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

Status:	Draft Report for Panel Review
Release Date:	November 10, 2021
Panel Meeting Date:	December 6-7, 2021

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

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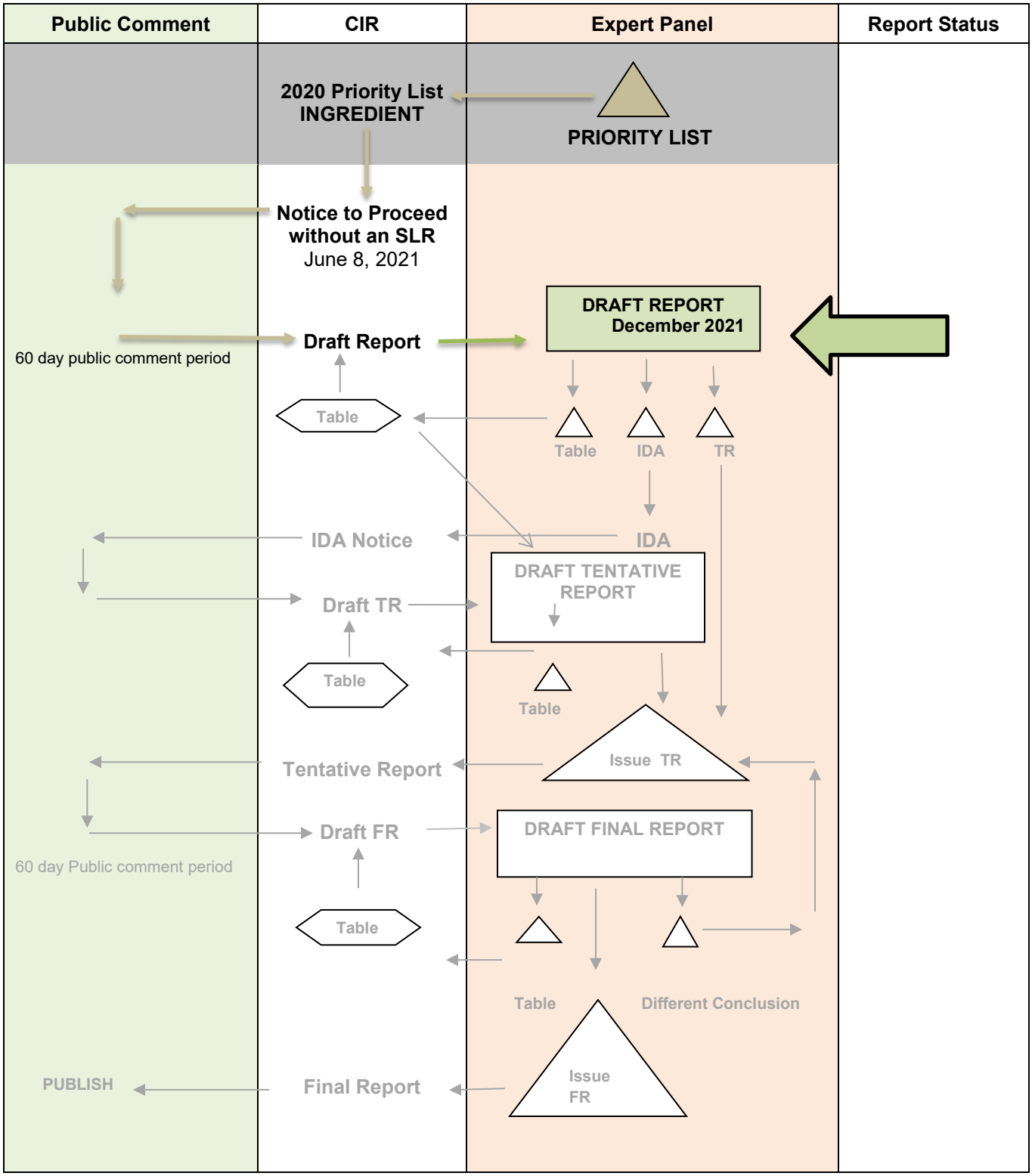
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Fatty Ester End-Capped Alkoxylates

MEETING December 2021



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: November 10, 2021
Subject: Safety Assessment of Fatty Ester End-Capped Alkoxylates as Used in Cosmetics

Enclosed is the Draft Report of the Safety Assessment of Fatty Ester End-Capped Alkoxylates as Used in Cosmetics. (It is identified as *report_FattyEsterAlkoxylates_122021* in the pdf document.) The Notice to Proceed (NTP) without the preparation of a Scientific Literature Review (SLR), of these 14 ingredients, was issued by CIR on June 8, 2021. These ingredients are reported to function mainly as surfactants – emulsifying agents, skin-conditioning agents – emollients, and skin-conditioning agents – miscellaneous in cosmetic formulations.

The Council provided concentration of use survey data (*data1_FattyEsterAlkoxylates_122021*), molecular weight, method of manufacturing, impurities, dermal penetration data, acute oral toxicity data, HRIPT data, and in vitro ocular data on PEG/PPG-8/3-Diisostearate (*data2_FattyEsterAlkoxylates_122021*). No comments on the NTP were received from the Council.

According to 2021 VCRP survey data (*VCRP_FattyEsterAlkoxylates_122021*), PEG/PPG-8/3 Diisostearate is reported to be used in 155 formulations, with most of them being in bath soaps and detergents. All other in-use ingredients in the VCRP are reported to be used in one or two formulations. The results of the concentration of use survey conducted by the Council indicate PEG-12 Glyceryl Dimyristate has the highest concentration of use in a leave-on formulation; it is used at up to 1.8% in body and hand products. No concentration of use was reported for PEG/PPG-8/3 Diisostearate. There are 10 ingredients not reported to be in use, according to both the VCRP and industry surveys.

Additional supporting documents for this report package include a flow chart (*flow_FattyEsterAlkoxylates_122021*), report history (*history_FattyEsterAlkoxylates_122021*), a search strategy (*strategy_FattyEsterAlkoxylates_122021*), and a data profile (*profile_FattyEsterAlkoxylates_122021*).

If no further data are needed to reach a conclusion of safety, the Panel should formulate a Discussion and issue a Tentative Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an Insufficient Data Announcement.

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Fatty Ester End-Capped Alkoxylates History

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

July 27, 2021 – Unpublished data received.

Fatty Ester End-Capped Alkoxylates Profile* – December 2021 – Christina Burnett

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies		
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports	Other
PEG/PPG-8/3 Diisostearate	X	X	X		X			X																X		X				
PEG-15 Butylene Glycol Diisostearate																														
PEG-10 Glyceryl Diisostearate																														
PEG-20 Glyceryl Diisostearate																														
PEG-30 Glyceryl Diisostearate																														
PEG-60 Glyceryl Diisostearate																														
PEG-12 Glyceryl Dimyristate	X																										X			X
PEG-12 Glyceryl Dioleate								X																						
PEG-3 Glyceryl Distearate	X																													
PEG-4 Glyceryl Distearate																														
PEG-12 Glyceryl Distearate	X						X	X																						
PEG-23 Glyceryl Distearate							X																							
PEG-4 Polyglyceryl-2 Distearate																														
PEG-15 Glyceryl Diisostearate																														

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

Fatty Ester End-Capped Alkoxylates

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
PEG/PPG-8/3 Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-3 Glyceryl Distearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-4 Glyceryl Distearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-4 Polyglyceryl-2 Distearate	86360-24-9 or 72828-11-6	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-10 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-12 Glyceryl Dimyristate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-12 Glyceryl Dioleate		√	21CFR176.210? 21CFR177.2800	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-12 Glyceryl Distearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-15 Butylene Glycol Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-15 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-20 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-23 Glyceryl Distearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-30 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PEG-60 Glyceryl Diisostearate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy

PubMed – 0 relevant hits using the following search terms:

86360-24-9 or 72828-11-6
PEG/PPG-8/3 Diisostearate
PEG-3 Glyceryl Distearate
PEG-4 Glyceryl Distearate
PEG-4 Polyglyceryl-2 Distearate
PEG-10 Glyceryl Diisostearate
PEG-12 Glyceryl Dimyristate -
PEG-12 Glyceryl Dioleate
PEG-12 Glyceryl Distearate
PEG-15 Butylene Glycol Diisostearate
PEG-15 Glyceryl Diisostearate
PEG-20 Glyceryl Diisostearate
PEG-23 Glyceryl Distearate
PEG-30 Glyceryl Diisostearate
PEG-60 Glyceryl Diisostearate

Google Scholar using search terms used for PubMed got the following results:
PEG-12 Glyceryl Myristate – 5 potentially relevant hits
PEG-12 Glyceryl Distearate – 3 potentially relevant hits
PEG-23 Glyceryl Distearate – 2 potentially relevant hits

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

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

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

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ABBREVIATIONS

CIR = Cosmetic Ingredient Review
Council = Personal Care Products Council
ET_{50} = exposure time that induces a 50% reduction in viability
FDA = Food and Drug Administration
Panel = Expert Panel for Cosmetic Ingredient Safety
PEG = polyethylene glycol
PPG = polypropylene glycol
VCRP = Voluntary Cosmetic Registration Program
wINCI *Dictionary* = web-based *International Cosmetic Ingredient Dictionary and Handbook*

INTRODUCTION

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

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

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

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

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

CHEMISTRY

Definition and Structure

The definitions and structures of the fatty ester end-capped alkoxylate ingredients included in this review are provided in Table 1. Most of the fatty ester end-capped alkoxylates, presented in this safety assessment, each comprise a glycerin core which is PEGylated (i.e. substituted with multiple ethylene glycol repeat units) and end-capped with fatty acid esters, on 2 of the 3 termini (i.e. glycerin is tridentate (a triol), wherein all 3 alcohol functional groups are PEGylated ending in a terminal that may be esterified). Two of the 3 alcohols of glycerin are primary (i.e. the carbon the alcohol is attached to is only attached to 1 other carbon) and the remaining 1 is secondary (i.e. the carbon the alcohol is attached to is attached to 2 other carbons). The resulting PEG chains on those 2 primary alcohol functional groups, are the ones to be esterified. The number of units (e.g., "10" in PEG-Glyceryl Diisostearate) is representative of an average number of ethylene glycol repeat units (i.e., PEG-10 Glyceryl Diisostearate contains some PEG-9 and PEG-11 glyceryl diisostearate, in addition to PEG-10). In addition to the ethylene glycol repeat unit, PEG/PPG-8/3 Diisostearate also has polypropylene glycol (PPG) repeat units. For example, PEG-20 Glyceryl Diisostearate comprises a glycerin core that is PEGylated across those 3 alcohol functional groups and esterified on two of the resulting PEG chains with isostearic acid (Figure 1).

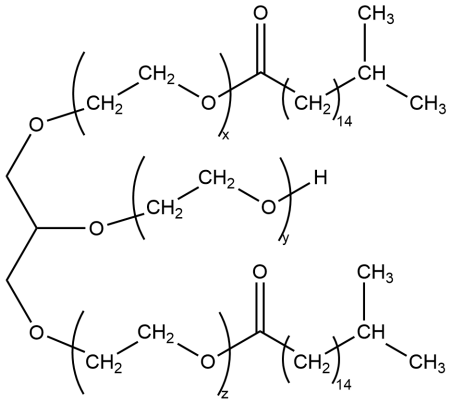


Figure 1. PEG-20 Glyceryl Diisostearate, wherein x + y + z = 20

Chemical Properties

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

No further chemical properties data were not found in the published literature, nor were additional unpublished data submitted.

Method of Manufacture

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

However, most of the ingredients in this report comprise a glycerin core, and are manufactured rather differently. While manufacturing methods specific to these ingredients were neither found in the published literature nor submitted as unpublished data, ingredients with structures such as these are typically synthesized from the appropriate glyceryl diester (i.e. no PEG yet).[6] In such methods, the PEGylation effectually results in transesterification, or direct insertion of the PEG chain between the glycerin molecule and the fatty acid. For example, PEG-20 Glyceryl Diisostearate could be synthesized by PEGylation of Glyceryl Diisostearate. The 20 equivalents of ethylene oxide (the "20" in "PEG-20") are thus distributed across the 3 termini: some at the free alcohol functional group of the glycerin core, and the rest inserted in the 2 isostearic esters.

Impurities

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

No further impurities data were not found in the published literature, nor were additional unpublished data submitted.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US FDA and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA 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.

According to 2021 VCRP survey data, PEG/PPG-8/3 Diisostearate is reported to be used in 155 formulations, with most of them being in bath soaps and detergents (Table 3).[11] All other in-use ingredients in the VCRP are reported to be used in one or two formulations. The results of the concentration of use survey conducted by the Council in 2019-2020 indicate PEG-12 Glyceryl Dimyristate has the highest concentration of use in a leave-on formulation; it is used at up to 1.8% in body and hand products.[12] No concentration of use was reported for PEG/PPG-8/3 Diisostearate. The ingredients not in use according to the VCRP and industry survey are listed in Table 4.

Fatty ester end-capped alkoxylates may be used in cosmetic formulations that may be used near the eye or come into contact with mucous membranes. For example, PEG-12 Glyceryl is reported to be used in an eye lotion at 0.7% and PEG/PPG-8/3 Diisostearate is reported to be used in bubble baths and bath soaps and detergents (concentrations not reported).[11,12] Additionally, some of the fatty ester end-capped alkoxylates are used in cosmetic sprays and could possibly be inhaled; for example, PEG-12 Glyceryl Dimyristate is reported to be used at 1% in hair sprays.[12] 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.[13,14] 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.[15,16]

All of the fatty ester end-capped alkoxylates named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[17]

Non-Cosmetic

PEG-12 Glyceryl Dioleate, PEG-12 Glyceryl Distearate, PEG-12 Glyceryl Dimyristate, and PEG-23 Glyceryl Distearate have been studied for use as oral and topical drug carriers and/or solubilizers in pharmaceutical and nutraceutical products.[9,18-21]

TOXICOKINETIC STUDIES

Dermal Penetration

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

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

PEG/PPG-8/3 Diisostearate

A supplier reported that the LD_{50} for PEG/PPG-8/3 Diisostearate in an acute oral rat study was greater than 2000 mg/kg.[22] Data was from initial reacted materials. No further details were provided.

Short-Term Toxicity Studies

Dermal

PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate

PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate were used in a base cream that was used as a placebo and as part of a pharmaceutical test compound in a dermal efficacy study in groups of 7 female Wistar rats.[18] The placebo and test compounds were applied to damaged skin twice daily for up to 15 d. The amount of PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate in the base cream was not reported. No mortalities were observed during the testing period in either the placebo or treatment groups.

Oral

PEG-12 Glyceryl Dioleate and PEG-12 Glyceryl Distearate

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

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

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

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

GENOTOXICITY STUDIES

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

CARCINOGENICITY STUDIES

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

DERMAL IRRITATION AND SENSITIZATION

Sensitization

Human

PEG/PPG-8/3 Diisostearate

The dermal irritation and sensitization potential of a material identified as PEG/PPG-8/3 Diisostearate was studied in 114 subjects.[23] The subjects were induced with four 24-h applications of the test material (150 µl, as supplied) for 3 wk on the left upper back, followed by a week hiatus prior to four, 24-h challenge patches on naïve sites. Patches were occlusive devices with a 2 cm^2 absorbent pad centered on the adhesive-coated surface of a 4 cm^2 water-impermeable plastic film. No clinically significant adverse effects were detected during the induction or challenge phases. The test material was determined to be non-irritating and non-sensitizing.

OCULAR IRRITATION STUDIES

In Vitro

PEG/PPG-8/3 Diisostearate

A supplier has reported that PEG/PPG-8/3 Diisostearate in 10% corn oil was non-irritating in an EpiOcular™ tissue model.[22] The exposure time that induces a 50% reduction in viability (ET_{50}) was greater than 256 min, and the estimated Draize score was 0. No further details were provided.

Animal

PEG-12 Glyceryl Dimyristate

The ocular irritation potential of a topical drug formulation containing PEG-12 Glyceryl Dimyristate (100 mg; 10% w/v) was assessed in 32 male New Zealand White rabbits.[21] The rabbits received 1 drop (50 µl) of the test formulation in the right eye, every 2 h, 6 times/d (number of treatment days not reported). Control eyes received a saline balanced placebo solution. Clinical eye evaluations were then carried out under anesthesia at 10, 30, and 60 min, 6, 12, and 24 h, and 7 and 14 d post treatment. Four rabbits were killed after each clinical evaluation to obtain ocular tissue and fluids. No major findings or adverse effects were reported during the study. A Draize score of 1 was reported 30 min post-dosing, which resolved by the end of the 14-d observation period. No details regarding the scoring parameter that achieved this score at this observation point were provided. No increase in intraocular pressure was observed in any of the animals.

CLINICAL STUDIES

Ocular

PEG-12 Glyceryl Dimyristate

The tolerability, safety, and efficacy of a topical formulation containing PEG-12 Glyceryl Dimyristate (100 mg; 10% w/v) was evaluated in one eye of 12 patients with refractory pseudophakic cystoid macular edema.[19] The patients received one drop of the test material every 2 h for 90 d or until best-corrected visual acuity was achieved. No ocular surface abnormalities or adverse events were observed.

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

The same formulation containing PEG-12 Glyceryl Dimyristate was also used to assess biologic activity in 4 patients with diabetic macular edema.[21] The patients received topical doses (1 drop) in one eye 6 times/d for 6 mo. Follow-up ophthalmic clinical evaluations were performed monthly. No systemic or severe adverse effects were reported. None of the patients showed intraocular hypertension.

SUMMARY

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

According to 2021 VCRP survey data, PEG/PPG-8/3 Diisostearate is reported to be used in 155 formulations, with most of them being in bath soaps and detergents. All other in-use ingredients in the VCRP are reported to be used in one or two formulations. The results of the concentration of use survey conducted by the Council indicate PEG-12 Glyceryl Dimyristate has the highest concentration of use in a leave-on formulation; it is used at up to 1.8% in body and hand products. No concentration of use was reported for PEG/PPG-8/3 Diisostearate.

A supplier reported that the LD_{50} for PEG/PPG-8/3 Diisostearate in an acute oral rat study was greater than 2000 mg/kg. In a short-term toxicity study, PEG-12 Glyceryl Distearate and PEG-23 Glyceryl Distearate, used in a base cream for pharmaceutical efficacy testing, caused no mortalities in female rats when applied twice daily for up to 15 d. PEG-12 Glyceryl Dioleate and PEG-12 Glyceryl Distearate at up to 1000 mg/kg in corn oil caused no mortalities or clinical signs of toxicity in a 28-d oral toxicity study in male and female rats. No abnormalities were observed at necropsy or in histopathological examination.

In a repeated insult patch test in 114 subjects, PEG/PPG-8/3-Diisostearate tested neat was non-irritating and non-sensitizing. PEG/PPG-8/3-Diisostearate in corn oil was determined to be non-irritating in an in vitro ocular study. In male rabbits, PEG-12 Glyceryl Dimyristate (100 mg; 10% w/v) was not an ocular irritant in a topical drug formulation where the

rabbits were treated 6 times/d for several days. The same formulation was tested for tolerability, safety, and efficacy in healthy human volunteers and in patients with macular edema: no abnormalities or adverse events were observed.

Minimal data on chemical properties, impurities, and toxicokinetics were made available via unpublished data submissions and no data were found in the published literature. No DART studies, genotoxicity studies, or carcinogenicity studies were found in the published literature; and unpublished data were not submitted. No relevant toxicokinetic studies were found in the published literature.

DISCUSSION

To be determined.

CONCLUSION

To be determined.

TABLES

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

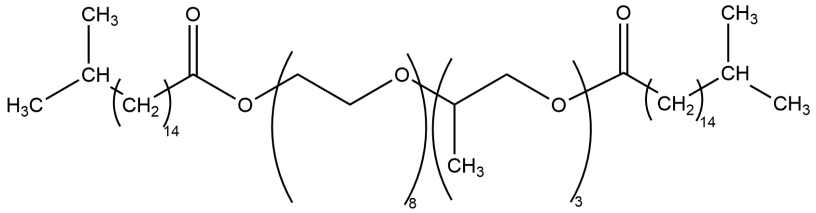
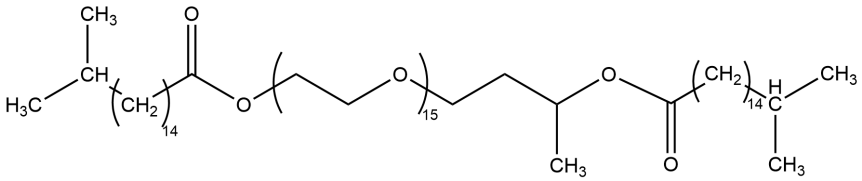
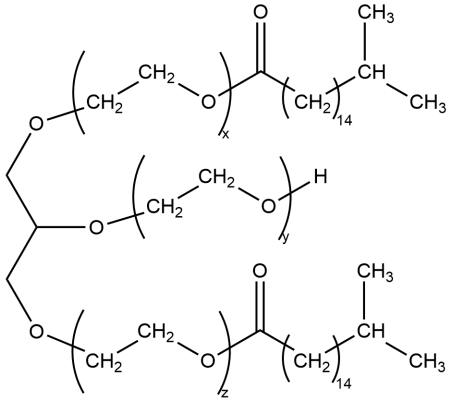
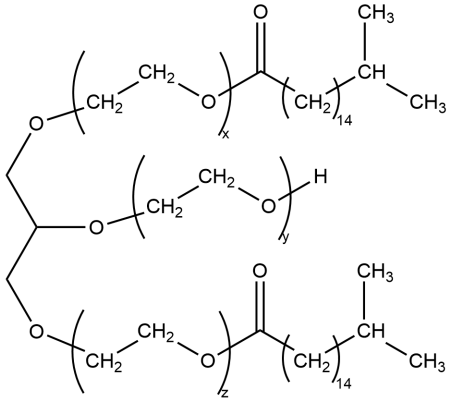
Ingredient & CAS No.	Definition	Function(s)
PEG/PPG-8/3 Diisostearate	PEG/PPG-8/3 Diisostearate is the polyethylene glycol ether of the propoxylated diester of isostearic acid containing an average ethoxylation value of 8 and propoxylation value of 3. (*Drawn block-style; connectivity may be different.*)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

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

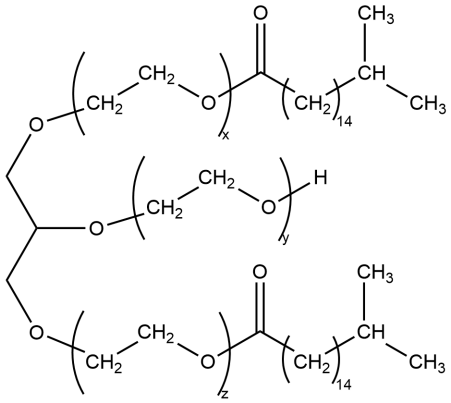
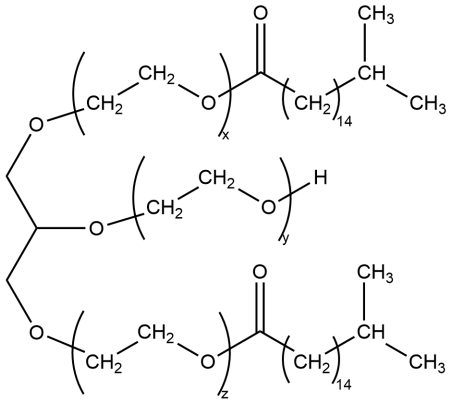
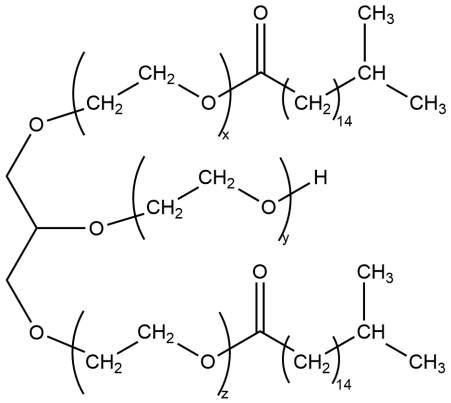
Ingredient & CAS No.	Definition	Function(s)
PEG-20 Glyceryl Diisostearate	PEG-20 Glyceryl Diisostearate is the polyethylene glycol ether of glyceryl diisostearate that conforms generally to the structure:  where x+y+z has an average value of 20.	Surfactant – Emulsifying Agent
PEG-30 Glyceryl Diisostearate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

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

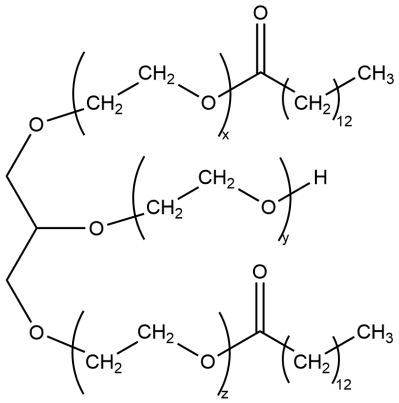
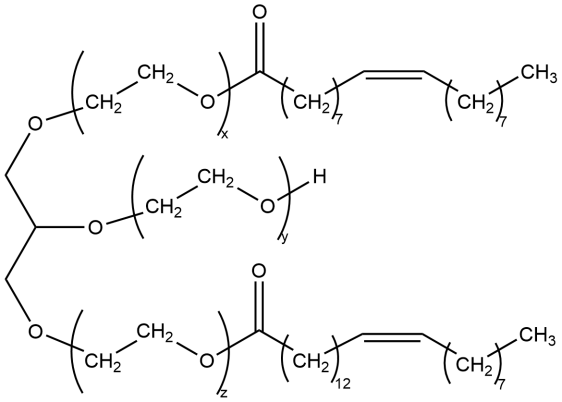
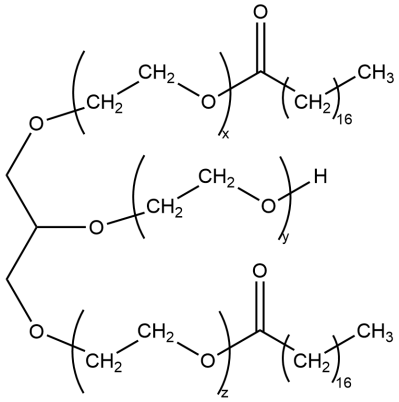
Ingredient & CAS No.	Definition	Function(s)
PEG-12 Glyceryl Dimyristate	PEG-12 Glyceryl Dimyristate is the polyethylene glycol ether of glyceryl dimyristate that conforms generally to the structure:  where x+y+z has an average value of 12.	Skin-Conditioning Agent – Misc.
PEG-12 Glyceryl Dioleate	PEG-12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

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

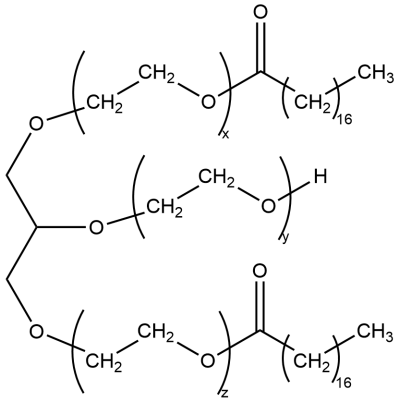
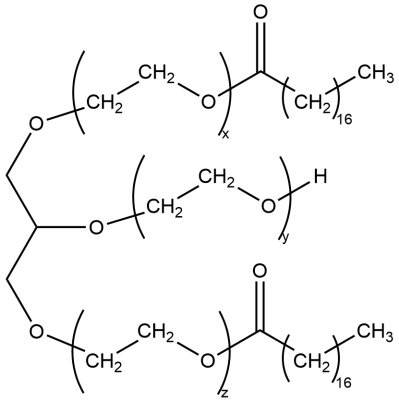
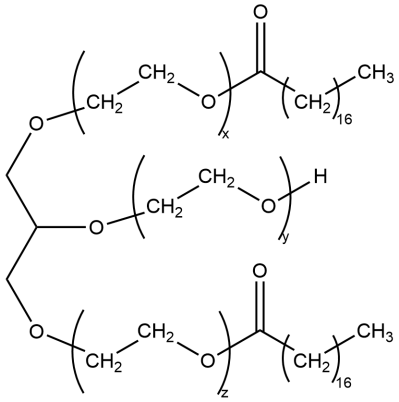
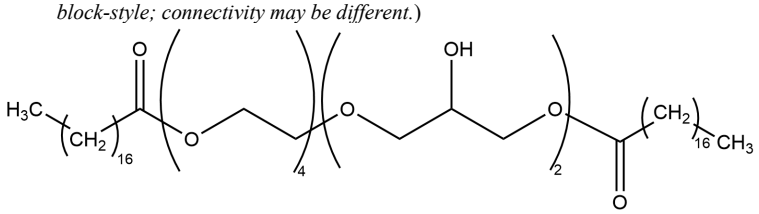
Ingredient & CAS No.	Definition	Function(s)
PEG-4 Glyceryl Distearate	PEG-4 Glyceryl Distearate is the polyethylene glycol ether of glyceryl distearate that conforms generally to the structure:  where x+y+z has an average value or 4.	Skin-Conditioning Agent – Emollient
PEG-12 Glyceryl Distearate	PEG-12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

Table 2. Relevant related safety assessments and Panel conclusions.

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

Table 3. Frequency (2021) [11] and concentration (2019-2020)[12] of use according to duration and exposure.

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	PEG/PPG-8/3 Diisostearate		**PEG-3 Glyceryl Distearate**	
Totals*	**155**	**NR**	**2**	**NR**
Duration of Use				
Leave-On	*NR*	*NR*	*1*	*NR*
Rinse Off	*152*	*NR*	*1*	*NR*
Diluted for (Bath) Use	*3*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1[a]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	155	NR	1	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	155	NR	NR	NR
Baby Products	NR	NR	NR	NR
	PEG-12 Glyceryl Dimyristate		**PEG-12 Glyceryl Distearate**	
Totals*	**2**	**0.7-1.8**	**1**	**1**
Duration of Use				
Leave-On	*2*	*0.7-1.8*	*1*	*1*
Rinse-Off	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	0.7	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	2[a]	1	NR	NR
Incidental Inhalation-Powder	NR	1.8[b]	NR	NR
Dermal Contact	1	0.7-1.8	1	1
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	1	1	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – not reported

Table 4. Ingredients not reported in use.[11,12]

PEG-15 Butylene Glycol Diisostearate
PEG-10 Glyceryl Diisostearate
PEG-20 Glyceryl Diisostearate
PEG-30 Glyceryl Diisostearate
PEG-60 Glyceryl Diisostearate
PEG-12 Glyceryl Dioleate
PEG-4 Glyceryl Distearate
PEG-23 Glyceryl Distearate
PEG-4 Polyglyceryl-2 Distearate
PEG-15 Glyceryl Diisostearate

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Concentration of use by FDA Product Category - PEG/PPG-8/3 Diisostearate and Related Ingredients*

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

Ingredient	Product Category	Maximum Concentration of Use
PEG-12 Glyceryl Dimyristate	Eye lotions	0.7%
PEG-12 Glyceryl Dimyristate	Hair sprays Aerosol	1%
PEG-12 Glyceryl Dimyristate	Body and hand products Not spray	1.8%
PEG-12 Glyceryl Distearate	Night products Not spray	1%

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

Information collected 2019-2020
Table prepared: February 26, 2020

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: July 27, 2021

SUBJECT: PEG/PPG-8/3 Diisostearate

Lubrizol Advanced Materials, Inc.. 2021. Summary Information – Hydramol PGPD Ester (PEG/PPG-8/3 Diisostearate).

Lubrizol Advanced Materials, Inc. 2021. Hydramol™ PGPD (PEG/PPG-8/3 Diisostearate) Process Flow Diagram.

Lubrizol Advanced Materials, Inc. 2021. Toxicology Summary Hydramol™ PGPD (PEG/PPG-8/3 Diisostearate).

Product Investigations, Inc. 2007. Determination of the irritating and sensitizing propensities of EX-1025 (Hydramol™ PGPD (PEG/PPG-8/3 Diisostearate)) on human skin.

July 2021

Lubrizol Advanced Materials

Summary Information – Hydramol PGPD Ester (PEG/PPG-8/3 Diisostearate)

Recommended use concentrations (based on product performance and cost): 1-10%

Chemistry

Method of manufacture: See attached process flow diagram and reaction description

Molecular weight: Approximately 1630 Daltons

The product supplied is >95% PEG/PPG-8/3-Diisostearate

Expected impurities: <5.0% isostearic acid

Bioavailability and Toxicity Data

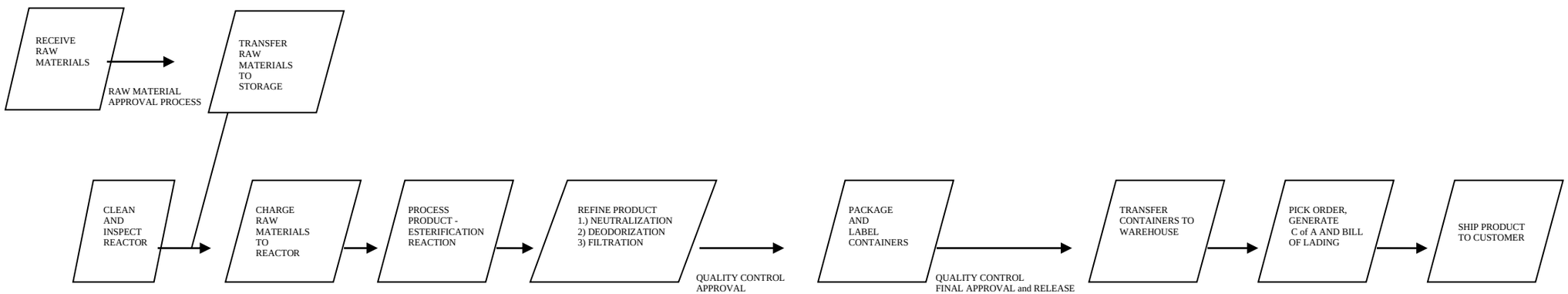
Due to its molecular weight, PEG/PPG-8/3-Diisostearate is not expected to penetrate the skin or be bioavailable.

General toxicity data: See attached toxicology summary

HRIPT: Ingredient tested undiluted (see attached study)

Lubrizol Advanced Materials, Inc.
9911 Brecksville Road
Cleveland, Ohio 44141-3247
216.447.5000

Hydramol™ PGPD Process Flow Diagram



Lubrizol Advanced Materials, Inc.
9911 Brecksville Road
Cleveland, Ohio 44141-3247
216.447.5000

Hydramol™ PGPD REACTION SUMMARY

Reaction of Fatty Acids with Alcohols: Hydramol PGPD is manufactured by the condensation of fatty acids (isostearic acid) with alcohols (polyethylene glycol/polypropylene glycol). The reaction is catalyzed by acidic catalysts. The by-product water is removed with the aid of heat and vacuum. No solvents are used in the manufacturing process.

Fatty Acid — Alcohol — Fatty Ester — Water

Lubrizol

TOXICOLOGY SUMMARY

HYDRAMOL™ PGPD

INCI NAME: PEG/PPG-8/3 DIISOSTEARATE

TEST	CONCLUSION
Oral Toxicity – Rats[1]	LD50 > 2000 mg/kg
EpiOcular Tissue Model (In-Vitro) - (10% in corn oil)	ET50: > 256 minutes Zero Draize score (estimated) Non-Irritating
Skin Irritation – Human[2]	Non-Irritating
Skin Sensitization – Human[2]	Non-Sensitizing

[1] Data from initial reacted materials
[2]114 subjects, product tested as supplied

PRODUCT INVESTIGATIONS, INC.

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REPORT: PII Nº 22094

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF EX-1025 ON HUMAN SKIN

PREPARED FOR

Noveon, Inc.
9911 Brecksville Road
Cleveland, OH 44141-3247

29 May 2007

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ABSTRACT

A sample identified as **EX-1025** was received by Product Investigations on 22 March, 2007. The sample was submitted by **Noveon, Inc.** for a patch test to determine the sample's skin-irritating and sensitizing potentials.

To accomplish this, Product Investigations, using a procedure based on that described in PROTOCOL -ISM 059.NOV, initiated a study on more than one-hundred qualified volunteers.

The regimen called for four twenty-four hour applications of the sample conducted seriatim during each of Weeks Nos. 1, 2, 3, and 7 on assigned skin sites on the right upper arm of each subject.

Examinations of the contacted skin and grading of its condition were conducted within moments after devices containing the sample were removed.

Weeks 1, 2, 3, and 4 formed the Initial or Induction Phase of the regimen. Data were acquired on one-hundred-and-nineteen subjects during this phase. No clinically significant adverse effects were detected on any of the subjects during this phase.

The Challenge or Diagnostic Phase of the regimen was conducted during Week #5. Data were acquired on one hundred-and-fourteen subjects during this phase. No clinically significant adverse effects were detected on any of the subjects during this phase.

On the basis of the above-cited observations, **EX-1025** was found to be devoid of clinically significant skin-irritating and skin-sensitizing propensities that can be detected under the conditions of this patch test procedure.

The investigator concluded that the data do not contraindicate usages of **EX-1025** entailing conditions of contact commensurate with or less stringent than those that prevailed during the course of this study.

COMPLIANCE WITH GOOD QUALITY ASSURANCE STANDARDS

In my review of the data I have found no discrepancies between the information presented in this report and the records that were kept during the conduct of this study.

All information and raw data relating to this study will be retained in the study file and will be archived on the premises of Product Investigations, Inc. for a period of not less than seven (7) years.

5/30/07

Date

Samuel J. Charles III
Director of Quality Assurance

Determination of the Irritating and Sensitizing Propensities of EX-1025 on Human Skin

1.00 OBJECTIVES:

.01 To identify and characterize the skin-damaging propensities that **EX-1025** induced to exercise under the conditions of this intensified patch test procedure.

.02 To adjudge whether the exercise of such propensities under the patch test conditions contraindicates the kind of skin contact that would be occasioned during the appropriate use of the product.

2.00 SPONSOR:

Noveon, Inc.
9911 Brecksville Road
Cleveland, OH 44141-3247

Project Director: Karen Jordan
Health, Toxicology & Product Safety

3.00 AUTHORIZATION:

Letter from Karen Jordan dated 6 March 2007

4.00 FEATURES OF THE METHOD:

.01 An intensified version of the Repeated Insult Patch Test regimen was conducted under double blind conditions on a panel consisting of more than one-hundred subjects at the outset.

.02 The regimen schedule entailed four 24-hour applications of the test sample conducted seriatim during each of weeks one, two, and three, and four 24-hour applications conducted seriatim on a naive site during the challenge week.

.03 The contacted skin was examined after each application to assess and grade the elicited effect.

.04 During the initial phase the responses that were in evidence after removal of the sample were used to determine whether applications were to be continued on the same site, switched to a new site, or terminated.

5.00 STUDY PRODUCT:

Type of Product:	Cosmetic Ingredient
Sponsor Identification:	**EX-1025**
INCI	PEG/PEG-8/3 Diisostearate
CAS No.:	0220326-00-1
Date of Receipt:	22 March, 2007
Description:	Clear Yellow Oil
Form used in study:	As supplied
PI Nº	22094

6.00 GOOD CLINICAL PRACTICES:

The study was conducted in compliance with the standards of good clinical practices generally applicable for the protection of the privileges and well-being of individuals who participate in patch test procedures.

7.00 SITE OF STUDY:

Product Investigations, Inc.
142 North Ninth Street, Suite 16
Modesto, CA 95350

STAFF:

Mecical Director:	Morris V. Shelanski, MDCM
Dir. Derm. Services:.	Joseph E. Nicholson III
Dermatologist:	Clinton E. Prescott, MD
Technician:	Lisa Cortez
Quality Assurance. :	Samuel J. Charles III

8.00 DATES OF STUDY:

Started:	9 April, 2007
Completed:	14 May, 2007

9.00 SELECTION OF SUBJECTS:

.01 RECRUITING:

Individuals interested in participating were recruited from local areas by telephone, flyers, and direct contact.

.02 INFORMED CONSENT:

An interested party had to obtain a reasonable understanding of the contents of an informed consent document containing the following information and sign it willingly before she/he was engaged as a subject.

a. The number of subjects that were to be enrolled in the study;
b. The intended use of the product;
c. The reasons for testing the product;
d. The regimen for the test procedures;
e. The different adverse effects that have been known to occur in patch test participants;
f. The different ways that participation may be detrimental to a subject's health or quality of life;
g. That not all detrimental effects could be foreseen and made known at the time the informed consent was presented for the prospective subject's signature;
h. The commitments which a subject was asked to make to ensure that meaningful data would be generated;
i. The rights endowed on a subject for her/his protection;
j. The avenues of recourse available to a subject who believes that she/he has been misused; and
k. The considerations a subject was entitled to receive and the conditions for receiving them.

.03 DETERMINATION OF ELIGIBILITY:

An individual's eligibility was determined by checking her/his medical history and the answers given in response to specific questions in the informed consent document against the criteria listed below.

a. Inclusion Criteria: Satisfaction of all the following items was obligatory for enrolment:

1) The candidate was at least eighteen years old, and
2) agreed to comply fully with the scheduled study regimen, and
3) expressed awareness that a participant would incur risks that would affect her/his well-being, and
4) denied that the stipend had induced her/him to volunteer against her/his better judgement, and
5) had assured the interviewer that she/he had read the informed consent form and had no questions about the informed consent's contents that had not been answered to her/his satisfaction, and
6) had signed the consent form willingly and without reservation.

b. Exclusion Criteria: Any one of the following items was cause for rejection:

1) The candidate had an illness that contraindicated participation; or
2) a condition that rendered the skin unsuitable for use in this study; or
3) was using dosages of medications that could alter the skin's tolerance; or
4) had a documented history of intolerance to the category of products submitted for study; or
5) was a female who was pregnant or was breast feeding an infant.

.04 PANEL INFORMATION:

a. Dedication: The subjects in Panel No. 07027 were engaged concomitantly in the studies of products submitted by sponsors other than Noveon, Inc.

b. Demographics:

SEX	Number	Age Range
Female	87	18 - 81
Male	33	18 - 63

10.00 SITE INFORMATION:

.01 The test material was assigned the four sites on Band #3 on the left side of the back of each subject, to wit:

O3	N3	M3	L3

a. L3, was designated the first site that was to be exposed to the test material.
b. M3, the site immediately lateral to L3, was designated as the first alternate site for use during the initial phase.
c. N3, the site immediately lateral to M3, was designated as the second alternate site for use during the initial phase.
d. O3, was the site designated to receive the challenge applications.

.02 IDENTIFICATION OF A CONTACT SITE:

The skin around the site in current use was freshly marked at each visit. The marks made it possible for the technicians to locate the site for grading, etc., in the absence of the device or other distinguishing features.

11.00 PATCHING DEVICES:

.01 TYPE OF DEVICE:

Occlusive patching devices were used to convey the material to the skin and to maintain it on its assigned site on each subject. These devices consisted of a 2 cm x 2 cm absorbent pad centered on the adhesive-coated surface of a 4 cm x 4 cm water-impermeable plastic film.

.02 PREPARATION OF A PATCHING DEVICE:

The webril pad of a patching device was infused with 150 µl of the test material.

.03 APPLYING A PATCHING DEVICE:

a. Each device was positioned on its designated site on a subject with the moistened webril pad in contact with the skin.
b. Firm pressure was applied to the backing of the device to effect intimate contact of the material with the skin and to bond the adhesive of the flanges fast to the surrounding skin.

.04 REMOVING A PATCHING DEVICE AND ITS CONTENTS:

When a subject returned to the clinic, a technician peeled the device and material off as gently as was feasible to prepare the subject for examination.

12.00 DATA ACQUISITION:

.01 GRADING PROCEDURE:

a. When a subject arrived, the technician examined the subject's back to ascertain whether the patch was present and on its proper site.
b. The technician removed the patching device and examined the skin.
   1) If no adverse effect was detected, the technician entered "0" in the space provided in the subject's record.
   2) If an adverse effect was detected, the technician entered a grade indicating her assessment of the response's intensity into the subject's record.
c. The subject was sent into the patching room with a note informing the patching technician of the grade assigned to the perceived effect. The grade was to be used by the patching technician to determine if the product was to be reapplied on the site in current use, applied on the next unused alternate site, or not applied altogether.
d. The patching technician examined the contact site to ascertain independently whether the site should or should not be used again. If she disagreed with the first technician's assessment, the application was held in abeyance until the issue could be resolved with the help of the supervisor and/or the investigator.
e. The supervisor or the investigator was called in when a disagreement had to be resolved but also to validate the technicians assessment
   1) When she assigns a grade of 2 or higher to a response, and
   2) When she assigns a grade that is two or more points lower than the previous day's grade.

.02 CRITERIA FOR GRADING THE INTENSITY OF A RESPONSE:

Grades were assigned in accordance with the following criteria to designate the intensity of the effects elicited on the skin by the material.

STAGES OF INFLAMMATION	VISIBLE CHANGE	CLINICAL SIGNIFICANCE	GRADE
ABSENT, or sub-clinical changes that are not perceptible on the skin surface	**None**	Indicates the absence of a gross inflammation-eliciting propensity.	0
VASCULAR DILATATION	**Redness**, faint; may not involve all of contact area	Indicates a very weak to weak inflammation-eliciting propensity.	1
	Redness, faint to moderate, all of contact area involved	Indicates a mild to moderate inflammation-eliciting propensity.	2
	Redness, intense, all of contact area involved	Indicates a strong inflammation-eliciting propensity, probably irritation.	3
VASCULAR LEAKAGE WITH INFILTRATION and/or INDURATION:	**Redness**, plus **edema** and/or **papules**.	Indicates a strong inflammation-eliciting propensity, possibly sensitization.	4
	Redness, plus **vesicles**, **blisters** or **bullae**	"	5
	Redness plus	"	6

.03 CRITERIA FOR CHANGING A CONTACT SITE:

a. Applications are continued on the initial contact site unless a response rated 3 or higher is elicited. When that happens, applications are discontinued on the affected site.

b. If a response of 3 or higher is elicited on or before Monday of Week 2 -
- applications are stopped and not resumed for the remainder of the study if it is deemed to be a recall response, i.e., one indicative of a sensitized status that antedates the study.
- applications are resumed on an alternate site on Monday of Week 2 if it is not deemed to be a recall response.

c. If a response of 3 or higher is detected on Tuesday , Wednesday, Thursday or Friday of Week 2, applications are resumed on an alternate site on Monday of Week 3.

d. If a response of 3 or higher is detected on Monday of Week 3, applications are switched immediately to an alternate site.

e. If a response of 3 or higher is detected on or after Tuesday of Week 3, applications are discontinued and not resumed for the remainder of the Initial Phase.

f. Applications are made for four consecutive days on the challenge site unless a response of 3 or higher is elicited. When that happens, applications are terminated.

13.00 SCHEDULE OF PROCEDURES:

.01 APPLICATIONS:

a. Initial/Induction Phase:

Week #1: Monday, Tuesday, Wednesday, Thursday.
Week #2: Monday, Tuesday, Wednesday, Thursday.
Week #3: Monday, Tuesday, Wednesday, Thursday.
Week #4: Hiatus, Make-up

b. Challenge/Diagnostic Phase:

Week #5: Monday, Tuesday, Wednesday, Thursday.

.02 EXAMINATIONS:

a. Initial/Induction Phase:

Week #1: Monday (Baseline), Tuesday, Wednesday, Thursday, Friday.
Week #2: Monday, Tuesday, Wednesday, Thursday, Friday.
Week #3: Monday, Tuesday, Wednesday, Thursday, Friday.
Week#4: Monday, as needed.

b. Challenge/Diagnostic Phase:

Week #5: Monday (Baseline), Tuesday, Wednesday, Thursday, Friday.
Week #6: Monday, etc. as needed.

14.00 STANDARD INSTRUCTIONS BEFORE INTERRUPTIONS IN THE REGIMEN:

.01 WEEKENDS:

Before being dismissed for the weekends during Weeks 1, 2, and 3, subjects were given instructions to notify the investigator without delay if the skin showed any of the following changes:

i) a substantial increase in the intensity of an already-elicited response,
ii) the spread of a response beyond the area of contact, or
iii) the outbreak of a rash on a hitherto unaffected site.

.02 INTERMEDIATE PHASE:

The same instructions were also given to each subject before she/he was dismissed for the hiatus in procedure before the challenge phase.

15.00 REGIMEN:

.01 INITIAL PHASE - WEEK #1 of the INITIAL PHASE:

MONDAY:

1) When a subject presented herself/himself at the clinic, the skin on which the assigned contact sites were to be situated was ascertained to be in fit condition for receipt of the product before applications were begun.
2) A freshly-prepared patching device containing the test material was applied on its assigned initial contact site.
3) The skin around the device was marked.
4) The subject was dismissed with instructions to return on Wednesday.

TUESDAY, WEDNESDAY, THURSDAY:

1) When a subject returned, the marks identifying the location of the contact site were reinforced.
2) The device and test material were removed by a technician.
3) The contact site was examined; skin status was graded; the grade was recorded.
4) A freshly-prepared patching device was applied on the site in current use.
5) The subject was dismissed with instructions to return on the following day.

FRIDAY:

1) When a subject returned, the marks identifying the location of the contact site were reinforced.
2) The device and test material were removed by a technician.
3) The contact site was examined; skin status was graded; the grade was recorded.
4) A freshly-prepared patching device was applied on the site in current use.
4) The subject was instructed to remove the patch at home on Saturday, to note the condition of the site, and to return on the following Monday.

SATURDAY AND SUNDAY:

No in clinic procedures were scheduled on these days.

.02 WEEKS #2 and #3 of the INITIAL PHASE:

MONDAY:

1) When a subject returned, the marks identifying the location of the contact site were reinforced.
2) The site was examined; skin status was graded; the grade was recorded.
3) A freshly-prepared patching device was applied on an appropriate site.
4) The subject was dismissed with instructions to return on Tuesday.

TUESDAY, WEDNESDAY, AND THURSDAY:

1) When a subject returned, the marks identifying the location of the contact site were reinforced.
2) The device and test material were removed by a technician.
3) The contact site was examined; skin status was graded; the grade was recorded.
4) A freshly-prepared patching device was applied on the site in current use.
5) The subject was dismissed with instructions to return on the following day.

FRIDAY:

1) When a subject returned, the marks identifying the location of the contact site were reinforced.
2) The device and test material were removed by a technician.
3) The contact site was examined; skin status was graded; the grade was recorded.
4) The subject was given the standard instructions, and dismissed until the following Monday.

SATURDAY and SUNDAY:

No procedures were scheduled on these days.

.02 INTERMEDIATE PHASE

WEEK 4: Make-up phase as needed

MONDAY:

1) When a subject returned, the marks identifying the location of the site in current use were reinforced.
2) The contact site was examined; site status was graded; the grade was recorded.
3) All subjects dismissed until Monday of the Challenge week.

.03 CHALLENGE PHASE

WEEK #5:

MONDAY

1) When a subject returned, all previously used contact sites were examined.
2) If no persistent or delayed response that might have necessitated postponing the challenge applications was present, a freshly-prepared device was applied on a naive contact site.
3) The skin around the device was marked.
5) The subject was dismissed with instructions to return on the following day.

TUESDAY, WEDNESDAY, THURSDAY:

1) When a subject returned, the marks identifying the location of the site were reinforced.
2) The device and material were removed by a technician.
3) The contact site was examined; skin status was graded; the grade was recorded.
   a) Absent a response ≥3, a freshly-prepared patching device was applied on the same site.
   b) If a response ≥3 was present, applications were stopped.
4) The subject was dismissed with instructions to return on the following day.

FRIDAY:

1) When a subject returned, the marks identifying the location of the site were reinforced.
2) The device and material were removed by a technician.
3) The contact site was examined; skin status was graded; the grade was recorded.
4) If a reaction was present, the subject was dismissed with instructions to return on the following Monday.
5) Absent a need for treatment or continued observation, the subject was discharged with instructions to notify the investigator without delay should a response reappear on a previously involved site or break out on a hitherto unaffected one.

.04 FOLLOW-UP PHASE

WEEK #6:
WEEK #7:

After the exit examination that was scheduled for the beginning of Week 6 was conducted, the subjects were given the balance of that week and all of Week 9 as a period to communicate any information that they believed was relevant to the effects of their exposure to the material as well as to express a need for treatment of persistent or newly-occurring responses.

Deviations in Procedure:

None were necessary.

16.00 TABULATION OF CYCLES COMPLETED:

Table Ia.

INITIAL (INDUCTION) PHASE - (WEEKS 1, 2, 3 AND 4)					
NUMBER OF AECs REQUIRED	NO DATA ACQUIRED		DATA ACQUIRED		
	DROP OUTS	EXCUSED	EXCUSED	NON-COMPLIANT	COMPLIANT
10	1 Subject	0 subjects	0 subjects	4 subjects	115 subjects

Table Ib.

CHALLENGE (DIAGNOSTIC) PHASE - (WEEK 5)					
NUMBER OF AECs REQUIRED	NO DATA ACQUIRED		DATA ACQUIRED		
	Drop outs	Excused	Excused	Non-compliant	Compliant
2	6 subjects	0 subjects	0 subjects	0 subjects	114 subjects

17.00 SUMMARY OF RESULTS:

Table II: MAXIMUM ASSIGNED GRADES PER INDIVIDUAL PARTICIPANT (MAGPIPs)

GRADE	TYPE OF RESPONSE	INDUCTION	CHALLENGE
0	NO VISIBLE CHANGE	119 SUBJECTS	114 SUBJECTS
1	FAINT REDNESS, UNDEFINED BORDER	0 "	0 "
2	MODERATE REDNESS, DEFINED BORDER	0 "	0 "
3	INTENSE REDNESS	0 "	0 "
4	REDNESS + DEFINITE EDEMA and/or PAPULES	0 "	0 "
	NUMBER OF RESPONDERS	0 SUBJECTS	0 SUBJECTS
	NUMBER OF SUBJECTS PATCHED	120 "	114 "
	NUMBER OF SUBJECTS PROVIDING DATA	119 "	114 "
	NUMBER PROVIDING NO DATA	1 "	6 "

Table III: WEEKLY INCIDENCE OF RESPONSES

	WEEK #1			WEEK #2			WEEK #3			WEEK #4			WEEK #5			#6
GRADE	M	T	W-F	M	T	W-F	M	T	W-F	M	T	W-F	M	T	W-F	M
1	B	0	0	0	0	0	0	0	0	0	0	0	B	0	0	-
2	B	0	0	0	0	0	0	0	0	0	0	0	B	0	0	-
3	B	0	0	0	0	0	0	0	0	0	0	0	B	0	0	-
4	B	0	0	0	0	0	0	0	0	0	0	0	B	0	0	-
TOTAL		0	0	0	0	0	0	0	0	0	0	0		0	0	-

18.00 SIGNIFICANCE OF THE RESPONSES:

.01 INITIAL/INDUCTION PHASE:

No responses were noted on any of the 119 subjects who participated in all or part of the induction phase of the study. The absence of responses characterize the product as one which is devoid of clinically significant skin-irritating propensities.

.02 CHALLENGE PHASE:

No responses were noted on any of the 114 subjects who participated in all or part of the challenge phase of the study. The absence of responses characterize the product as one which is devoid of clinically significant skin-sensitizing propensities.

.03 FOLLOW-UP PHASE:

The investigator received no communications from any of the subjects that provided a basis for altering his decision concerning the potential hazard presented by the product.

.04 GLOBAL:

Under the conditions prevailing in this patch test study, the product was found to be incapable of eliciting clinically significant skin damage on any of the more that one hundred individuals concerning whom data were acquired.

19.00 CLINICAL RELEVANCE:

.01 The inability of the material to elicit substantial and persistent adverse changes suffices to characterize the product as one devoid of skin-damaging propensities that can be detected under the regimen used in this study. This characterization can be expressed with a high level of confidence because the regimen has proven itself to be one that affords products ample time and opportunity to exercise any latent propensities for eliciting gross skin changes indicative of irritation and/or sensitization.

.02 If the real-life use of this material entails non-occlusive contact or occlusive contact of less than twenty-four hours in duration, one may anticipate with a high level of confidence that the risk of skin damage that will be associated with the use of this material will be lower than that which can be extrapolated from the data generated in this study.

20.00 CONCLUSIONS:

The data do not contraindicate exposure of the skin to the product represented by the sample identified as **EX-1025** for usages entailing repeated applications under conditions commensurate with or less stringent than those that prevailed during the course of this study.

PRODUCT INVESTIGATIONS, INC.

May 30, 2007
Date

Joseph E. Nicholson III
Director of Clinical Services

2021 FDA VCRP Raw Data

PEG/PPG-8/3 DIISOSTEARATE	Bubble Baths	3
PEG/PPG-8/3 DIISOSTEARATE	Bath Soaps and Detergents	152
PEG-3 GLYCERYL DISTEARATE	Shampoos (non-coloring)	1
PEG-3 GLYCERYL DISTEARATE	Moisturizing	1
PEG-12 GLYCERYL DIMYRISTATE	Tonics, Dressings, and Other Hair Grooming Aids	1
PEG-12 GLYCERYL DIMYRISTATE	Moisturizing	1
PEG-12 GLYCERYL DISTEARATE	Other Skin Care Preps	1