Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	May 19, 2023
Panel Meeting Date:	June 12-13, 2023

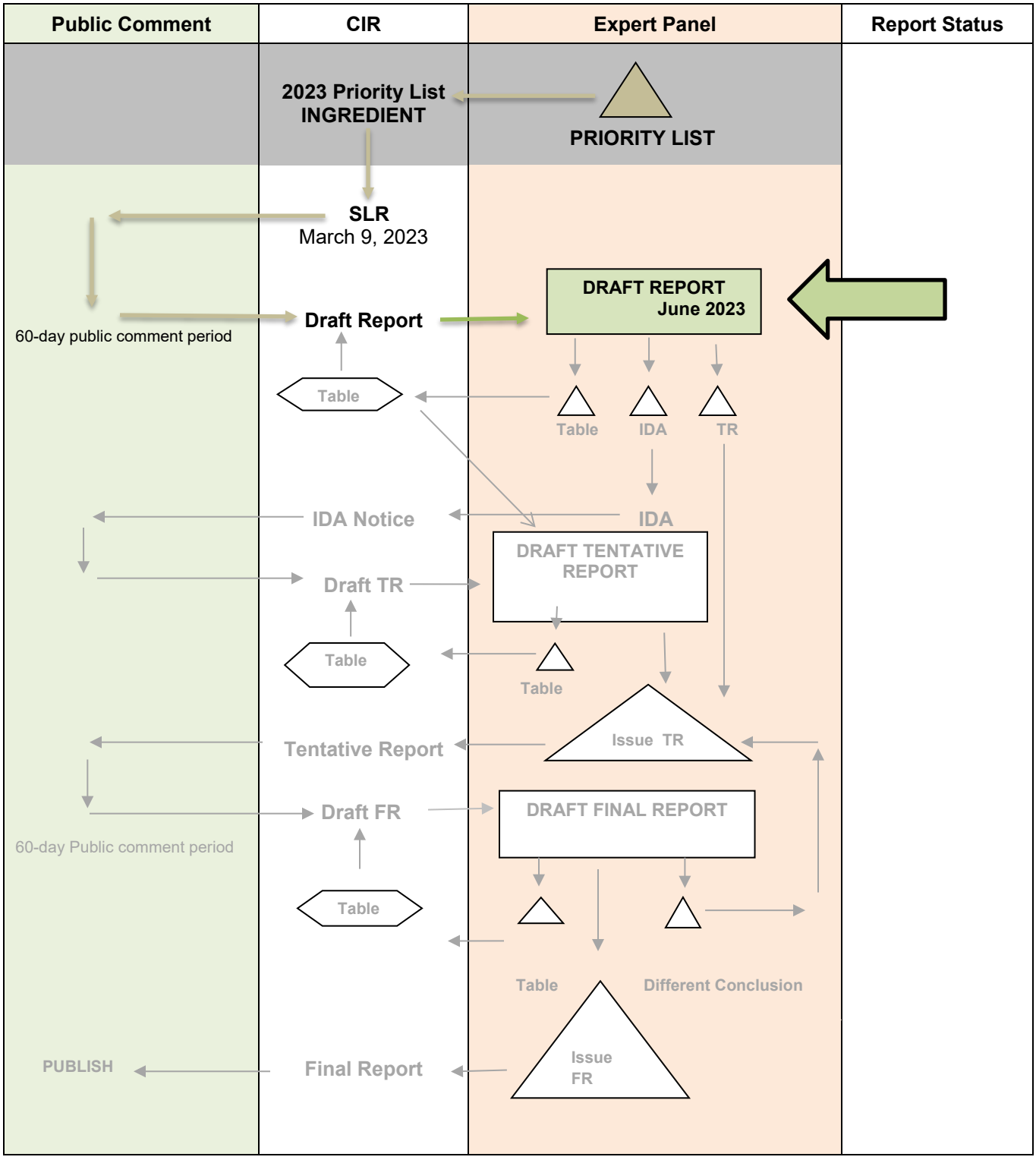
The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Preethi Raj, M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651
cirinfo@cir-safety.org

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Polyglycerins

MEETING June 2023



Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst/Writer, CIR
Date: May 19, 2023
Subject: Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics

Enclosed is the Draft Report of the Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics (identified as *report_Polyglycerins_062023* in the pdf). This is the first time the Panel is seeing a safety assessment of these 4 cosmetic ingredients. A Scientific Literature Review (SLR) was announced on March 9, 2023.

The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of glycerin; in 2019, a final report was published with the conclusion that glycerin is safe as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment. The full report is available on the CIR website (https://www.cir-safety.org/ingredients).

Data for repeated dose toxicity, developmental and reproductive toxicity, and carcinogenicity studies were not found for these ingredients. Of note, the European Chemicals Agency (ECHA) dossiers for these polyglycerins use studies on glycerin and polyglycerol polyricinoleate as read-across sources to address the repeated dose toxicity, developmental and reproductive toxicity, and carcinogenicity endpoints for ingredients in this report. ***Would the Expert Panel like to adopt a similar approach and use such read-across data (which would need to be added), or to state that no data was identified for these endpoints ?***

Comments on the SLR (*PCPCcomments_Polyglycerins_062023*) that were received from the Council have been addressed, and follow this memo. A comments response checklist is also included (*response-PCPCcomments_Polyglycerins_062023*).

The following documents are also included in the package, for your review:

- 2022 concentration of use data (*data_Polyglycerins_062023*)
- a flow chart (*flow_Polyglycerins_062023*)
- ingredient history (*history_Polyglycerins_062023*)
- search strategy (*search_Polyglycerins_062023*)
- data profile (*dataprofile_Polyglycerins_062023*)

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data are deemed insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 23, 2023

SUBJECT: Scientific Literature Review: Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics (release date: March 9, 2023)

The Personal Care Products Council respectfully submits the following comments on the Scientific Literature Review Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics.

Developmental and Reproductive Toxicity Studies – In this section, it would be helpful to state that the ECHA dossiers used read-across from studies on glycerin and polyglyceryl polyricinoleate to address the developmental and reproductive toxicity endpoint. The Expert Panel can then decide if they would like to use a similar approach, or just state that no data for this endpoint were identified.

Dermal Irritation and Sensitization – Please delete the word "similar" from "In a similar guinea pig maximization test…" as this study is presented after an LLNA not another maximization test. It would be helpful if the concentrations used in the injection induction exposures for all of the guinea pig maximization studies were stated in the text.

Summary – From the following: "Based on the radiolabeled test article found in the CO_2, urine, and carcass…" please delete "ed test article" as the "test article" is not in CO_2. Only the radioactivity (^{14}C) is in CO_2.

Table 2 – The units associated with Vapor Density (mmHg @ 20 ºC) are not correct. Reference 5 was consulted. The ECHA dossier states the Vapor Pressure using two types of units. The value 1.81×10^{-5} should be Pa (Pascal) and the value 1.36×10^{-7} should be mmHg @20 ºC (but called Vapor Pressure not Vapor Density).

Table 6, Irritation, Human – For the study of Diglycerin in 33 subjects, it would be helpful to state that the test sample was applied to the crooked side of the upper arm.

Table 6, Sensitization, Animal – Since all of the guinea pig maximization tests were done following OECD TG 406, it is not necessary to say "Similar procedure to maximization tests described above." The procedures were all the same.

Table 7 – The Procedure column of the first-row states "As described above" – there is nothing above the first row.

Diglycerin and Polyglycerins - June 12-13, 2023 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: March 23, 2023 (comments received on SLR posted March 9, 2023)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Developmental and Reproductive Toxicity Studies -State that the ECHA dossiers used read-across from studies on glycerin and polyglycerol polyricinoleate to address this endpoint. Allow the Expert Panel to decide on their approach.	-	✓
2	Dermal Irritation and Sensitization -delete the word 'similar', as an LLNA is presented after a GPMT -state the injection induction exposures for all GPMTs in the text	- deleted - have added/revised	
3	Summary -delete "ed test article" as the test article is not in CO_2	- deleted	
4	Table 2 - correct the units associated with Vapor Density (in ECHA dossier, two types of units are used for Vapor Pressure). - 1.81×10^{-5} is in Pa and 1.36×10^{-7} should be mmHg @ 20 °C (but called Vapor Pressure not Vapor Density)	- have corrected (also removed Vapor Density)	
5	Table 6, Irritation, Human - for clinical study testing Diglycerin in 33 subjects, state that the test sample was applied to the crooked side of the upper arm	- stated	
6	Table 6, Sensitization, Animal - Since all of the GPMTs were done following OECD TG 406, it is not necessary to say "similar procedure to maximization tests described above."	- Have deleted	
7	Table 7 - The Procedure column of the first row states "As described above", when there is nothing above the first row (correct).	- Have corrected	

CIR History of:

Diglycerin and Polyglycerins

July 2022

-Concentration of use data submitted by Council

February 2023

-Updated frequency of use data received from the VCRP program

March 2023

-SLR posted on CIR website

-Comments on SLR received from Council

June 2023

-A Draft Report is being presented to the Panel.

Diglycerin and Polyglycerins Data Profile* – June 12-13, 2023 – Writer, 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/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
Diglycerin	X	X	X	X				X							X					X	X		X				X		
Polyglycerin-3	X		X	X		X		X							X					X	X		X				X		
Polyglycerin-6	X			X											X												X		
Polyglycerin-10	X			X																									

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

Diglycerin and Polyglycerins

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Diglycerin	25618-55-7 59113-36-9	✓*	✓	NR	NR	NR	NR	NR	✓	✓ LM: 5/5/2021	NR	NR	✓*	✓*	✓*	NR	
Polyglycerin-3	25618-55-7 56090-54-1	✓*	✓*	NR	NR	NR	NR	NR	✓	✓ LM: 4/12/2018	NR	NR	✓*	✓*	✓*	NR	
Polyglycerin-6	36675-34-0	✓*	✓*	NR	NR	NR	NR	NR	NR	✓*	NR	NR	✓*	NR	✓*	NR	
Polyglycerin-10	9041-07-0	✓*	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓*	NR	✓*	NR	

✓- data available; ✓* - present in database, but not relevant; LM – last modified/updated; NR – not reported

Search Strategy

[*total # of hits / # hits that were useful*]

Diglycerin – 9430/0
Diglycerin cosmetic safety – 5/0

PubMed search updated on 04/13/2023
((((((((((((((((((((((((diglycerin) OR (25618-55-7)) OR (59113-36-9)) OR (Propanediol, Oxybis)) OR (diglycerin 801)) OR (diglycerin S)) OR (diglycerol)) OR (polyglycerin-3)) OR (56090-54-1)) OR (triglycerin)) OR (triglycerol)) OR (polycast 3)) OR (polyglycerin 03P)) OR (polyglycerol-3)) OR (polyglycerin-6)) OR (hexaglycerin)) OR (hexaglycerol)) OR (polyglycerin 06P)) OR (polyglycerin-10)) OR (9041-07-0)) OR (decaglycerin)) OR (decaglycerol)) OR (polyglycerine 10PS)) – 720/0

-AND toxicity – 70/0
-AND cosmetic safety – 1/0
- AND oral toxicity – 1/0
-AND genotoxicity – 3/0
-AND mutagenicity – 0/0
-AND carcinogenicity – 7/0
-AND dermal irritation – 0/0
-AND dermal sensitization – 0/0
Google search
Polyglycerin toxicokinetics
Polyglycerin toxicokinetic absorption – 74/0
Polyglycerin toxicokinetic distribution – 63/0
Polyglycerin toxicokinetic metabolism – 62/0
Polyglycerin toxicokinetic excretion – 79/0
Synthetic manufacture polyglycerin – 112/2
Cyclic vs linear glycerins – 5,040,000/4

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
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- 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/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- 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
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- 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) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: May 19, 2023
Panel Meeting Date: June 12-13, 2023

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.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Preethi Raj, M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651
cirinfo@cir-safety.org

ABBREVIATIONS

ANS	Food Additives and Nutrient Sources added to Food
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
CO_2	carbon dioxide
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
DMSO	dimethyl sulfoxide
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
FCA	Freund's Complete Adjuvant
FDA	Food and Drug Administration
LLNA	local lymph node assay
LD_{50}	median lethal dose
NA	not applicable
NR	not reported
NS	not specified
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
R_f	retention factor
RPMI	Roswell Park Memorial Institute
SI	stimulation index
SLS	sodium lauryl sulfate
TLC	thin layer chromatography
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program
wINCI; *Dictionary*	web-based *International Cosmetic Ingredient Dictionary and Handbook*

INTRODUCTION

This assessment reviews the safety of Diglycerin, Polyglycerin-3, Polyglycerin-6, and Polyglycerin-10 as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all 4 of these ingredients are reported to function in cosmetics as skin-conditioning agents (Table 1).[1]

These ingredients are being reviewed together because they are polymers of glycerin. Diglycerin is a dimer comprised of two glycerin units, and the number of glycerin units contained in a molecule is denoted in the numeric suffix for the remaining ingredients.

The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of glycerin. In 2019, the Panel published a final report with the conclusion that glycerin is safe as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment.[2] The 2019 report on the safety of glycerin is 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 extensive search of the world's literature; the search was last conducted April 2023. 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 found on the European Chemicals Agency (ECHA) website.[3-5] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited. The ECHA dossiers were prepared for ingredients with the CAS No. 25618-55-7 (a generic CAS No. for several ingredients, including Diglycerin and Polyglycerin-3),[3,4] and CAS No. 59113-36-9 (Diglycerin).[5] According to several studies obtained from the ECHA dossiers, the test material is a polyglycerol mixture; the proportion of each ingredient included in the mixture is identified in parentheses.

CHEMISTRY

Definition and Structure

The ingredients named in this report are polymers of glycerin, a polyhydric alcohol.[1] (See Figure 1.) However, as the greatest number of repeat units for this group of ingredients is 10 (for Polyglycerin-10), the term "oligomers" may be more appropriate.

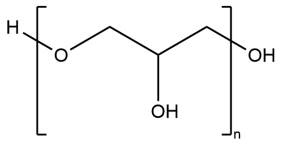


Figure 1. Polyglycerins, wherein n equals the number of glycerin residues. For example, Diglycerin is when n equals 2, and Polyglycerin-3 is when n is 3.

The definitions of the ingredients included in this review are provided in Table 1. These ingredients are polyols, which contain 3 or more hydroxyl groups per molecule.[1] Diglycerin and Polyglycerin-3 are identified by the ingredient-specific CAS Nos. 59113-36-9 and 56090-54-1, respectively, and both are also identified by the generic CAS No. 25618-55-7. Polyglycerin-6 is identified by the CAS No. 36675-34-0.

Chemical Properties

Diglycerin and Polyglycerin-3 are viscous, colorless to slight yellow liquids at room temperature; Diglycerin has a density of 1.28 g/ml and Polyglycerin has a specific gravity of 1.29.[3-5] Chemical properties of the ingredients included in the report are presented in Table 2.

Method of Manufacture

The following methods of manufacture are general to the production of polyglycerins, and it is unknown whether these are used in the manufacture of cosmetic ingredients. Polymers of glycerin can exist in linear, cyclic, or hyperbranched (dendritic) forms; however, the ingredients herein appear to be linear polyglycerins, which can be prepared from protected glycidol derivatives (glycidyl eithers) via oxyanionic ring-opening polymerization, followed by acidic deprotection of the acetal protecting group.[6] The most commonly used monomers for the synthesis of linear polyglycerins are: trimethylsilyl glycidyl ether, ethoxyethyl glycidyl ether, *t*-butyl glycidyl ether, or isopropylidene glyceryl glycidyl ether. In a cationic polymerization method, glycidol may be polymerized by citric acid, which acts as the proton donor and initiator, under ambient conditions.[7] Condensation polymerization may also be used to produce polyglycerins via acid or base catalysis.[8,9]

Diglycerin

In a method describing the manufacture of Diglycerin, epichlorohydrin is hydrolyzed via alkaline catalysis to produce glycidol. Glycidol is then reacted with glycerol or residual epichlorohydrin to produce Diglycerin.[9]

Impurities

Diglycerin and Polyglycerin-3 are reported to be produced at 99.8 and 100% purity, respectively.[3-5] Polyglycerins, such as Diglycerin and Polyglycerin-3, can contain monomers, oligomers, or cyclic and branched components.[6] Purified glycerol (industrial standards require 85% purity) tends to be utilized in the polymerization process.[8] In an industrial manufacturing process, glycidol produced during the hydrolysis of epichlorohydrin was then reacted with glycerol or nonconverted epichlorohydrin to create Diglycerin.[9] After removal of the residual glycerol and water, the resulting product was distilled, yielding 90% linear Diglycerin, with some residual glycerol and Polyglycerin-3.[9]

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, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 VCRP survey data, Diglycerin is reported to be used in 222 formulations and Polyglycerin-3 is reported to be used in 221 formulations (Table 3).[10] The results of the concentration of use survey conducted by the Council in 2022 indicate Diglycerin has the highest concentration of use; it is used at up to 28% in skin cleansing products.[11] The highest concentration of use reported for products resulting in leave-on dermal exposure is 5% Diglycerin in face and neck products.

A few of these ingredients are reported to be used in products that may lead to incidental ocular exposure and to incidental ingestion. For example, Diglycerin is reported to be used at up to 3% in eye lotions, and it is used at up to 3.6% in lipstick formulations.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[12]

Non-Cosmetic

In 2013, the European Food Safety Authority (EFSA) Panel on Food Contact Materials, Enzymes, Flavorings, and Processing Aids concluded that polyglycerol is safe to be used as a plasticizer in food contact materials (all food types and at room temperature and below) at a maximum concentration of 6.5% w/w in polymer blends of aliphatic-aromatic polyesters.[13] Polyglycerols are used to produce other cross- and co-linked polymers which are utilized in various biomedical applications, such as drug delivery, bone regeneration, and tissue engineering and scaffolding.[14]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Polyglycerin-3

Polyglycerin-3 may be too hydrophilic to cross the lipid-rich environment of the stratum corneum.[3] Due to its relatively low molecular weight (~240 g/mol) and high water solubility (> 1000 g/l), it is expected that Polyglycerin-3 will be absorbed in the gastrointestinal tract through aqueous pores.[3] However, the hydrophilic character of the major components (log P_{ow} -3.3) will limit this passive diffusion. Furthermore, once absorbed, the extracellular concentration of Polyglycerin-3 is expected to be higher than the intracellular concentration. For risk assessment purposes, the oral absorption of Polyglycerin-3 is assumed to be 100%.

It is unlikely for Polyglycerin-3 to reach the nasopharyngeal, tracheobronchial, or pulmonary regions of the lungs, due to its low vapor pressure (6.76×10^{-6} Pa).[3] If Polyglycerin-3 were to reach the tracheobronchial region, it may be retained within the mucous and subsequently absorbed through aqueous pores.

Animal

Oral

Polyglycerin-3 and Polyglycerin-10

Groups of 4 male Sprague-Dawley rats received either 1% [^{14}C]-labeled-Polyglycerin-3 or 1% [^{14}C]-labeled-Polyglycerin-10, in a liquid diet (6 – 8 g) containing sucrose, milk solids, vitamins, salt, water, and fat, via gavage.[15] Each animal was cannulated (thoracic duct) prior to being fed and placed in an individual metabolism chamber; one group was not cannulated, for comparison. At the end of the experimental period (51 h), urine, feces, respired carbon dioxide (CO_2), gastrointestinal tract, and carcass contents were sampled and evaluated. No controls were used and radioactivity was measured in lymph, CO_2, feces, and urine. Radio-labelled metabolites excreted in the urine were analyzed via thin layer chromatography (TLC). Based on radioactivity found in the CO_2, urine, and carcass, it was assumed that > 90% of Polyglycerin-3 and approximately 40% of Polyglycerin-10 was absorbed. The amounts of detected radioactivity were the following for Polyglycerin-3 and Polyglycerin-10, in non-cannulated rats, respectively, in: expired CO_2 (2.1 and 4.2%), urine (88.3 and 34.1%), feces (5.5 and 23.9%), gastrointestinal content (2.9 and 35.2%), and in the carcass (1.2 and 5.3%). For the cannulated animals, only a small amount of radioactivity was detected in the lymph; 69.5 and 20.2% Polyglycerin-3 was excreted in the urine and feces, respectively, while 45.4 and 34% Polyglycerin-10 was excreted in the urine and feces, respectively. The radioactive compound excreted in the urine of the rats had the same retention factor ($R_f = 0.47$) as the solvent used in the TLC analysis; therefore, it was concluded that Polyglycerin-3 was not metabolized by the rat (a similar conclusion was reached for other linear polyglycerols of higher molecular weight, such as Polyglycerin-10).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute oral toxicity studies summarized below can be found in Table 4.

The acute oral LD_{50} values for 20 and 25% Diglycerin, in water, were reported to be > 2000 mg/kg bw and > 5000 mg/kg bw, respectively, in two separate studies performed in rats in accordance with Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 401.[3,5] Male and female Wistar rats were administered a single, undiluted, 2000 mg/kg bw dose of 100% Polyglycerin-3 in accordance with OECD TG 401, via gavage.[3,4] Decreased body weight was observed in 1 female, and reduced weight gain was observed in 2 females on day 14. Abnormal gross pathological findings (details not provided) found in one female rat were considered possibly test-related; the LD_{50} value was determined to be > 2000 mg/kg bw. Female Sprague-Dawley rats were administered 2000 mg/kg bw of a polyglycerol mixture comprising mostly Polyglycerin-3 and Diglycerin (50.8 and 28.2%, respectively), in accordance with OECD TG 423, via gavage.[3,4] No deaths or clinical abnormalities were observed and the LD_{50} was determined to be > 2000 mg/kg bw.

Short-Term, Subchronic, and Chronic Toxicity Studies

No repeated-dose toxicity studies were found in the published literature, and unpublished data were not submitted. However, ECHA safety dossiers regarding glycerin have been proposed as a read-across source to target this endpoint for the ingredients reviewed herein.[3-5]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity data were not found in the published literature for the ingredients reviewed in this report, and unpublished data were not submitted. However, ECHA safety dossiers regarding glycerin and polyglycerol polyricinoleate have been proposed as read-across sources to target this endpoint for the ingredients reviewed herein.[3-5]

GENOTOXICITY STUDIES

Details of the in vitro genotoxicity studies summarized below are described in Table 5.

Diglycerin was not genotoxic at concentrations up to 5000 µg/plate, with or without metabolic activation, in two separate Ames tests, performed in accordance with OECD TG 471, using *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 and *Escherichia coli* WP2 uvr A.[5] A polyglycerol mixture containing Diglycerin and Polyglycerin-3 (90.7 and 2.4%, respectively) was not genotoxic, with or without metabolic activation, in an in vitro mammalian chromosome aberration test using cultured human peripheral lymphocytes (OECD TG 473), or in a mammalian cell mutation test using mouse lymphoma L5178Y cells (OECD TG 476), both at concentrations of up to 1662 µg/ml.[5] Similarly, a mixture comprising mostly Polyglycerin-3 and Diglycerin (50.8 and 28.2%, respectively), and another mixture containing 43% Polyglycerin-3 and 27% Diglycerin were not genotoxic, with or without metabolic activation, at concentrations of up to 5000 µg/plate in two separate Ames tests (OECD TG 471).[3,4] A polyglycerol mixture containing Polyglycerin-3, Diglycerin, and Polyglycerin-6 (46, 27.9, and 2.6%, respectively) was not genotoxic when tested at up to

5000 µg/ml in a mammalian chromosome aberration test using human peripheral lymphocytes (OECD TG 473), or in a mammalian cell mutation test using mouse lymphoma L5178Y cells (OECD TG 476).[3,4]

CARCINOGENICITY STUDIES

Carcinogenicity data were not found in the published literature for the ingredients reviewed in this report, and unpublished data were not submitted. However, ECHA safety dossiers regarding polyglycerol polyricinoleate have been proposed as a read-across source to target this endpoint for the ingredients reviewed herein.[3,4]

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details of the dermal irritation and sensitization studies summarized below are described in Table 6.

Diglycerin was not irritating when applied neat (0.5 ml) for 4 h in two separate acute dermal irritation tests, in which test sites were both unwiped and wiped; the tests were performed in accordance with OECD TG 404 and used 3 and 6 New Zealand white rabbits, respectively.[3,5] Polyglycerin-3 (100%) and a polyglycerol mixture containing Polyglycerin-3 and Diglycerin (50.8 and 28.2%, respectively) were not irritating in two acute dermal irritation tests performed in New Zealand white rabbits.[3,4] In one, 24-h human patch test, Diglycerin (100%) was not irritating when applied under occlusion to 33 subjects; in a 48-h human patch test, Diglycerin (100%) produced questionable erythema in 5 out of 34 subjects.[5] Results from both of these studies were not considered reliable due to methodological deficiencies (per the ECHA dossier). Diglycerin (50%, in water; volume not specified) was not irritating when applied to 50 subjects for 24 h.[5] Similarly, 100% Polyglycerin was not irritating when applied (volume not specified) to 50 subjects for 24 h.[4]

Groups of 4 female CBA mice were tested with 0, 25, 50, or 100% Diglycerin in ethanol/water (7:3; v:v) in a local lymph node assay (LLNA) performed in accordance with OECD TG 429.[3] The stimulation index (SI) values were determined to be 1.4, 2.1, and 1.9 for the 25, 50, and 100% groups, respectively; the test article was deemed non-sensitizing. In a guinea pig maximization test, Diglycerin was administered to groups of 10 female Dunkin-Hartley guinea pigs, via a 20% v/v intradermal injection (in water) followed by an undiluted epicutaneous application during induction and challenge.[5] Post-challenge, 2 of the animals evaluated at 24 h and 3 of the animals evaluated at 48 h exhibited positive reactions to the undiluted test article; the test article was considered to be a sensitizer. Diglycerin (100% in water, 99.8% in saline, and 5% in water) was not sensitizing in 3 separate guinea pig maximization tests performed in accordance with OECD TG 406.[5] Intradermal injections of each test substance were made during the induction phase at concentrations up to 25%. Two polyglycerol mixtures containing Polyglycerin-3 and Diglycerin (50.8 and 28.2%; 43 and 27%, respectively), both injected at 5% during the induction phase, were not sensitizing in 2 separate guinea pig maximization tests.[3,4]

OCULAR IRRITATION STUDIES

Details of the ocular irritation studies summarized below are described in Table 7.

In one acute eye irritation test performed in rabbits, 0.1 ml of undiluted Diglycerin was instilled neat; mean scores for eye irritation indices were 0 (eyes were rinsed).[3] In a similar acute eye irritation test, iridial inflammation and mild to moderate conjunctival redness in treated eyes was reversible in 48 h (eyes were not rinsed).[5] The ocular irritation potential of a polyglycerol mixture containing Diglycerin and Polyglycerin-3 (95.4 and 2.7%, respectively) was tested in the eyes of 3 rabbits in a 24-h acute eye irritation test in which eyes were not rinsed.[5] Lacrimation was seen in the eyes of 2 rabbits, and minimal redness of the conjunctiva was seen in all rabbits at 1 h; no further irritating effects were observed. Slight to moderate redness and swelling of the conjunctival sac was reversible within 48 h when undiluted Polyglycerin-3 was instilled neat to unrinsed rabbit eyes in an acute eye irritation test.[3,4] Minimal to moderate conjunctival irritation was observed in two separate acute eye irritation tests performed in rabbits with a polyglycerol mixture containing Polyglycerin-3 and Diglycerin (50.8 and 28.2%, respectively).[3,4] The test article was instilled neat in one study and at 50% in water in the other study (eyes were not rinsed in both studies); signs of irritation resolved within 48 and 24 h, respectively. In another study, the conjunctivae of the eyes of 3 male New Zealand white rabbits were slightly irritated 1 h after the neat instillation of a polyglycerol mixture containing Polyglycerin-3, Diglycerin, and Polyglycerin-6 (45.6, 22.2, and 2.5%, respectively) in which treated eyes were not rinsed; signs of irritation resolved in 24 h.[3,4]

SUMMARY

This report addresses the safety of Diglycerin, Polyglycerin-3, Polyglycerin-6, and Polyglycerin-10, as used in cosmetic formulations. All 4 of these ingredients are polymers of glycerin, and according to the *Dictionary*, all are reported to function in cosmetics as skin-conditioning agents. According to 2023 VCRP data, Diglycerin and Polyglycerin-3 are reported to be used in 222 cosmetic formulations and 221 formulations, respectively. The highest concentration of use reported in 2022 was for Diglycerin, at up to 28% in skin cleansing products; for dermal exposure, Diglycerin is reported to be used at up to 5% in non-spray face and neck products.

In 2013, the EFSA concluded that polyglycerol is safe to be used as a plasticizer in food contact materials, at a maximum concentration of 6.5% w/w in polymer blends of aliphatic-aromatic polyesters. Polyglycerols are utilized in various biomedical applications, such as drug delivery, bone regeneration, tissue engineering and scaffolding.

The absorption and metabolism of [^{14}C]Polyglycerin-3 and [^{14}C]Polyglycerin-10, administered via gavage in a liquid diet, was evaluated in groups of male Sprague-Dawley rats. At the end of the experimental period (51 h), urine, feces, respiratory CO_2, lymph, gastrointestinal tract, and carcass contents were sampled and evaluated. Rats received a thoracic duct cannula prior to being fed; one group of treated rats was not cannulated for comparison. Based on the radiolabel found in the CO_2, urine, and carcass, it was assumed that > 90% of Polyglycerin-3 and approximately 40% of Polyglycerin-10 was absorbed. Detected radioactivity recovery was the following for Polyglycerin-3 and Polyglycerin-10, respectively: 2.1 and 4.2% in expired CO_2, 88.3 and 34.1% in urine, 5.5 and 23.9% in feces, 2.9 and 35.2% in gastrointestinal content, and 1.2 and 5.3% in the carcass, for non-cannulated rats. For cannulated animals, a small amount of radioactivity was detected in the lymph; 69.5 and 20% Polyglycerin-3, and, 45.4 and 34% Polyglycerin-10 was excreted in the urine and feces, respectively. The radioactive compound excreted in the urine of the rats had the same R_f (0.47) as the solvent used in the TLC analysis; therefore, it was concluded that Polyglycerin-3 was not metabolized by the rat; a similar conclusion was reached for Polyglycerin-10.

The acute oral LD_{50} values for 20 and 25% Diglycerin, in water, were reported to be > 2000 mg/kg bw and > 5000 mg/kg bw in rats, respectively. Male and female Wistar rats were administered a single, undiluted, 2000 mg/kg bw dose of Polyglycerin-3, via gavage; decreased body weight was observed in 1 female, and reduced weight gain was observed in 2 females on day 14. Abnormal gross pathological findings (details not provided) found in one female rat were considered possibly test-related; the LD_{50} value was determined to be > 2000 mg/kg bw. No deaths or clinical abnormalities were noted in Sprague-Dawley rats that received 2000 mg/kg bw of a polyglycerol mixture comprising mostly Polyglycerin-3 and Diglycerin (50.8 and 28.2%), in water, via gavage; the LD_{50} value was determined to be > 2000 mg/kg bw.

Diglycerin was not genotoxic, with or without metabolic activation, in two separate Ames tests at concentrations up to 5000 µg/plate in *S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537, and *E. coli* WP2 uvr A. A polyglycerol mixture containing Diglycerin and Polyglycerin-3 (90.7 and 2.4%) was not genotoxic at concentrations of up to 1662 µg/ml, with or without metabolic activation, in an in vitro mammalian chromosome aberration test using cultured human peripheral lymphocytes, or in a mammalian cell mutation test using mouse lymphoma L5178Y cells. Similarly, two polyglycerol mixtures comprising mostly Polyglycerin-3 and Diglycerin (50.8 and 28.2%; 43 and 27%) were not genotoxic in two separate Ames tests at up to 5000 µg/plate, with or without metabolic activation. A polyglycerol mixture containing Polyglycerin-3, Diglycerin, and Polyglycerin-6 (46, 27.9, and 2.6%, respectively) was non-genotoxic, with or without metabolic activation, at concentrations of up to 5000 µg/plate in a mammalian chromosome aberration test using human peripheral lymphocytes or in a mammalian cell mutation test using mouse lymphoma L5178Y cells.

Diglycerin was not irritating when applied neat (0.5 ml) for 4 h to rabbit skin. Polyglycerin-3 (undiluted) and a polyglycerol mixture containing Polyglycerin-3 and Diglycerin (50.8 and 28.2%, respectively) were not irritating in 2 acute dermal irritation tests performed in rabbits. In 2 human patch tests, Diglycerin (undiluted) was not irritating when applied neat to 33 subjects for 24 h, and produced questionable erythema in 5 out of 34 subjects when applied neat for 48 h; these results were not considered reliable due to methodological deficiencies. Neither 50% Diglycerin nor undiluted Polyglycerin-3 were irritating when applied neat to 50 subjects for 24 h in 2 separate human patch tests (unspecified volume). The sensitizing potential of Diglycerin was tested in groups of female CBA mice at concentrations of 0, 25, 50, or 100%, in ethanol/water (7:3; v:v) in an LLNA; the stimulation index values were determined to be 1.4, 2.1, and 1.9, respectively. The test article was deemed non-sensitizing. Diglycerin, tested in saline or water, was not sensitizing in three separate guinea pig maximization tests (up to 25% intradermal injection and undiluted epicutaneous application during induction; undiluted challenge application). In another maximization test, Diglycerin was administered to Dunkin-Hartley guinea pigs via a 20% intradermal injection (in water) followed by an undiluted epicutaneous application during induction and challenge. Two of the animals evaluated at 24 h and three of the animals evaluated at 48 h exhibited positive reactions to the undiluted test article; the test article was considered to be a sensitizer. Two polyglycerol mixtures containing Polyglycerin-3 and Diglycerin, intradermally injected at 5% during induction, were not sensitizing in two guinea pig maximization tests (50.8 and 28.2%; 43.8 and 27%, respectively).

In one acute eye irritation test evaluating undiluted Diglycerin, mean scores for eye irritation indices were 0. In a similar acute eye irritation test, iridial inflammation and mild to moderate conjunctival redness in treated eyes was reversible in 48 h. A polyglycerol mixture containing Diglycerin and Polyglycerin-3 (95.4 and 2.7%, respectively) was tested in the eyes of 3 rabbits in a 24-h acute eye irritation test; lacrimation was seen in the eyes of 2 rabbits, and minimal redness of the conjunctiva was seen in all rabbits at 1 h; no further irritating effects were observed. Slight to moderate redness and swelling of the conjunctival sac was reversible within 48 h when undiluted Polyglycerin was instilled in an acute eye irritation test using rabbits. Signs of minimal to moderate conjunctival irritation resolved within 48 and 24 h, respectively, in two separate acute eye irritation tests evaluating a polyglycerol mixture containing Polyglycerin-3 and Diglycerin (50.8 and 28.2%, respectively). In an acute eye irritation test evaluating a polyglycerol mixture containing Polyglycerin-3, Diglycerin, and Polyglycerin-6 (45.6, 22.2, and 2.5%, respectively), signs of slight irritation in the conjunctivae of 3 male New Zealand white rabbits resolved in 24 h.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions and functions of the ingredients in this assessment

Ingredient/CAS No.	Definition	Function
Diglycerin 25618-55-7 (generic) 59113-36-9	Diglycerin is a dimer of glycerin. *See Figure 1, when n = 2.*	Humectants; Skin-conditioning agents - humectant
Polyglycerin–3 25618-55-7 (generic) 56090-54-1	Polyglycerin-3 is a glycerin polymer containing 3 glycerin units. *See Figure 1 when n = 3.*	Skin-conditioning agents - humectant
Polyglycerin–6 36675-34-0	Polyglycerin-6 is a glycerin polymer containing 6 glycerin units. *See Figure 1 when n = 6.*	Skin-conditioning agents - humectant
Polyglycerin-10 9041-07-0	Polyglycerin-10 is a glycerin polymer containing 10 glycerin units. *See Figure 1 when n = 10.*	Skin-conditioning agents - humectant

Table 2. Chemical properties

Property	Value	Reference
	Diglycerin	
Physical Form	liquid, viscous	3,5
Color	colorless to slightly yellow	3
Molecular Weight (g/mol)	166.17	16
Density (g/ml @ 20 ºC)	1.28	3,5
Viscosity (dynamic: mPa/s; kinematic: mm^2/s@ 20 ºC)	15,400; 17,474	3,5
Vapor Pressure (mmHg @ 20 °C)	1.36×10^{-7}	5
Boiling Point (ºC)	≥ 274; > 250	3,5
Water Solubility (g/l @ 20 ºC & pH 6.5)	> 550	3
log K_{ow} (@ 20 ºC)	-2; -2.5 (estimated)	3,5
	Polyglycerin-3	
Physical Form	liquid, viscous	4
Color	colorless to pale yellow	4
Odor	odorless	4
Molecular Weight (g/mol)	240.25	17
Specific Gravity (@ 20 ºC)	1.29	4
Viscosity (mm^2/s @ 20 ºC)	48,390	4
Vapor pressure (mmHg @ 20 ºC)	5.05×10^{-8}	4
Melting Point (ºC)	> 275	4
Boiling Point (ºC)	> 1000	4
Water Solubility (g/l @ 20 ºC & pH 7.2)	> 1000	4
log K_{ow} (@ 20 ºC)	-3.3 to -3.9 (estimated)	4
	Polyglycerin-6	
Molecular Weight (g/mol)	462.5	18
log K_{ow} (temperature not specified)	-5.6 (estimated)	18
	Polyglycerin-10	
Molecular Weight (g/mol)	758.8	19
log K_{ow} (temperature not specified)	-8.6 (estimated)	19

Table 3. Frequency (2023)[10] and concentration (2022)[11] of use according to likely duration and exposure and by product category

	Diglycerin		Polyglycerin-3		Polyglycerin-6		Polyglycerin-10	
	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Totals	**222**	**0.2 – 28**	**221**	**0.038 – 2.3**	**7**	**0.02**	**31**	**0.9**
summarized by likely duration and exposure*								
Duration of Use								
Leave-On	*191*	*0.2 – 8*	*211*	*0.038 – 2.3*	6	*NR*	*26*	*NR*
Rinse-Off	*31*	*0.5- 28*	*10*	*0.35 – 1.4*	1	*0.02*	*5*	*0.9*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	NR	*NR*	*NR*	*NR*
Exposure Type*								
Eye Area	9	3	6	NR	NR	NR	2	NR
Incidental Ingestion	97[a]; 60[b]	1.8 – 3.6	104	0.071 – 2.3	3	NR	NR	NR
Incidental Inhalation-Spray	60[b]	8[a]	41[a]; 40[b]	NR	2[a]; 1[b]	NR	12[a]; 8[b]	NR
Incidental Inhalation-Powder	NR	1.8 – 5[c]	40[b]	0.15 – 1.2[c]	1[b]	NR	8[b]	NR
Dermal Contact	199	0.2 – 28	113	0.038 – 1.5	4	0.02	31	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	23	8	4	NR	NR	NR	NR	0.9
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	1.8 – 3.6	104	0.071 – 2.3	4	NR	2	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
as reported by product category								
Eye Makeup Preparations								
Eye Shadow			1	NR				
Eye Lotion	7	3	4	NR			1	NR
Other Eye Makeup Preparations	2	NR	1	NR			1	NR
Hair Preparations (non-coloring)								
Hair Conditioner	4	NR	1	NR			NR	0.9
Shampoos (non-coloring)	6	NR	1	NR				
Tonics, Dressings, and Other Hair Grooming Aids	3	8						
Other Hair Preparations	10	NR	2	NR				
Makeup Preparations								
Blushers (all types)	1	NR						
Foundations	NR	2	1	NR				
Lipstick	NR	1.8 - 3.6	104	0.071 - 2.3	3	NR		
Makeup Bases							1	NR
Rouges			1	NR				
Other Makeup Preparations			2	NR			2	NR
Personal Cleanliness Products								
Other Personal Cleanliness Products					1	NR	2	NR
Shaving Preparations								
Other Shaving Preparations	1	NR	1	NR				
Skin Care Preparations								
Cleansing	17	1.3-28	4	1.4			2	NR
Face and Neck (exc shave)	36	1.8 - 5 (not spray)	23	0.15 - 1.2 (not spray)			7	NR
Body and Hand (exc shave)	24	2 (not spray)	17	0.6 (not spray)	1	NR	1	NR
Moisturizing	80	1 (not spray)	33	0.038 - 0.48	2	NR	10	NR
Night	11	2.5 (not spray)	6	NR			1	NR
Paste Masks (mud packs)	2	0.5-25	3	0.35	NR	0.02	1	NR
Skin Fresheners	3	NR					1	NR
Other Skin Care Preparations	11	0.2 – 2	14	0.15 - 1.5			1	NR

Table 3. Frequency (2023)[10] and concentration (2022)[11] of use according to likely duration and exposure and by product category

	Diglycerin		Polyglycerin-3		Polyglycerin-6		Polyglycerin-10	
	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Suntan Preparations								
Suntan Gels, Creams, and Liquids	NR	0.4 (not spray)	2	0.9 (not spray)				

*likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
**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] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.
NR – not reported

Table 4. Acute oral toxicity studies

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50} Results	Reference
Diglycerin	water	Wistar rats; 5/sex	20% (w/w); 2000 mg/kg bw	OECD TG 401. Administered via gavage	> 2000 mg/kg bw.	3
Diglycerin	water	Sprague-Dawley rats; 10/sex	25%; 5000 mg/kg bw	OECD TG 401; Administered via gavage	> 5000 mg/kg bw	5
Polyglycerin-3, 100% pure	NA	Wistar rats; 5/sex	undiluted; 2000 mg/kg bw	OECD TG 401. Administered via gavage	> 2000 mg/kg bw. Decreased body weight in one female and reduced weight gain in 2 females on day 14. Abnormal gross pathological findings in one female rat may be test material related.	3,4
Mixture, comprising: 50.8% Polyglycerin-3 28.2% Diglycerin 15.9% polyglycerin-4 4.9% polyglycerin-5 and higher oligomers 0.2% water	water	6 Female Sprague-Dawley rats	2000 mg/kg bw	OECD 423. Administered via gavage	> 2000 mg/kg bw. No deaths or clinical abnormalities were noted. Higher value was estimated from flow chart.	3,4

NA – not applicable; OECD – Organisation for Economic Cooperation and Development; TG – test guideline

Table 5. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	Reference
			IN VITRO			
Diglycerin, > 98%	water	Up to 5000 µg/plate, with and without metabolic activation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* WP2 uvr A	OECD TG 471. Ames test	Not genotoxic	[5]
Diglycerin	DMSO	Up to 5000 µg/plate, with and without metabolic activation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 tested separately	OECD TG 471. Ames test	Not genotoxic; a statistically significant increase in revertants was only seen in the TA102 strain, at 40, 200 and 1000 µg/plate without metabolic activation and at 200 µg/plate with metabolic activation.	[5]
Mixture comprising: 90.7% Diglycerin 6.1% cyclic triglycerol 2.4% Polyglycerin-3	RPMI 1640 medium	333, 1000 or 1662 µg/ml, with and without metabolic activation	cultured human peripheral lymphocytes	OECD TG 473. In vitro mammalian chromosome aberration test	Not genotoxic	[5]
Mixture comprising: 90.7% Diglycerin 6.1% cyclic triglycerol 2.4% Polyglycerin-3	exposure medium	1, 3, 10, 33, 100, 333, 1000 or 1662 µg/ml, with and without metabolic activation	mouse lymphoma L5178Y cells	OECD TG 476. In vitro mammalian cell mutation test	Not genotoxic	[5]
Mixture comprising: 50.8% Polyglycerin-3 28.2% Diglycerin 15.9% polyglycerin-4 4.9% polyglycerin-5 and higher oligomers 0.2% water	NS	Up to 5000 µg/plate, with and without metabolic activation	*S. typhimurium* strains TA 98, TA100, TA1535, TA1537 and *E.coli* WP2 uvr A	OECD TG 471. Ames test	Not genotoxic	[3,4]
Mixture comprising: 43% Polyglycerin-3 27% Diglycerin 16% polyglycerin-4 14% polyglycerin 5-8	water	Up to 5000 µg/plate, with and without metabolic activation	*S. typhimurium* strains TA 98, TA100, TA1535, TA1537	OECD TG 471. Ames test	Not genotoxic	[3,4]
Mixture comprising: 46% Polyglycerin-3 27.9% Diglycerin 17.9% polyglycerin-4 5.6% polyglycerin-5 2.6% Polyglycerin-6 and higher oligomers	RPMI 1640 medium	Up to 5000 µg/ml, with and without metabolic activation	Human peripheral lymphocytes	OECD TG 473. In vitro mammalian chromosome aberration test	Not genotoxic	[3,4]
Mixture comprising: 46% Polyglycerin-3 27.9% Diglycerin 17.9% polyglycerin-4 5.6% polyglycerin-5 2.6% Polyglycerin-6 and higher oligomers	exposure medium	Up to 5000 µg/ml, with and without metabolic activation	mouse lymphoma L5178Y cells	OECD TG 476. In vitro mammalian cell mutation test	Not genotoxic	[3,4]

DMSO – dimethyl sulfoxide; NS – not specified; OECD – Organisation for Economic Cooperation and Development; RPMI – Roswell Park Memorial Institute; TG – test guideline

Table 6. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
ANIMAL						
Diglycerin	NA	0.5 ml, applied neat	3 New Zealand white rabbits	OECD TG 404. Acute dermal irritation test. A semi-occlusive application of the test article was made for 4 h to 2.5 cm^2 of shaved skin. Reactions were scored 30-60 min, 24, 48, and 72 h after patch removal.	Not irritating; mean erythema/eschar scores were 0	[3]
Diglycerin	NA	0.5 ml, applied neat	6 New Zealand white rabbits	OECD TG 404. Acute dermal irritation test. Application as described above. Test sites were wiped with cotton soaked in water 4 h after exposure. Reactions were scored 24, 48, and 72 h after patch removal.	Not irritating; mean erythema scores were 0	[5]
Polyglycerin-3, 100% pure	NA	0.5 ml, applied neat	3 New Zealand white rabbits	OECD TG 404. Acute dermal irritation test. A semi-occlusive application of the test article was made for 4 h to a 6 cm^2 area of shaved skin. Not known if test sites were wiped. Test sites were observed for up to 5 d after application.	Not irritating Slight to moderate erythema was reversible within 5 d. Mean erythema scores were 1.67 for the first animal (between 24 h and 4 d), 1 for the second animal (between 24-48 h), and 0 for the third animal.	[3,4]
Mixture comprising: 50.8% Polyglycerin-3 28.2% Diglycerin 15.9% polyglycerin-4 4.9% polyglycerin-5 and higher oligomers 0.2% water	NA	0.5 ml, applied neat	3 New Zealand white rabbits	OECD TG 404. Acute dermal irritation test. A semi-occlusive application of the test article was made for 4 h to a 2.5 cm^2 area of shaved skin. Test sites were wiped with cotton soaked in water. Reactions were scored 1, 24, 48, and 72 h after patch removal.	Not irritating	[3,4]
HUMAN						
Diglycerin	NA	NR, applied neat	33 subjects	24-h, occlusive application of the test substance to the crooked side of the upper arm (further details on dosage and protocol not provided). Reactions were scored 4 h after patch removal; no signs of irritation were observed.	Not irritating These results were not considered reliable (per the ECHA dossier) due to several methodological deficiencies, such as: not being performed under GLP circumstances, exposure dose not provided, lack of approval of study by a relevant ethical committee, and no ethical or medical history information provided for the human volunteers.	[5]
Diglycerin	NA	0.05 ml/patch, applied neat	34 male subjects	The test article was applied for 48 h to a 15 mm^2 area (further details on occlusion, preparation of the test site, and scoring were not provided).	Questionable erythema was observed in around 15% of the subjects (5 subjects). These results were not considered reliable (per the ECHA dossier) due to several methodological deficiencies, such as: lack of guidelines, no data on the purity/composition of the test article, no data on application conditions, or on selection of volunteers.	[5]
Diglycerin	water	50%, NR	50 subjects	24- h, occlusive application (further details not provided). Test sites were evaluated 24 h, 48, and 72 h after removal of the test substance. Details on test guidelines used and data on the test substance (volume applied) were not available.	Not irritating	[5]
Polyglycerin-3	NA	NR, applied neat	50 subjects	As described above.	Not irritating	[4]

Table 6. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
SENSITIZATION						
ANIMAL						
Diglycerin	ethanol/ water (7:3; v:v)	0, 25, 50, or 100%	Groups of 4 female CBA mice	OECD TG 429. LLNA. The test article was applied to the back of each ear lobe (left and right) for 3 consecutive days. Five days after the first application, mice received an injection of radio-labelled thymidine; 5-h post-injection, aurical lymph nodes were excised and analyzed. A vehicle control group was used and positive controls received hexyl cinnamic aldehyde at concentrations of 5, 10, or 25% in acetone:olive oil (4:1, v/v).	Not sensitizing; SI values were determined to be: 25%: 1.4 50%: 2.1 100%: 1.9 About 3 h after the first topical application, slight erythema was observed on both dosing sites for all mice in the 100% group, which persisted for 4 d. On day 2, a slight ear erythema was observed at both dosing sites for all mice in the 50% group, which persisted for 2 d.	[3]
Diglycerin	water	Induction: intradermal: 5%, dermal: 100% Challenge: 100%, 0.5 ml	Groups of 20 male and female Pirbright white guinea pigs; 10 negative controls	OECD TG 406. Guinea pig maximization test. Animals received pairs of injections containing 5% of the test article, intradermally (diluted in water and FCA). After pretreatment with 10% SLS, 100% Diglycerin was occlusively applied on day 7 to a 4 x 5 cm^2 test area for 48 h. Occlusive challenge applications were made 14 d after induction, undiluted, to a 5 x 5 cm^2 shaved area for 24 h. Positive controls were challenged with benzocaine. Reactions were scored 24, 48, and 72 h after patch removal.	Not sensitizing	[5]
Diglycerin	water	Induction: intradermal: 20% v/v in FCA, dermal: 100% Challenge: 100%	Groups of 10 female Dunkin-Hartley guinea pigs; 5 negative controls	OECD TG 406. Guinea pig maximization test. Positive controls were challenged with α - hexylcinnamaldehyde. Reactions were scored 24 and 48 h post-challenge.	Sensitizing; Two out of 10 animals at 24 h and 3 out of 10 animals at 48 h exhibited positive reactions to the undiluted test substance.	[5]
Diglycerin, 99.8% pure	physiological saline	Induction: intradermal: 12.5 or 25%, dermal: 100% Challenge: 50% or 100%, 0.5 ml	Groups of 11 female Dunkin-Hartley guinea pigs; 5 negative controls	OECD TG 406. Guinea pig maximization test. Challenge applications were made at a concentration of 50% or 100% in the vehicle for 24 h on day 21. Positive controls were challenged with α- hexylcinnamaldehyde. Reactions were scored 24 and 48 h after challenge.	Not sensitizing; Two animals challenged with 100% of the test article had slight patches of erythema 24-h post-challenge. No other reactions, mortality, or clinical abnormalities were observed.	[5]
Diglycerin, 5%	water	Induction: intradermal: 10%, dermal: 100% Challenge: 100%	Groups of 10 female Dunkin-Hartley guinea pigs; 5 negative controls	OECG TG 406. Guinea pig maximization test. Positive controls were challenged with mercaptobenzothiazole. Reactions were scored 24 and 48 h post-challenge.	Not sensitizing	[5]
Mixture comprising: 50.8% Polyglycerin-3 28.2% Diglycerin 15.9% polyglycerin-4 4.9% polyglycerin-5 and higher oligomers 0.2% water	water	Induction: intradermal: 5%, dermal: 100% Challenge: 100%	Groups of 10 male Dunkin-Hartley guinea pigs; 5 controls	OECD TG 406. Guinea pig maximization test. Reactions were scored 24 and 48 h post-challenge.	Not sensitizing; Discrete or patchy to moderate and confluent erythema was noted at the intradermal and topical induction sites, as well as in 2 challenge sites of animals at the 24 h evaluation.	[3,4]
Mixture comprising: 43% Polyglycerin-3 27% Diglycerin 16% polyglycerin-4 14% polyglycerin 5-8	water	Induction: intradermal: 5%, dermal: 100% Challenge: 100%	Groups of 20 male and female Pirbright white guinea pigs; 10 controls	OECD TG 406. Guinea pig maximization test. Positive controls were challenged with benzocaine. Challenge applications were made for 48 h; reactions were scored 24 and 48 h post-challenge.	Not sensitizing	[3,4]

FCA – Freund's Complete Adjuvant; LLNA – local lymph node assay; NA – not applicable; NR – not reported; OECD – Organisation for Economic Cooperation and Development; SI – stimulation index; SLS – sodium lauryl sulfate; TG – test guideline

Table 7. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL						
Diglycerin	NA	0.1 ml, instilled neat	3 New Zealand white rabbits	OECD TG 405; 24-h, acute eye irritation test. Untreated eyes served as controls. Eyes were washed with saline at 24 h. Mean scores were calculated across 3 scoring times (24, 48, and 72 h after instillation) for each animal to evaluate corneal opacity, iris redness, chemosis of the conjunctivae, separately.	Mean scores were 0 Transient changes, such as reddening of conjunctivae, discharge and chemosis were present at 1 h, which resolved by 24 h.	[3]
Diglycerin	NA	0.1 ml, instilled neat	6 New Zealand white rabbits	OECD TG 405; acute eye irritation test. Eyes were not rinsed after treatment.	Iridial inflammation noted in 5 treated eyes at 1 h. Minimal to moderate conjunctival redness persisted in 2 treated eyes at 24 h. All effects were reversible in 48 h.	[5]
Mixture comprising: 95.4% Diglycerin 2.7% Polyglycerin-3 1.4% glycerin 0.5% unidentified components	NA	0.1 ml, instilled neat	3 New Zealand white rabbits	OECD TG 405; 24-h, acute eye irritation test. Eyes were not rinsed after treatment.	Lacrimation was seen in 2 rabbits, and minimal redness of the conjunctiva was seen in all rabbits at 1 h. No further irritating effects were observed.	[5]
Polyglycerin-3	NA	0.1 ml, instilled neat	3 New Zealand white rabbits	OECD TG 405; acute eye irritation test. Eyes were not rinsed after treatment.	Slight to moderate redness and swelling of conjunctival sac, as well as slight ocular secretion, which was reversible within 48 h.	[3,4]
Mixture comprising: 50.8% Polyglycerin-3 28.2% Diglycerin 15.9% polyglycerin-4 4.9% polyglycerin-5 and higher oligomers 0.2% water	NA	0.1 ml, instilled neat	3 New Zealand white rabbits	OECD TG 405; acute eye irritation test. Eyes were not rinsed after treatment.	Moderate conjunctival irritation was noted at 1 h, as well as minimal conjunctival irritation at 24 h, in all treated eyes. These symptoms resolved in 48 h.	[3,4]
Mixture comprising: 50.8% Polyglycerin-3 28.2% Diglycerin 15.9% polyglycerin-4 4.9% polyglycerin-5 and higher oligomers 0.2% water	water	50%, 0.1 ml	3 New Zealand white rabbits	OECD TG 405; acute eye irritation test. Eyes were not rinsed after treatment.	Minimal conjunctival irritation was seen in one eye 1 h after treatment, which resolved in 24 h.	[3,4]
Mixture comprising: 45.6% Polyglycerin-3 22.2% Diglycerin 21.3% polyglycerin-4 6.7% polyglycerin-5 2.5% Polyglycerin-6 1.1% polyglycerin-7 0.6% other unidentified components	NA	0.1 ml, instilled neat	3 male New Zealand white rabbits	OECD TG 405; acute eye irritation test. Eyes were not rinsed after treatment.	Conjunctivae were slightly irritated in all rabbits 1 h after treatment, which resolved in 24 h.	[3,4]

NA – not applicable; OECD – Organisation for Economic Cooperation and Development; TG – test guideline

REFERENCES

1. Nikitakis J, Kowcz A. Web-Based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*). https://incipedia.personalcarecouncil.org/winci/. Washington, D.C.: Personal Care Products Council. Last Updated: 2023. Accessed: 03/06/2023.

2. Becker LC, Bergfeld WF, Belsito DV, et al. Safety Assessment of Glycerin as Used in Cosmetics. *Int J Toxicol.* 2019;38(Suppl 3):6S-22S.

3. European Chemical Agency (ECHA). REACH registration dossier: 1,2,3-Propanetriol, homopolymer (Diglycerin; CAS 25618-55-7). https://echa.europa.eu/registration-dossier/-/registered-dossier/14285/1/2. Last Updated: 2021. Accessed: 06/28/2022.

4. European Chemical Agency (ECHA). REACH registration dossier: 1-(1,3-dihydroxypropoxy)propane-1,3-diol; 3-{3-[3-(2,3-dihydroxypropoxy)-2-hydroxypropoxy]-2-hydroxypropoxy}propane-1,2-diol; nonane-1,2,4,5,6,8,9-heptol (Polyglycerin-3; CAS 25618-55-7). https://echa.europa.eu/registration-dossier/-/registered-dossier/13319/1/1. Last Updated: 2018. Accessed: 06/28/2022.

5. European Chemical Agency (ECHA). Oxybispropanediol (Diglycerin; CAS No. 59113-36-9). https://echa.europa.eu/registration-dossier/-/registered-dossier/13661/1/2. Last Updated: 2022. Accessed: 08/02/2022.

6. Thomas A, Müller SS, Frey H. Beyond poly (ethylene glycol): linear polyglycerol as a multifunctional polyether for biomedical and pharmaceutical applications. *Biomacromolecules.* 2014;15(6):1935-1954.

7. Mohammadifar E, Bodaghi A, Dadkhahtehrani A, Nemati Kharat A, Adeli M, Haag R. Green synthesis of hyperbranched polyglycerol at room temperature. *ACS Macro Lett.* 2017;6(1):35-40.

8. Ardila-Suárez C, Rojas-Cristancho J, Pineda-Martínez J, Ramirez-Caballero GE, Ramirez-Garcia A. Effect of impurities present in crude glycerol polymerization reaction to produce polyglycerol. *CT&F-Ciencia, Tecnología y Futuro.* 2019;9(2):89-97.

9. Ciriminna R, Katryniok B, Paul Sb, Dumeignil F, Pagliaro M. Glycerol-derived renewable polyglycerols: A class of versatile chemicals of wide potential application. *Org Process Res Dev.* 2015;19(7):748-754.

10. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). 2023. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients (VCRP). (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2023; received February 2, 2023.)

11. Personal Care Products Council. 2022. Concentration of Use by FDA Product Category: Polyglycerins. (Unpublished data submitted by the Personal Care Products Council on July 6, 2022.)

12. European Union. EUR-Lex: Access to European Union law. https://eur-lex.europa.eu/homepage.html. Last Updated: 2023. Accessed: 04/13/2023.

13. European Food Safety Authority (EFSA) Panel on Food Contact Materials, Enzymes, Flavourings, and Processing Aids (CEF). Scientific opinion on the safety assessment of the substance, polyglycerol (CAS No 25618-55-7) for use in food contact materials. *EFSA J.* 2013;11(10):3389.

14. Zamboulis A, Nakiou EA, Christodoulou E, et al. Polyglycerol hyperbranched polyesters: synthesis, properties and pharmaceutical and biomedical applications. *Intl J Mol Sci.* 2019;20(24):6210.

15. Michael WR, Coots RH. Metabolism of polyglycerol and polyglycerol esters. *Toxicol Appl Pharmacol.* 1971;20(3):334-345.

16. National Library of Medicine. PubChem : Diglycerol (CAS No. 59113-36-9). https://pubchem.ncbi.nlm.nih.gov/compound/Diglycerol#section=Chemical-and-Physical-Properties. Last Updated: 07/29/2022. Accessed: 08/02/2022.

17. National Library of Medicine. PubChem : Triglycerol (CAS No. 56090-54-1). https://pubchem.ncbi.nlm.nih.gov/compound/92007#section=Chemical-and-Physical-Properties. Last Updated: 07/30/2022. Accessed: 08/02/2022.

18. National Library of Medicine. Pubchem: Polyglycerin-6 (CAS No. 36675-34-0). https://pubchem.ncbi.nlm.nih.gov/compound/3084634#section=Chemical-and-Physical-Properties. Last Updated: 07/30/2022. Accessed: 08/02/2022.

19. National Library of Medicine. Pubchem: Decaglycerol. https://pubchem.ncbi.nlm.nih.gov/compound/Decaglycerol#section=Chemical-and-Physical-Properties. Last Updated: 07/30/2022. Accessed: 08/02/2022.

Concentration of Use by FDA Product Category – Polyglycerins*

Diglycerin Polyglycerin-10 Polyglycerin-4
Polyglycerin-3 Polyglycerin-6

Ingredient	Product Category	Maximum Concentration of Use
Diglycerin	Eye lotions	3%
Diglycerin	Tonics, dressings, and other hair grooming aids	8%
Diglycerin	Foundations	2%
Diglycerin	Lipstick	1.8-3.6%
Diglycerin	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	1.3-28%
Diglycerin	Face and neck products Not spray	1.8-5%
Diglycerin	Body and hand products Not spray	2%
Diglycerin	Moisturizing products Not spray	1%
Diglycerin	Night products Not spray	2.5%
Diglycerin	Paste masks and mud packs	0.5-25%
Diglycerin	Other skin care preparations	0.2-2%
Diglycerin	Suntan products Not spray	0.4%
Polyglycerin-3	Lipstick	0.071-2.3%
Polyglycerin-3	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	1.4%
Polyglycerin-3	Face and neck products Not spray	0.15-1.2%
Polyglycerin-3	Body and hand products Not spray	0.6%
Polyglycerin-3	Moisturizing products Not spray	0.038-0.48%
Polyglycerin-3	Paste masks and mud packs	0.35%
Polyglycerin-3	Other skin care preparations	0.15-1.5%
Polyglycerin-3	Suntan products Not spray	0.9%
Polyglycerin-10	Hair conditioners	0.9%
Polyglycerin-6	Paste masks and mud packs	0.02%

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

Information collected in 2022
Table prepared: July 6, 2022