCERETH-20	1
12F - Moisturizing	GLYCERETH-20	2
03A - Eyebrow Pencil	GLYCERETH-26	1
Glycereth-26; Total: 437		
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	27
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	14
12B - Depilatories	GLYCERETH-26	1
12C - Face and Neck (exc shave)	GLYCERETH-26	126
12D - Body and Hand (exc shave)	GLYCERETH-26	12
12F - Moisturizing	GLYCERETH-26	99
12G - Night	GLYCERETH-26	8
12H - Paste Masks (mud packs)	GLYCERETH-26	7
12I - Skin Fresheners	GLYCERETH-26	8
12J - Other Skin Care Preps	GLYCERETH-26	35
13B - Indoor Tanning Preparations	GLYCERETH-26	7
13C - Other Suntan Preparations	GLYCERETH-26	2

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: December 19, 2019

SUBJECT: Glycereth-12 and Glycereth-26 (more details on study summaries submitted April 23, 2019 memo 3)

AMA Laboratories, Inc. 2014. Summary of results: 100 human subject repeat insult patch test skin irritation/sensitization evaluation (occlusive patch) product containing 0.35% Glycereth-12.

Consumer Product Testing Co. 2016. Individual results: Repeated insult patch test (product containing 5% Glycereth-26.

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AMA LABORATORIES, INC.
216 Congers Road, Bldg. 1
New City, NY 10956 USA
(845) 634-4330
FAX. (845) 634-5565
www.amalabs.com

100 HUMAN SUBJECT REPEAT INSULT PATCH TEST
SKIN IRRITATION/SENSITIZATION EVALUATION
(Occlusive Patch)

AMA Ref. No.: [redacted] product containing

Date: June 2, 2014 0.35% Glycereth-12

Sponsor: [redacted]

1.0 Objective:

Consumer products or raw materials designed for consistent reapplication to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certain individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/sensitization potential if such exists.

2.0 Test Material:

2.1 Test Material Description:

On April 1, 2014 one test sample labeled Mascara [redacted] was received from [redacted] and assigned AMA Lab No. [redacted]

2.2 Handling:

Upon arrival at AMA Laboratories, Inc., the test material is assigned a unique laboratory code number and entered into a daily log identifying the lot number, sample description, sponsor, date received and tests requested.

Samples are retained for a period of three months beyond submission of final report unless otherwise specified by the sponsor or, if sample is known to be in support of governmental applications, representative retained samples are kept two years beyond final report submission.

Sample disposition is conducted in compliance with appropriate federal, state and local ordinances.

TABLE
SUMMARY OF RESULTS
(Occlusive Patch)

AMA Lab No.: N-4479
Client No.: Mascara [redacted]

No.	Subject ID	RACE	SEX	Response 1	2	3	4	5	6	7	8	9	Chall. 24 HR	48 HR	Score
1	00 0002	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
2	36 7970	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
3	38 8908	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
4	40 0533	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
5	42 8272	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
6	44 5103	C	F	0	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
7	44 7314	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
8	44 8790	C	F	0	0	0	0	0	0	0	0	0	0	0	0 0
9	44 9681	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
10	46 3788	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
11	50 2448	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
12	50 7536	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
13	52 4898	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
14	54 0548	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
15	54 2951	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
16	56 0875	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
17	56 1117	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
18	56 2799	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
19	56 6503	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
20	56 6523	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
21	56 9114	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
22	58 8637	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
23	60 0082	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
24	60 0162	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
25	60 0587	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
26	60 2360	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
27	60 3605	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
28	60 7979	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
29	62 0956	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
30	62 2435	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
31	62 5697	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
32	62 7114	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
33	64 0805	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
34	64 4610	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
35	64 9831	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
36	68 0458	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
37	70 2480	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
38	72 5980	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
39	73 6193	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
40	74 0600	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
41	74 1783	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
42	74 2192	C	M	0	0	0	0	0	Dc	Dc	Dc	Dc	Dc	Dc	N/A
43	74 4424	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
44	74 4514	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
45	74 7215	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
46	78 2670	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
47	78 8260	A	F	0	0	0	0	0	0	0	0	0	0	0	0.0
48	80 1527	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
49	80 8190	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
50	82 3297	A	M	0	0	0	0	0	0	0	0	0	0	0	0.0
51	82 6379	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
52	82 9684	C	F	0	0	0	0	0	0	0	0	0	0	0	0 0

TABLE (CONT'D)
SUMMARY OF RESULTS
(Occlusive Patch)

AMA Lab No.: N-4479
Client No.: Mascara [redacted]

No.	Subject ID	RACE	SEX	Response 1	2	3	4	5	6	7	8	9	Chall. 24 HR	Chall. 48 HR	Score
53	32 4178	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
54	40 1589	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
55	44 7255	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
56	44 8295	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
57	44 9509	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
58	48 0946	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
59	48 1642	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
60	48 2675	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
61	48 4541	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
62	50 1810	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
63	50 9982	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
64	52 2110	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
65	52 4017	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
66	52 6418	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
67	54 2855	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
68	54 7647	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
69	56 1236	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
70	56 1367	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
71	56 3659	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
72	56 5529	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
73	56 6301	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
74	56 9543	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
75	58 9750	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
76	60 3225	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
77	60 4516	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
78	60 7847	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
79	60 9466	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
80	62 0602	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
81	62 4269	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
82	64 2319	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
83	68 1609	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
84	68 3636	C	F	0	0	1	0	0	0	0	0	0	0	0	0.0
85	68 7601	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
86	70 2436	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
87	72 3555	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
88	74 7791	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
89	76 3053	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
90	76 7056	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
91	76 8434	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
92	80 0080	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
93	80 0847	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
94	80 3313	C	F	0	0	0	0	0	Dc	Dc	Dc	Dc	Dc	Dc	N/A
95	80 6056	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
96	80 7035	A	M	0	0	0	0	0	0	0	0	0	0	0	0.0
97	80 8499	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
98	82 7066	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
99	82 7228	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
100	82 7507	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
101	84 0266	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
102	84 4033	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
103	84 9903	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0

Evaluation Period:

This study was conducted from April 23, 2014 through May 30, 2014.

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Consumer Product Testing Co.

FINAL REPORT

CLIENT: [redacted]02

ATTENTION: [redacted]

TEST: Repeated Insult Patch Test
Protocol No.: CP-01.01S

TEST MATERIAL: [redacted] Mask [redacted] Lot: HW6109

product containing 5% Glycereth-26

EXPERIMENT REFERENCE NUMBER: C16-2973.04

Reviewed by: Richard R. Eisenberg, M.D.
Medical Director
Board Certified Dermatologist

Approved by: Michael Caswell, Ph.D., CCRA, CCRC
Vice President, Clinical Evaluations
24 Aug 2016

Approved by: Joy Frank, R.N.
Executive Vice President, Clinical Evaluations
8/25/16

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report nor the name of these Laboratories nor any member of its staff, may be used in connection with the advertising or sale of any product or process without written authorization.

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

Table 1
Panel #20160183

Individual Results

[redacted] Mask [redacted] Lot: [redacted]

Subject Number	Induction Phase									Virgin Challenge Site	
	Day1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal

[redacted]

Table 1
(continued)
Panel #20160183

Individual Results

[redacted] Mask [redacted] Lot: [redacted]

Subject Number	Day1*	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site Day 1*	Day 3
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	DID NOT COMPLETE STUDY							
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0[m]	0	0	0	0	0
50	0	0	0	0	0	0	0[m]	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal
m = Additional makeup day granted at the discretion of the clinic supervisor

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 16, 2020

SUBJECT: Glycereth-26

Food and Drug Research Laboratories Incorporated. 1973. Repeated insult patch test: Glycereth-26 (10% aqueous solution tested).

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

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Food and Drug Research Laboratories
INCORPORATED

Maurice Avenue at 58th Street
Maspeth, New York 11378
Telephone: TWining 4-0800
Cable: Foodlabs, New York

Industrial Biology Division
151 E. 10th Avenue, P.O. Box 424
Conshohocken, Pa. 19428
Telephone: (215) 825-0517

13 April 1973

Enclosed please find our reports to cover the repeated insult patch tests for the following materials:

[redacted] (raw ingredient), No. RM 0501 Glycereth-26

[redacted]

[redacted]

If you have any questions regarding these reports, please let me know. Thank you for this opportunity of being of service to you.

Sincerely yours,

INDUSTRIAL BIOLOGY DIVISION

Morris V. Shelanski, M.D., C.M.
Director

MVS:ak
Enclosures

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Food and Drug Research Laboratories
INCORPORATED

Maurice Avenue at 58th Street
Maspeth, New York 11378
Telephone: (212) 894-0500
Cable: Foodlabs, New York

Industrial Biology Division
151 E. 10th Avenue, P.O. Box 424
Conshohocken, Pa. 19428
Telephone: (215) 825-0517

Subject: Evaluation of Potential Hazards by Dermal Contact

April 12, 1973

Client:

Test Material: I. B. L. No.

[redacted]

Glycereth-26 I 0501 104-73

[redacted]

Description of Material:

I. B. L. No.	Description of Material	Tested As
[redacted]		
104-73	Clear liquid	10% aqueous solution
[redacted]		

Assay: Repeated Insult Patch Test

Purpose: To determine if the test material is capable of irritating the skin of humans under controlled test conditions; and, if so, to classify the test material as a primary irritant, fatiguing agent, and/or sensitizer on the basis of visible clinical responses.

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Subject: Evaluation of Potential Hazards by Dermal Contact

12 April 1973
I.B.L. Nos. 100-73 through 108-73

Client:

No. Subjects: 200 Human Volunteers

Panel No.: 287/73

Authorized: 15 December 1972 Received: 15 December 1972

Procedure: A group of 200 individuals who qualified were selected from a local population. The criteria for selecting these individuals were:

1. General well-being.
2. Absence of any skin disease which might be confused with skin reactions from the test material.
3. Willingness to cooperate.
4. Dependability and intelligence in following directions.
5. Reading, understanding, and signing an informed-consent contract. (In the case of minors, parental consent was obtained.)

Sites on the upper arm of each individual were designated for contact with the test material. A series of sixteen applications, each of twenty-four hours' duration, were scheduled to be carried out.

Lintine discs were moistened with the test material as supplied. The lintine disc was then placed on its predesignated site, covered, and sealed with overlapping strips of Blenderm tape. This cover was kept intact for twenty-four hours. At the end of twenty-four hours, the seal was broken and the patch removed. The skin sites were examined and gross changes, if present, were graded on a scale of 1 to 4. Absence of any visible changes was assigned a 0 value. After the patch was removed, the contact sites were rested for twenty-four hours. They were then re-examined to determine if any changes had occurred since the previous examination. If the contact sites manifested no changes, the test material was re-applied to the same site. If significant irritation (2+ or more) was observed, the investigator, at his discretion, had the option either of resting the individual or of applying the test material to a new site for the next contact period. This cycle was repeated in this manner on Mondays, Wednesdays, and Fridays. On weekends, a forty-eight-hour rest period was permitted between removal and re-application of the test material.

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Subject: Evaluation of Potential Hazards by Dermal Contact

12 April 1973
I. B. L. Nos. 100-73 through 108-73

Client:

Procedure: (Cont'd)

After the fifteenth application, the participants rested for two weeks before being challenged. The sites of contact used previously were challenged with the test material for twenty-four hours under occlusion. After removal, the contact site was examined immediately and following at intervals of twenty-four and forty-eight hours.

Results:

[redacted]

[redacted]

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Subject: Evaluation of Potential Hazards by Dermal Contact

12 April 1973
I. B. L. Nos. 100-73 through 108-73

Client:

Results: (Cont'd)

[redacted]

), No. RM 0501: Glycerin-20

1. Skin Changes Accompanying Application No. 1:

No visible skin changes signifying reaction to injury were observed in any of the 200 subjects.

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Subject: Evaluation of Potential Hazards by Dermal Contact

12 April 1973
I. B. L. Nos. 100-73 through 108-73

Client:

Results: (Cont'd)

t), No. RM 0501: Glycereth-26

2. Skin Changes Accompanying Application Nos. 2 through 15:

No visible skin changes signifying reaction to injury were observed in any of the 200 subjects.

3. Skin Changes Accompanying Challenge Application:

No visible skin changes signifying reaction to injury were observed in any of the 200 subjects.

[redacted]

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Subject: Evaluation of Potential Hazards by Dermal Contact

12 April 1973
I. B. L. Nos. 100-73 through 108-73

Client:

Conclusions:

[redacted]

No. RM 0501: Glycereth -26

Under the test conditions, [redacted] ingredient), No. RM 0501, did not produce any responses which were compatible with a diagnosis of primary irritancy, fatiguing, or hypersensitization.

[redacted]

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Subject: Evaluation of Potential Hazards by Dermal Contact

12 April 1973
I.B.L. Nos. 100-73 through 108-73

Client:

Conclusions: (Cont'd)

[redacted]

In the opinion of the investigator, the above materials may be considered safe to use in contact with the skin insofar as primary irritation, fatiguir or hypersensitization are concerned if the conditions of contact do not exceed those of the test procedure.

Insofar as sensitization is concerned, the extrapolation of these results to a general population is limited statistically by the number of test subjects. In this case, since 200 subjects were used, we may predict with 95% certainty that at least 98.17% of a general population will not be sensitized by this material.

INDUSTRIAL BIOLOGY DIVISION

MORRIS V. SHELANSKI, M.D., C.M.
Director

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Product Profile No. Raw Ingredient

TO: Dr. Yale Gressel DATE: 5/1/73

SUBJECT: Human Contact Allergy Testing

Glycereth-26

Formula No. RM 0501

has been tested on humans for contact sensitization potential by Food And Drug Research Labs, Conshohocken, Pa.*

Based on the results obtained, the above material did not produce any responses which were compatible with a diagnosis of allergic sensitization.

*See final report FDRL I.B.L. No. 104-73, dated April 12, 1973.

[redacted]

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Personal Care Products Council
Committed to Safety, Quality & Innovation

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: December 3, 2019

SUBJECT: Draft Tentative Report: Safety Assessment of Glycerin Ethoxylates as Used in Cosmetics (draft prepared for the December 2019 CIR Expert Panel meeting)

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

Introduction - In the Introduction, it is misleading to state that the identity of the material was not stated in the ECHA dossier when the Chemistry section states that the average ethoxylation value was between 1 and 6.5.

Impurities, Glycereth-26 - The physical chemical properties of Glycereth-26 should be presented in the Physical and Chemical Properties section (they are correctly included in Table 2) and not in the Impurities section.

Ocular Irritation, Glycereth-26; Summary - The fact that Glycereth-26 did not directly reduce MTT when cells were not present means that the assay was valid. The result of the assay was that the ET_{50} was greater than 4 hours (not irritating). The result of the assay, rather than the lack of a direct effect of Glycereth-26 on MTT should be reported in the Summary.

Ocular Irritation, Glycereth-26 - Rather than "mixed sexes" it would be more precise to state that rabbits of "both sexes" were used in the eye irritation studies.

Summary - The following sentence is not correct: "Both reviewed and read-across ingredients are polyethylene glycol ethers of glycerin." The read-across ingredients are propoxylated rather than ethoxylated, and propoxylated nitrilotriethanol is not a glycerin containing compound.

Table 2 - The impurities reported for Glycereth-26 do not belong in Table 2 Physical and Chemical Properties.

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