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

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ABBREVIATIONS

4NQO	4-nitroquinoline-1-oxide
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
LD_{50}	median lethal dose
LOAEL	lowest observed adverse effect level
LLNA	local lymph node assay
NA	not applicable
NOAEL	no observed adverse effect level
NOEL	no observable effect level
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
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI)

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Diglycerin, Polyglycerin-3, Polyglycerin-6, and Polyglycerin-10 as used in cosmetic formulations. These ingredients are reported to function in cosmetics as skin-conditioning agents. The Panel reviewed the available data and concluded that these ingredients are safe in cosmetics in the present practices of use and concentrations described in this safety assessment.

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 Panel considered that since the polyglycerins reviewed in this report are polymers of glycerin, it is appropriate to use data on glycerin to support the safety of these ingredients, as needed. Accordingly, excerpts from this safety assessment of glycerin are included throughout the text of this document, as appropriate, and are identified by *italicized* text. (This information is not included in the tables or Summary section.) For complete and detailed information, the original report can be accessed 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 July 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.

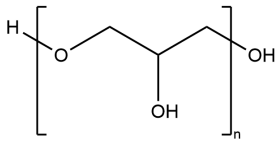

Figure 1. Polyglycerins, wherein n equals the number of glycerin residues. For example, Diglycerin is when n equals 2, and Polyglycerin-3 is when n is 3.

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, and Polyglycerin-10 is identified by the CAS No. 9041-07-0.

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-3 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 reviewed in this report appear to be linear polyglycerins, which can be prepared from protected glycidol derivatives (glycidyl ethers) via oxyanionic ring-opening polymerization, followed by acidic deprotection of the acetal protecting group.[6] The most commonly used monomeric starting materials 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.

Some of these ingredients are reported to be used in products that may be used near the eye or incidentally ingested. 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. Additionally, these ingredients are used in products which may be applied via spray or as a powder (e.g., face and neck products). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e. they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

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

Dermal Penetration

Polyglycerin-3

Polyglycerin-3 may be too hydrophilic to cross the lipid-rich environment of the stratum corneum.[3]

Absorption, Distribution, Metabolism, and Excretion (ADME)

Polyglycerin-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.

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. Samples of lymph, respired carbon dioxide (CO_2), feces, and urine were obtained during the 51-h experimental period and were assayed for total radioactivity. Gastrointestinal tract and carcass contents were collected and evaluated for distribution of radioactivity at the end of the experimental period. No controls were used. Radiolabeled 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 in cannulated rats. In non-cannulated rats, the amounts of radioactivity detected after dosing with Polyglycerin-3 were: 2.1% in expired CO_2, 88.3% in urine, 5.5% in feces, 2.9% in gastrointestinal content, and 1.2% in the carcass. The amounts of radioactivity detected in non-cannulated rats after dosing with Polyglycerin-10 were: 4.2% in expired CO_2, 34.1% in urine, 23.9% in feces, 35.2% in gastrointestinal content, and 2.5% in the carcass. For the cannulated animals, only a small amount of radioactivity was detected in the lymph; 69.5 and 20.2% [^{14}C] labeled-Polyglycerin-3 was recovered in the urine and feces, respectively, while 45.4 and 34% [^{14}C] labeled-Polyglycerin-10 was recovered 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

The Panel considered toxicological data for the monomer, glycerin, appropriate to use as supporting safety data for the polymers being reviewed in this assessment. Thus, glycerin data for repeated dose toxicity, developmental and reproductive toxicity, and carcinogenicity have been included herein for inference to polyglycerins.

Acute Toxicity Studies

Details of 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 (the highest dose tested), 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 2000 mg/kg bw dose of 100% Polyglycerin-3 via gavage, in accordance with OECD TG 401.[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 50.8% Polyglycerin-3 and 28.2% Diglycerin via gavage, in accordance with OECD TG 423.[3,4] No deaths or clinical abnormalities were observed and the LD_{50} was determined to be > 2000 mg/kg bw.

Short-Term Toxicity Studies

Oral

Glycerin

Undiluted glycerin administered to Charles River female rats (10 test animals/group; 20 controls) at 0, 0.75, 1.5, or 3 mg/kg for 3 d, via gavage, caused a dose-dependent increase in the number of animals showing hyperemia, petechial hemorrhage, and erosions in the gastrointestinal tract.[2] Male Wistar rats (24 test animals; 18 controls) were given glycerin in an amount equivalent to 53.4% carbohydrate in feed for 20 d. Controls were fed stock carbohydrate or a stock diet calculated to deliver the same calories as the glycerin diet. Controls gained weight at 6% per day, while glycerin-fed and pair-fed controls gained 3% body weight per day. Livers were 6% of the body weight in the glycerin-fed rats and 4.6% of the body weight in controls; kidneys of the glycerin-fed rats were 45% heavier than normal. Enzyme (e.g., pyruvate kinase, phosphofructokinase) levels and activity were increased and remained high in kidneys and livers of the glycerin-fed rats. No adverse effects were observed with regard to weight gain, feed intake, epididymal adipose tissue dry weight, and total liver lipids and cholesterol in male Carworth rats administered a diet containing 20% glycerin for 4 wk. Groups of 20 male rats were given 115, 575, 1150, or 2300 mg/kg glycerin in water for 44 d. No adverse effects were observed for growth curves, lethality, and histological examination of the kidneys, livers, and bladders; mortality was 15% in all groups. The no-observed-adverse-effect-level (NOAEL) was determined to be between 115 and 2300 mg/kg. Ten guinea pigs were administered 0 or 50% glycerin, in saline, via gavage or from a drinking cup for 30 - 40 d. Guinea pigs administered > 5 ml of the 50% glycerin solution, via gavage, died with acute symptoms. Necropsies revealed no pathological changes and plasma cholesterol levels had no changes attributed to glycerin treatment. Two guinea pigs treated with the 50% glycerin solution via gavage and 1 treated via drinking water had a lowered red blood count, suggesting a probable anemic effect for glycerin intake in guinea pigs. Glycerin (0 or 50%) was well-tolerated in 4 rabbits when administered at up to 10 ml in saline, via gavage, or from a drinking cup, for 30 - 40 d. Male or female Mongrel dogs (number not specified) received 950, 1900, or 3800 mg/kg glycerin thrice a day for 3 d. Stomach mucosa was severely hyperemic with petechial hemorrhages in the 1900 mg/kg group. Similar effects were seen in the 3800 mg/kg group with either a normal duodenum, or a duodenum with hyperemic areas. The oral no-observable-effect-level (NOEL) was determined to be 950 mg/kg in mongrel dogs.

Inhalation

Glycerin

Glycerin was administered as an aerosol (particle size < 1.5 µm), nose-only, to Sprague-Dawley rats (10/sex/group) at concentrations of 0, 1000, 2000, or 4000 mg/m^3, for 6 h/d, 5 d/wk, for 2 wk.[2] Two males in the 1000 mg/m^3 group and 1 male and 1 female from the 2000 mg/m^3 group died. No clinical signs, or treatment-related effects for hematology, organ weights, or gross pathology were observed. Body weight gains were decreased in both sexes at all concentrations, and the difference was statistically significant for all groups of exposed female rats (28 - 58%). Glucose levels measured in serum decreased in females at all concentrations (19 - 28%); this effect was not seen in male rats. Minimal to mild squamous metaplasia of the epiglottis was observed in males and females. No dose-related increase in the frequency of metaplasia was observed, but the incidence of mild metaplasia was greatest in the highest dose group (7 animals with minimal and 6 with mild). The inhalation lowest-observed-adverse-effect-level (LOAEL) for glycerin in rats was determined to be 1000 mg/m^3.

Subchronic Toxicity Studies

Oral

Glycerin

In a subchronic oral toxicity study, rats (10/sex/group) were administered 5 or 20% glycerin in the diet for 90 d.[2] No adverse effects were noted in the low-dose group; slight pathological changes were observed in the livers of treated rats in the high-dose group.

Inhalation

Glycerin

In a subchronic inhalation toxicity study, glycerin was administered as an aerosol (particle size < 2.0 µm), nose-only, to Sprague Dawley rats (15/sex/group) at doses of 0, 0.033, 0.167, or 0.662 mg/l for 5 h/d, 5 d/wk, for 13 wk.[2] Three animals per sex were necropsied from the high dose and control groups at 10 wk, and from all dose groups at 13 wk; the lungs of these animals were examined with an electron microscope. All other animals were killed 24 h after the final exposure at 13 wk. No clinical signs or mortality and no treatment-related effects on body weight, clinical chemistry, hematology, organ weights, or gross pathology were observed. Minimal squamous metaplasia of the epiglottis occurred in 2/25, 1/19, 4/20, and 10/21 rats, from the control, low-, mid-, and high-dose groups, respectively. One male in the 0.662 mg/l group showed mild squamous metaplasia. No differences in morphology of the Clara cells in the control and high-dose rats at histological examination of the lungs were observed. Thus, the inhalation NOEL was determined to be 0.167 mg/l in rats.

Chronic Toxicity Studies

Dermal

Glycerin

In a chronic dermal toxicity study, groups of 12 female rabbits had 0.5 or 4 ml of undiluted natural or synthetic glycerin administered to 30% of the body surface for 8 h/d, 5 d/wk, for 45 wk.[2] No treatment-related effects in weight gain, urinalysis, blood counts, skin condition, or gross and microscopic examination were observed at necropsy.

Oral

Glycerin

Groups of 5 female rats received either 5% natural or synthetic glycerin in drinking water for 6 mo.[2] Macroscopic incidental findings included a small thymus in 2 rats and slight interstitial pneumonia in 1 rat treated with natural glycerin; small spleen (with small lymph nodes and moderate hemosiderin deposits) and thymus atrophia were found in an animal treated with synthetic glycerin that died. Calcified masses in kidney tubules were observed between the cortex and medulla of 3 rats treated with natural glycerin and 3 rats treated with synthetic glycerin. In a 2-yr oral toxicity study, no treatment-related effects in hematology, urinalysis, albumin, organ weights, gross pathology, and liver glycogen and lipids were observed in Long-Evans rats (6 - 7/sex/group) administered 0, 5, 10, or 20% natural or synthetic glycerin in the diet. In another chronic oral toxicity study, dogs received 0 or 35% glycerin in feed for 50 wk. Body weights and erythrocyte counts were similar between groups. Treated animals exhibited weight loss (16%) after 36 wk.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Glycerin

Glycerin was tested in several oral developmental and reproductive toxicity studies.[2] Groups of 25 female CD-1 mice were administered 12.8, 59.4, 276, or 1280 mg/kg/d glycerin, via gavage, on day 6 to day 15 of gestation; the NOAEL for maternal toxicity and teratogenicity was determined to be 1280 mg/kg/d. In another study, groups of 28 female Wistar rats received 13.1, 60.8, 282, or 1310 mg/kg/d glycerin, via gavage, on day 6 to day 15 of gestation; the NOAEL for maternal toxicity and teratogenicity was determined to be 1310 mg/kg/d. Groups of 25 female Dutch-belted rabbits received 11.8, 54.8, 254.5, or 1180 mg/kg/d glycerin, via gavage, on day 6 to day 18 of gestation; the NOAEL for maternal toxicity and teratogenicity was determined to be 1180 mg/kg/d. For all 3 studies, the number of implantations, resorptions, litter sizes, weights, sex ratio, as well as external, visceral, and skeletal abnormalities, were similar among groups. In a 2-generation reproductive study using rats (10/sex/group), glycerin was administered at 0 or 20% (~ 2000 mg/kg/d) in drinking water of the parent (F_0) generation for 8 wk prior to mating and until the weaning of pups. No adverse effects on the reproductive efficiency of the parent F_0 generation, or the growth, fertility, or reproductive performance of the untreated offspring (F_1) generation were observed. Additionally, no histological changes occurred in the tissues, and the onset of estrus cycles, weight gain, and microscopic observations of the endocrine organs were comparable to those of the controls in both the F_1 and F_2 generations. All 10 females in the F_0 generation, and 9 out of 10 females in the F_1 generation became pregnant and the F_0 generation had a litter size similar to controls (9.0 vs 8.1).

Other Routes

Glycerin

In a reproductive toxicity study, groups of 12 male rats received 2 intratesticular injections of 50 - 200 µl glycerin, 7 d apart, into the right testes, and underwent further testing for 21 wk.[2] The left testes served as control. The testis of rats treated with 50 µl glycerin had a 45 - 60% reduction in weight compared to the control side along with complete loss of spermatogenic cells. Rats that received testicular injections of 200 µl glycerin had decreased prostate and seminal vesicle weights. When treated males were mated with virgin females at wk 2, 3, 4, 5, and 6 (at the same frequency as controls), the treated males were all infertile after the third mating and remained infertile for the 21-wk post-treatment testing period, i.e., there was no resumption of spermatogenesis. Suppressed spermatogenesis was observed in rats and squirrel monkeys that received an intratesticular injection of 862 mg/kg or 119 mg/kg glycerin, respectively, 1 d prior to mating. No further evidence of toxic or endocrine effects was observed.

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 2 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 90.7% Diglycerin and 2.4% Polyglycerin-3 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

50.8% Polyglycerin-3 and 28.2% Diglycerin, 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 2 separate Ames tests (OECD TG 471).[3,4] A polyglycerol mixture containing 46% Polyglycerin-3, 27.9% Diglycerin, and 2.6% Polyglycerin-6 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

Oral

Glycerin

Male and female rats (24/sex/group) were administered 5 or 10 g/kg glycerin in the diet for 2 yr.[2] No increase in the incidence of tumors was observed. In another long-term study, male and female Long-Evans rats (22/sex/treatment group; 26 controls) received 0, 5, or 10% glycerin (natural and synthetic) in the diet for 2 yr or 20% glycerin (natural and synthetic) in the diet for 1 yr. No increase in the incidence of tumors or in body weight gain was observed in the treated animals, compared to controls. Malignant neoplasms were observed in the control group (5/26). The incidence of malignant neoplasms in the animals treated with 5, 10, and 20% natural glycerin was 1/22, 5/22, and 0/22, respectively; the incidence of malignant neoplasms in the animals treated with 5, 10, and 20% synthetic glycerin was 0/21, 5/22, and 0/22, respectively. Benign neoplasms occurred in none of the controls, 2 animals treated with 5% natural glycerin, 1 animal treated with 10% glycerin, 4 animals treated with 5% synthetic glycerin, 4 animals treated with 10% synthetic glycerin, and 1 animal treated with 20% synthetic glycerin. Among the benign tumors, 3 rats were found with pheochromocytomas and 2 rats were found with granulosa cell tumors.

Co-Carcinogenicity

The synergistic effect of glycerin upon pulmonary tumorigenesis was evaluated in several studies. Groups of 18 – 20 ddy mice were administered 0 or 5% glycerin in drinking water 1 - 4 wk prior to receiving a single subcutaneous injection of 4-nitroquinoline 1-oxide (4NQO), and 21 wk after 4NQO treatment. The number of mice with tumors was: 1/20 (controls: no 4NQO), 8/20 (controls: 4NQO), 11/20 (1 wk glycerin + 4NQO), 11/19 (2 wk glycerin + 4NQO), 7/18 (3 wk glycerin +4NQO), and 15/19 (4 wk glycerin + 4NQO). An increased number of pulmonary tumor-bearing mice and mean number of induced tumors/mouse were observed in mice treated with glycerin after 4NQO treatment, compared to mice treated with 4NQO alone. Groups of 20 male ddy mice were treated with 5% glycerin in drinking water for 25 wk with and without an injection of 4NQO, 4 wk prior (0.3 mg/mouse; dissolved in an olive oil and cholesterol mixture (20:1)). The number of mice that had pulmonary tumors was 2/20 in the control group, 2/20 in the glycerin-only group, 5/20 in the 4NQO-only group, and 17/20 in the combined 4NQO + glycerin group. The mean number of tumors/mouse increased in the combined 4NQO and glycerin group (2.9/mouse) compared to 0.1 – 0.45/mouse in the other groups. All tumors in the 4NQO-treated group were identified as type II adenomas. In the 4NQO + glycerin-treated mice, 52 tumors were identified as type II adenomas and 6 as Clara cell adenomas. In a similar tumorigenesis study, groups of 10 male ddy mice received 0 or 5% glycerin in water for 25 wk, or, following a single injection with 4NQO for 4 wk, 25 wk, or 21 wk (after an interval of 4 wk). No tumors were observed in the control and glycerin-only treated group; tumors were seen in 1/10 animals in the 4NQO-only group, 8/10 animals treated with 4NQO + 4 wk glycerin, 8/9 animals treated with 4NQO + 25 wk glycerin, and 7/10 animals treated with 4NQO + 21 wk glycerin. The mean number of tumors/mouse was the highest in mice treated with 4NQO + 4 wk glycerin (3.5/mouse) compared to 2.3/mouse for those treated with 4NQO + 25 wk glycerin and 1.9/mouse for mice treated with 4NQO + 21 wk glycerin. No morphological or statistical differences were seen between groups receiving combined treatment of 4NQO and glycerin. All pulmonary tumors were adenomas.

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 50.8% Polyglycerin-3 and 28.2% Diglycerin were not irritating in two acute dermal irritation tests performed in New Zealand white rabbits.[3,4] Diglycerin (50%, in water; volume not specified) was not irritating when applied to 50 subjects for 24 h.[5] 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). Similarly, 100% Polyglycerin-3 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. Four guinea pig maximization tests were performed to evaluate the sensitizing potential of Diglycerin, 3 in which the conclusion was non-sensitizing, and 1 in which the number of test animals utilized was inadequate to yield a positive result.[5]

In one study, Diglycerin, 5% aq., was injected intradermally at 10% during induction, and applied dermally (undiluted) during induction and challenge; the test article was not sensitizing. In another study, undiluted Diglycerin was injected intradermally at 5% in water and Freund's complete adjuvant (FCA); undiluted epicutaneous applications were made after pretreatment with 10% sodium lauryl sulfate (SLS) during induction and at challenge; no reactions were observed and the test article was deemed non-sensitizing. In a third test, Diglycerin (99.8% pure) in saline was injected intradermally at 12.5 or 25% during induction; an undiluted dermal application was made during induction and challenge applications were made at 50 or 100%; the test article was not sensitizing. Conversely, in a study in which Diglycerin was administered to 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, 2 of the animals evaluated at 24 h and 3 of the animals evaluated at 48 h after challenge exhibited positive reactions to the undiluted test article. However, as per OECD TG 406, the number of animals tested was not sufficient to decisively conclude that the test article was a sensitizer; the number of test animals used was considered inadequate to reach a conclusion. Two polyglycerol mixtures, one containing 50.8% Polyglycerin-3, 28.2% Diglycerin, 15.9% polyglycerin-4, and 4.9% polyglycerin-5 and higher oligomers and the other containing 43% Polyglycerin-3, 27% Diglycerin, 16% polyglycerin-4, and 14% polyglycerin 5-8, both injected at 5% (of the mixture) during the intradermal induction phase, applied at 100% during epicutaneous induction, and applied at 100% at challenge, 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 95.4% Diglycerin and 2.7% Polyglycerin-3 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 conjunctival irritation was observed in rabbit eyes that were treated with a polyglycerol mixture containing 50.8% Polyglycerin-3 and 28.2% Diglycerin (instilled at 50% in water); signs of irritation resolved in 24 h.[3,4] In a similar acute eye irritation test using the same mixture (instilled neat), moderate conjunctival irritation was noted in all treated rabbit eyes 1 h after treatment with minimal conjunctival irritation at 24 h; signs of irritation resolved in 48 h.[3,4] In another study in which treated eyes were not rinsed, 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 45.6% Polyglycerin-3, 22.2% Diglycerin, and 2.5% Polyglycerin-6; 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 1% [^{14}C] labeled-Polyglycerin-3 and 1% [^{14}C] labeled-Polyglycerin-10, administered via gavage in a liquid diet, was evaluated in groups of male Sprague-Dawley rats. Samples of urine, feces, respiratory CO_2, lymph were collected throughout the 51-h experimental period and were evaluated, along with gastrointestinal tract and carcass contents, for radioactivity distribution. 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. The amounts of recovered radioactivity for Polyglycerin-3 in non-cannulated rats was 2.1% in expired CO_2, 88.3% in urine, 5.5% in feces, 2.9% in gastrointestinal content, and 1.2% in carcass. The detected radioactivity for Polyglycerin-10 in non-cannulated rats was: 4.2% in expired CO_2, 34.1% in urine, 23.9% in feces, 35.2% in gastrointestinal content, and 2.5% in the carcass. For cannulated animals, a small amount of radioactivity was detected in the lymph; 69.5 and 20.2% [^{14}C] labeled-Polyglycerin-3 and 45.4 and 34% [^{14}C] labeled-Polyglycerin-10 was recovered 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 (the highest dose tested) in rats, respectively. Male and female Wistar rats were administered a single 2000 mg/kg

bw dose of undiluted 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 female Sprague-Dawley rats that received 2000 mg/kg bw of a polyglycerol mixture comprising mostly 50.8% Polyglycerin-3 and 28.2% Diglycerin, 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 2 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 90.7% Diglycerin and 2.4% Polyglycerin-3 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, a polyglycerol mixture comprising 50.8% Polyglycerin-3 and 28.2% Diglycerin, and another mixture containing 43% Polyglycerin-3 and 27% Diglycerin were not genotoxic in 2 separate Ames tests at up to 5000 µg/plate, with or without metabolic activation. A polyglycerol mixture containing 46% Polyglycerin-3, 27.9% Diglycerin, and 2.6% Polyglycerin-6 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 in 2 acute dermal irritation tests. Polyglycerin-3 (undiluted) and a polyglycerol mixture containing 50.8% Polyglycerin-3 and 28.2% Diglycerin were not irritating in 2 acute dermal irritation tests performed in rabbits. Diglycerin (50% aq.) was not irritating when applied neat to 50 subjects for 24 h in a human patch test. 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. Undiluted Polyglycerin-3 was not irritating when applied (volume not specified) to 50 subjects for 24 h.

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 SI values were determined to be 1.4, 2.1, and 1.9, respectively. In a guinea pig maximization test, Diglycerin tested at 5% in water, was not sensitizing when injected at 10% during induction and applied dermally at 100% during induction and challenge. In another guinea pig maximization test, undiluted Diglycerin, injected at 5% in water and FCA, and applied dermally at 100% during induction and challenge was not sensitizing. 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 3 of the animals evaluated at 48 h exhibited positive reactions to the undiluted test article; however, the number of animals tested were not adequate for the results to be conclusive. Diglycerin tested at 99.8% in saline, that was injected at 12.5 or 25% during induction, applied dermally at 100% during induction, and at 50 or 100% during challenge was not sensitizing in a guinea pig maximization test. Two polyglycerol mixtures, one containing 50.8% Polyglycerin-3, 28.2% Diglycerin, 15.9% polyglycerin-4, and 4.9% polyglycerin-5 and higher oligomers and the other containing 43% Polyglycerin-3, 27% Diglycerin, 16% polyglycerin-4, and 14% polyglycerin 5-8, both injected at 5% (of the mixture) during the intradermal induction phase, and applied at 100% during epicutaneous induction and challenge, were not sensitizing in 2 separate guinea pig maximization tests.

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 95.4% Diglycerin and 2.7% Polyglycerin-3 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-3 was instilled in an acute eye irritation test using rabbits. Minimal conjunctival irritation resolved within 24 h in an acute eye irritation test evaluating a polyglycerol mixture containing 50.8% Polyglycerin-3 and 28.2% Diglycerin, instilled at 50% in water; moderate conjunctival irritation resolved within 48 h in a similar test, in which the same mixture was instilled neat. In an acute eye irritation test evaluating a polyglycerol mixture containing 45.6% Polyglycerin-3, 22.2% Diglycerin, and 2.5% Polyglycerin-6, signs of slight irritation in the conjunctivae of 3 male New Zealand white rabbits resolved in 24 h.

DISCUSSION

The Panel assessed the safety of Diglycerin, Polyglycerin-3, Polyglycerin-6, and Polyglycerin-10 as used in cosmetic formulations. The Panel reviewed the available data and concluded that these 4 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

The Panel noted that the toxicological profile for these ingredients, including negative dermal irritation and sensitization data, demonstrated safety. The Panel noted a lack of carcinogenicity studies on these ingredients; however, concern for the lack of these data was mitigated by negative genotoxicity results. Moreover, the Panel discussed that these ingredients are not likely to be absorbed in the skin (based, in part, on log p values). Additionally, the Panel noted that these polyglycerins

exist as mixtures of polymers of varying lengths. The Panel considered its prior safety determination of glycerin and deemed it appropriate for use as supporting data for endpoints that were absent in this assessment, i.e., repeated-dose toxicity, developmental and reproductive toxicity, and carcinogenicity. Thus, these data further substantiated safety.

The Panel discussed the potential for incidental inhalation exposure that could result from the use of these ingredients in products which may be applied via spray or as a powder (e.g. in face and neck products). However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

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

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 4 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Diglycerin
Polyglycerin-3
Polyglycerin-6
Polyglycerin-10

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)				

NR – not reported

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

**likely duration and exposure are derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[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.

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 TG 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	water	50%, NR	50 subjects	24- h, occlusive application (further details not provided). Test sites were evaluated 24, 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]
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 under 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]
Polyglycerin-3	NA	NR, applied neat	50 subjects	24-h occlusive application. Test sites were evaluated 24, 48, and 72 h after patch removal.	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, 5% aq.	water	Induction: intradermal: 10%, (effective concentration: 0.5%) dermal: 100% (effective concentration: 5%) Challenge: 100% (effective concentration: 5%)	10 female Dunkin-Hartley guinea pigs; 5 negative controls	OECD TG 406. Guinea pig maximization test. Positive controls were challenged with mercaptobenzothiazole. Reactions were scored 24 and 48 h post-challenge.	Not sensitizing	5
Diglycerin	water	Induction: intradermal: 5%, dermal: 100% Challenge: 100%, 0.5 ml	10 male and 10 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, 99.8% pure	physiological saline	Induction: intradermal: 12.5 or 25%, dermal: 100% Challenge: 50% or 100%, 0.5 ml	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	water	Induction: intradermal: 20% v/v in FCA, dermal: 100% Challenge: 100%	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.	Results were inconclusive. 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. As per OECD TG 406, the number of animals utilized was inadequate to confirm a positive result.	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

Table 6. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
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	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: 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: 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

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