Safety Assessment of Glycerin Ethoxylates as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (i.e., August 18, 2020) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 8 glycerin ethoxylates as used in cosmetic formulations. All of these ingredients are reported to function as skin-conditioning agents, and most are also reported to function as viscosity-decreasing agents. The Panel reviewed relevant data relating to the safety of these ingredients. The Panel noted the need for additional experimental details for some of the sensitization studies, and concluded that the available data are insufficient to make a determination of safety that these glycerin ethoxylates are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

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

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

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

The rationale for this grouping of ingredients stems from the fact that these ingredients are structurally-related as polyethylene glycol ethers of glycerin. The Panel has reviewed the safety of other similar, structurally-related, families of ingredients. In 2010, the Panel issued a final report on the safety of polyethylene glycols (PEGs); the Panel concluded that the PEGs are safe in the present practices of use and concentration.[2] In 2015, the Panel issued a safety assessment on glycerin, with the conclusion that glycerin was safe as a cosmetic ingredient in the practices of use and concentration described in the safety assessment.[3] Additionally, the Panel has issued safety assessment reports of structurally-related polyethoxylated compounds, such as alkyl PEG ethers and PEGs cocamine, in which it was concluded that these ingredients are safe in the present practices of use and concentration.[4,5] These reports are available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

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

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

CHEMISTRY

Definition and Structure

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

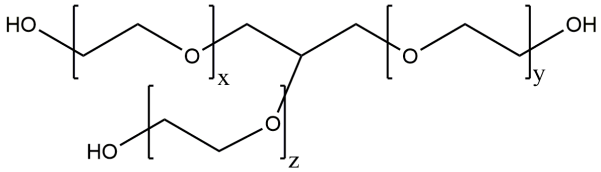


Figure 1. Glycerin ethoxylates, wherein the average ethoxylation value equals x + y + z (e.g., x + y + z = 3 in the case of Glycereth-3)

The definition of each ingredient, as given in the *Dictionary*, is provided in Table 1. This group of ethoxylated glycerin ingredients is identified by the CAS No. 31694-55-0.[1] For the data summarized herein as "ethoxylated glycerol," the REACH dossier describes the average ethoxylation value as between 1 and 6.5, inclusive of 1 and 6.5. Thus, the average

ethoxylation value for "ethoxylated glycerol" may be described as $1.0 \leq x + y + z \leq 6.5$ for the test material evaluated in those summaries. While ethoxylated glycerin is not precisely defined as a cosmetic ingredient, comparing this range of average ethoxylation values to those of the ingredients in this report, Glycereth-3 (i.e., $x + y + z = 3$) falls in that range. Accordingly, structurally, ethoxylated glycerin is a suitable candidate for a read-across source to these ingredients, especially Glycereth-3. Justifications for the use of propoxylated nitriloethanol, propoxylated glycerol, and ethoxylated glycerol as read-across sources are provided in Table 2, and such use is described in the body of the report.

Physical and Chemical Properties

Ethoxylated glycerin is a non-volatile (vapor pressure 0.0000389 hPa at 20ºC), slightly viscous liquid at room temperature, and it is fully miscible with water.[6] Physical and chemical properties of glycerin ethoxylates are presented in Table 3.

Method of Manufacture

These ingredients, in general, are the products resulting from the reaction of glycerin and ethylene oxide.[7] Glycerin ethoxylates belong to the chemical class of alkoxylated alcohols which are also polyether alcohols (specifically, polyethylene glycol ethers of glycerin). Polyether alcohols are often formed from the reaction of an alcohol with an alkylene oxide, such as ethylene or propylene oxide.[1] Since the ether formed from the reaction of one molecule of an alcohol with one molecule of the alkylene oxide is also an alcohol, the reaction with the alkylene oxide can continue until the latter is consumed.

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

Impurities

A previous Panel safety assessment of the chemically similar alkyl PEG ethers confirms that dioxane (1,4-dioxane) and ethylene oxide can be present as reaction by-products.[4]

Glycereth-26

In a certificate of analysis provided by a manufacturer, it was noted that Glycereth-26 contained < 0.0005% 1,4-dioxane, < 0.0001% ethylene oxide, 0% free glycerin, and 0.05% water.[8]

USE

Cosmetic

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

These ingredients are used in a variety of rinse-off and leave-on cosmetics products. According to 2020 VCRP survey data, Glycereth-26 is reported to be used in 437 formulations, and Glycereth-7 is reported to be used in 80 formulations (Table 4).[9] The three other in-use ingredients are reported to be used in 21 formulations or less. The results of the concentration of use survey conducted by the Council in 2018, and updated in 2019, indicate Glycereth-26 has the highest maximum concentration of use, at 39.5% in skin cleansing products.[10] The highest concentration of use reported for products resulting in leave-on dermal exposure is 6% Glycereth-26 in eye lotion formulations.

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

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

deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[13,14]

The ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[15]

Non-Cosmetic

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

TOXICOKINETICS STUDIES

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute dermal, oral, and inhalation studies summarized below are described in Table 5.

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

The oral LD_{50} of Glycereth-3 tested at concentrations of 1 - 50% was > 10 mL/kg in male and female rats.[6] In an acute oral toxicity study of Glycereth-26, the LD_{50} was determined to be > 5000 mg/kg in male and female albino rats.[16] In female Wistar rats, the oral LD_{50} of "ethoxylated glycerol" was > 2000 mg/kg.[6] In another oral toxicity study, the LD_{50} of "ethoxylated glycerol" in Sprague-Dawley rats was > 10,000 mg/kg.

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

Short-Term Toxicity Studies

Oral short-term toxicity data were not found for the glycerin ethoxylates reviewed in this report. However, data for propoxylated nitrilotriethanol were reported [6] which enabled read-across evaluation of short-term toxicity. This read-across source is of similar structure to glycerin ethoxylates, with a small core structure modified with propoxy groups. These molecules are predicted to have similar absorption, distribution, metabolism, and chemical reactivity to glycerin ethoxylates and these compounds are expected to have similar toxicological profiles.

Oral

Propoxylated nitrilotriethanol (a read-across source)

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

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

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity data were not found for the glycerin ethoxylates reviewed in this report. However, data for propoxylated nitrilotriethanol were reported,[6] which enabled evaluation of developmental and reproductive toxicity. The read-across source is of similar structure to glycerin ethoxylates, with a small core structure modified with propoxy groups. These molecules are predicted to have similar absorption, distribution, metabolism and chemical reactivity to glycerin ethoxylates and these compounds are expected to have similar toxicological profiles.

Oral

Propoxylated nitrilotriethanol (a read-across source)

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

GENOTOXICITY

Genotoxicity data were not found for the glycerin ethoxylates reviewed in this report. However, data for ethoxylated glycerol, propoxylated glycerol and propoxylated nitrilotriethanol were reported,[6] which enabled evaluation of genotoxicity. These read-across sources are mixtures of compounds similar or identical to glycerin ethoxylates. These molecules are predicted to have similar absorption, distribution, metabolism and chemical reactivity to glycerin ethoxylates and these compounds are expected to have similar toxicological profiles.

In Vitro

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

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

Propoxylated glycerol (a read-across source)

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

Propoxylated nitrilotriethanol (a read-across source)

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

CARCINOGENICITY STUDIES

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

DERMAL IRRITATION AND SENSITIZATION

Irritation

In vitro dermal irritation data were not found for the glycerin ethoxylates reviewed in this report. However, data for "ethoxylated glycerol" were reported,[6] which enabled in vitro evaluation of skin irritation. The read-across source is a mixture of compounds similar to glycerin ethoxylates. These molecules are predicted to have similar absorption, distribution, metabolism and chemical reactivity to glycerin ethoxylates and these compounds are expected to have similar toxicological profiles.

In Vitro

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

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

Animal

Glycereth-3

Skin irritation potential was evaluated using 2 Vienna white rabbits using a test method comparable to OECD TG 404.[6] Glycereth-3 (1 mL) was applied neat to shaved skin area of 2.5 cm x 2.5 cm by an occlusive dressing for 20 h, and the test sites were observed at 24 h, 48 h, and 8 days. No edema and erythema findings were observed. The test article was considered to be non-irritating to rabbit skin.

Glycereth-26

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

Sensitization

Animal skin sensitization data were not found for glycerin ethoxylates. However, data for propoxylated glycerol were reported,[6] which enabled evaluation of skin sensitization. The read-across source is a mixture of compounds similar to glycerin ethoxylates. These molecules are predicted to have similar absorption, distribution, metabolism and chemical reactivity to glycerin ethoxylates and these compounds are expected to have similar toxicological profiles.

Animal

Propoxylated glycerol (a read-across source)

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

Human

Glycereth-7

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

A leave-on product containing 1% Glycereth-7 was tested in an HRIPT in 199 subjects.[18] The test material was applied occlusively for 24 to 48 h via 9 applications made over a 3-week induction period. After a 2-week rest period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24, 48, 72, and 96 h after application. Four subjects exhibited low-level reactions (0 - 1 score, on a 0 - 4 scale) during induction; no other responses were noted during induction, or during challenge. The researchers concluded that the test material did not induce dermal sensitization.

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

Glycereth-12

An HRIPT of a mascara formulation containing 0.35% Glycereth-12 was performed in 100 subjects.[19] The test material (0.2 g) was applied with an occlusive, hypoallergenic patch to the infrascapular regions of the back for 9 applications. After a 14-day rest period, the same concentration and amount of the test substance was used in the challenge

phase; patches were applied to a previously untested site, and reactions were scored 24 and 48 h after application. Of the 103 initial study participants, only 3 did not complete the study; discontinuation was not due to adverse reactions. There were no signs of irritation or sensitization in those who completed the study.

Glycereth-26

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

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

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

A product containing 5% Glycereth-26 was tested in an HRIPT on 55 subjects.[21] The test material was applied to a 1 in^2 absorbent pad portion of an adhesive dressing and applied to the skin under semi-occlusion for 24 h. Nine induction applications were made. After a 2-week non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24 and 72 h after application. The test material did not demonstrate a potential for eliciting dermal irritation or allergic contact sensitization.

An HRIPT of a 10% aqueous solution of Glycereth-26 was performed in 200 subjects.[22] Discs of lintine paper were moistened with the test material (amount not specified) and secured to a site on the upper arm for 24 h. After 24 h, the patch was removed and the contact site was rested for 24 h. Repeated 24-h patch applications were applied 3 times/wk , for 5 wks, for a total of 15 applications. After a 2-wk non-treatment period, the challenge patch was applied on the same contact sites with the test material (amount not specified) for 24 h under occlusion. Upon removal of the challenge patch, the contact site was examined immediately and after 24 and 48 h. No visible skin changes occurred upon challenge, and test substance was deemed a non-sensitizer.

OCULAR IRRITATION STUDIES

In addition to ocular irritation data found for glycerin ethoxylates, data for ethoxylated glycerol were reported,[6] which further enabled evaluation of ocular irritation. The read-across source is a mixture of compounds identical to glycerin ethoxylates. These molecules are predicted to have similar absorption, distribution, metabolism and chemical reactivity to glycerin ethoxylates and these compounds are expected to have similar toxicological profiles.

In Vitro

Glycereth-12

In an EpiOcular™ assay, a 20% aqueous dilution of a product containing 0.35% Glycereth-12 was tested at 100 µL; the effective test concentration was 0.07% Glycereth-12.[23] Appropriate negative and positive controls were used. The estimated Draize ocular irritation score of the test material at 100% was predicted to be 0, and it was classified to be non-irritant.

Glycereth-26

The ocular irritation potential of undiluted Glycereth-26 (100 µL) was evaluated in vitro in an EpiOcular™ human cell assay.[24] The cell cultures were tested in duplicate, with exposure times of 0.33, 1, 2, and 4 h. Appropriate negative and positive controls were used. The ET_{50} (time to reduce tissue viability as measured using MTT) was > 4 h for Glycereth-26; this was predicted to be non-irritating.

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

The potential irritation of "ethoxylated glycerol" was studied in a bovine corneal opacity and permeability (BCOP) test conducted according to OECD TG 437.[6] "Ethoxylated glycerol" (750 µL) was applied directly to the epithelial surface of the cornea using a syringe (open chamber method) for 10 minutes. Highly deionized water was used as the negative control, and a 1% (w/v) solution of sodium hydroxide in highly de-ionized water served as the positive control (treatment group consisted of 3 corneas). The opacity and permeability assessments of the cornea were derived by an in vitro irritancy score (IVIS), which is used to classify the irritancy level of the test article. The calculated mean IVIS was 3.0 ± 1.2, 2.6 ± 3.3, and 184.0 ±

20.9 in the test group, the negative control group, and the positive control group, respectively. It was concluded the test substance does not cause serious eye damage in the BCOP test.

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

Animal

Glycereth-3

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

Glycereth-26

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

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

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

SUMMARY

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

These ingredients are mostly used in leave-on formulations. Glycereth-26 has the highest reported frequency of use (437 formulations), and Glycereth-7 has the second greatest reported number of uses (80). Glycereth-26 has the highest concentration of use, at 39.5% in skin cleansing products. The highest concentrations of use reported for products resulting in leave-on dermal exposure is 6% Glycereth-26 in eye lotions.

No acute toxicity was observed when Glycereth-3 was administered orally at concentrations ranging from 1 - 50% to male and female rats. The oral LD_{50} was determined to be > 10 mL/kg. In an acute oral toxicity study of Glycereth-26, the LD_{50} was determined to be > 5000 mg/kg dose. No evidence of toxicity was observed in an acute oral toxicity study using female Wistar rats where the oral LD_{50} of "ethoxylated glycerol" was > 2000 mg/kg. Similarly, no evidence of toxicity was reported when "ethoxylated glycerol" was administered orally to Sprague-Dawley rats, and the LD_{50} was > 10,000 mg/kg. The acute dermal LD_{50} of "ethoxylated glycerol" was calculated to be > 5000 mg/kg in rats.

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

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

A reproductive/developmental toxicity screening test was performed with 12 male and 12 female Wistar rats. Animals were administered a propoxylated nitrilotriethanol (average MW = 280 g/mol) in water at doses up to 1000 mg/kg. The rats in each dose group were allowed to deliver. Transient salivation was noted in both sexes of the parental rats dosed with 1000 mg/kg. Slight body weight loss occurred in females of the 1000 mg/kg dose group during lactation and marginal body weight

gains were noted during the premating period at all doses. There were no effects on total body weights or viability of offspring, and no embryotoxic or teratogenic effects were reported. The NOAEL was > 1000 mg/kg bw/day.

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

According to the results of an EpiDerm™ assay, "ethoxylated glycerol" is not expected to be irritating. In a dermal irritation study, Glycereth-3 was applied for 20 h to a shaved skin area of 2.5 cm x 2.5 cm on 2 Vienna white rabbits using an occlusive dressing. The test article was considered to be non-irritating to the skin. In another study, 3 male and 3 female rabbits had 0.5 mL of Glycereth-26 applied once under an occluded patch on both abraded and non-abraded sites, with no signs of irritation observed at 24 and 72 h after application. The test article was deemed to have no irritation potential.

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

A leave-on product containing 0.68% Glycereth-7 was tested undiluted for skin sensitization potential using in an HRIPT completed in 199 subjects. Three subjects exhibited low-level reactions during induction; the test material did not induce dermal sensitization. A 1% leave-on and a 2% rinse-off Glycereth-7 product were tested for skin sensitization potential via occlusive HRIPT, in up to 211 subjects. Four subjects exhibited low level reactions during induction for the leave-on product. Two subjects exhibited low-level reactions during induction, and eleven subjects during challenge, for the rinse-off product. The test materials were deemed non-sensitizing. A mascara formulation containing 0.35% Glycereth-12 was evaluated for skin sensitization potential in an HRIPT using 100 subjects. Neither irritation nor sensitization were observed. A product containing 3% Glycereth-26 was evaluated in an HRIPT in 200 subjects. Eight subjects exhibited low-level reactions during induction, and 1 subject exhibited a high-level reaction during induction; the researchers concluded that the test material did not induce significant dermal irritation and allergic contact sensitization. A rinse-off product containing 3% Glycereth-26 was tested undiluted in a semi-occlusive HRIPT in 103 subjects; one participant withdrew due to an adverse reaction, and low-level reactions during induction and challenge supported the potential for cumulative dermal irritation potential. A leave-on product containing 3% Glycereth-26 was tested undiluted in an occlusive HRIPT in 208 subjects; 38 subjects exhibited low-level reactions during induction; the test material did not induce dermal sensitization. The skin sensitization potential of a product containing 5% Glycereth-26 was evaluated in a maximization test involving 55 subjects. No adverse reactions were observed, and there were no instances of dermal irritation or allergic contact sensitization. An HRIPT was performed in 200 subjects on a 10% aqueous solution of Glycereth-26; neither changes in skin nor signs of sensitization were observed during the induction or challenge applications.

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

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

DISCUSSION

The 8 glycerin ethoxylates reviewed in this document are structurally-related as polyethylene glycol ethers of glycerin. The Panel has previously reviewed structurally-related ingredients, such as alkyl PEG ethers and PEGs cocamine, which were determined to be safe in the present practices of use and concentration, when formulated to be non-irritating.

Data for a few toxicological endpoints were not available for these ingredients; however, several endpoints for read-across sources, including short-term toxicity, oral developmental and reproductive toxicity, genotoxicity, in vitro dermal irritation, animal sensitization, and animal ocular irritation, have been included this report. The Panel considered propoxylated nitrilotriethanol, propoxylated glycerol, and ethoxylated glycerol to have similar chemical and toxicological profiles to the ingredients being reviewed, and felt that these read-across sources could be utilized, as appropriate, to mitigate data gaps. Furthermore, the Panel deemed these read-across sources as representative of lower molecular weight glycerin ethoxylates, and were reassured due to their previous review of polyethoxylated ingredients.

The Panel discussed the issue of incidental inhalation exposure from formulations which are aerosolized, such as the body and hand spray formulations containing 1% Glycereth-26. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns. Results from an acute inhalation study of rats with Glycereth-3, the smallest and most volatile of these ingredients, produced no mortality and no clinical or gross pathology. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

Finally, the Panel did not suspect any mechanistic basis for sensitization by these ingredients, as this family of polyether alcohols does not have the propensity to react with proteins, or to produce metabolites that would cause concern. However, HRIPT summaries for several ingredients reported low-level reactions during the induction, and sometimes challenge, phase. Because these studies did not include subject-level details, the Panel could not evaluate the reason for the reactions. An additional negative HRIPT of 10% aqueous Glycereth-26 was submitted; however, this study was also without subject-level detail. Because the reasons for the reported reactions could not be clarified, and because the study of 10% aqueous Glycereth-26 did not contain subject-level detail, concern for the sensitization potential of these ingredients was not mitigated. Accordingly, the Panel deemed that the available data are insufficient to make a determination of safety for the glycerin ethoxylates. The data requests remain:

- Full experimental details for the previously submitted sensitization summaries/studies; or
- A newly completed HRIPT, with fully-disclosed experimental data, at or above maximum concentrations of use for Glycereth-26, with $n \geq 100$ participants

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination that the following 8 ethoxylated glycerin ingredients are safe under the intended conditions of use in cosmetic formulations.

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

** Not reported to be in current use.*

TABLES

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

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

Table 2. Read across justification

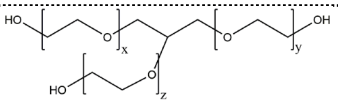
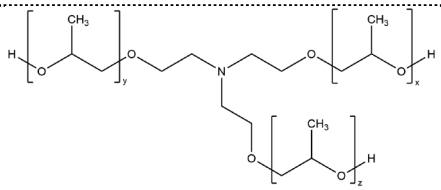
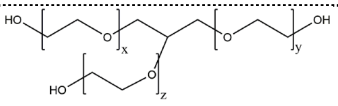
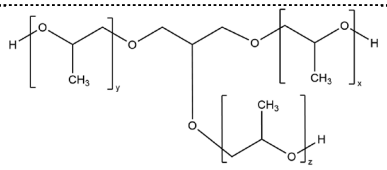
	Target Ingredient(s)	Read-Across Source
Name	***Glycerin ethoxylate ingredients***	*Propoxylated nitriloethanol*[6]
CAS No.	31694-55-0	31694-55-0
Structure		
read-across endpoints		• short-term toxicity – oral • DART, oral • genotoxicity; in vitro
justification	similar small core structure modified with propoxyl groups; molecules are predicted to have similar absorption, distribution, metabolism, chemical reactivity, and toxicological profiles	
Name	***Glycerin ethoxylates ingredients***	*Propoxylated glycerol*[6]
CAS No.	31694-55-0	31694-55-0
Structure		
read-across endpoints		• genotoxicity; in vitro • dermal sensitization; animal
justification	similar small core structure modified with propoxyl groups; molecules are predicted to have similar absorption, distribution, metabolism, chemical reactivity, and toxicological profiles	

Table 2. Read across justification

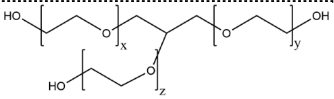
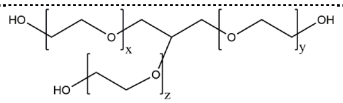
	Target Ingredient(s)	Read-Across Source
Name	***Short-chain glycerin ethoxylate ingredients, especially Glycereth-3***	*Ethoxylated glycerol*[6]
CAS No.	31694-55-0	31694-55-0
Structure		
read-across endpoints		• acute toxicity; dermal, oral; inhalation • genotoxicity; in vitro • dermal irritation; in vitro • ocular irritation; in vitro, animal
justification	mixture of compounds similar to glycerin ethoxylates; molecules are predicted to have similar absorption, distribution, metabolism and chemical reactivity to glycerin ethoxylates and these compounds are expected to have similar toxicological profiles	

Table 3. Physical and Chemical Properties

Property	Value	Reference
	"ethoxylated glycerol"	
Physical Form	clear liquid	6
Density/Specific Gravity (@ 20ºC)	1.163	6
Viscosity (mPa·s @ 20 ºC)	399	6
Vapor pressure (hPa @ 20ºC)	0.0000389	6
Melting Point (ºC)	-49.1	6
Boiling Point (ºC)	260	6
Water Solubility (g/L @ 20ºC)	1000	6
	Glycereth-3	
Molecular Weight (g/mol)	224.25	25
log P	-1.79 (estimated)	25
	Glycereth-7	
Physical Form	Yellow to amber color, mild odor	26
Molecular Weight (g/mol)	400.47	25
log P	-2.42 (estimated)	25
	Glycereth-8	
Molecular Weight (g/mol)	444.52	25
log P	-2.57 (estimated)	25
	Glycereth-12	
Molecular Weight (g/mol)	620.73	25
log P	-3.19 (estimated)	25
	Glycereth-18	
Molecular Weight (g/mol)	885.05	25
log K_{ow}	-7.19 (estimated)	27
	Glycereth-20	
Molecular Weight (g/mol)	972.57	25
log K_{ow}	-7.73 (estimated)	27
	Glycereth-26	
Physical Form	Yellow to amber color, mild odor	28
Molecular Weight (g/mol)	1237.47	25
log K_{ow}	-9.38 (estimated)	27
Acid value (mg KOH/g)	0.2	8
Hydroxyl value (mg KOH/g)	133.40	8
Ash content (following pyrolyzation)	0.04%	8
Specific gravity (at 25°C)	1.134	8
Dissociates in water (at pH, in 5% aq solution)	6.6	8
	Glycereth-31	
Molecular Weight (g/mol)	1457.74	25
log K_{ow}	-10.75 (estimated)	27

Table 4. Frequency (2020)[9] and concentration (2019)[10] of use data for glycerin ethoxylates

	# of Uses[9]	Max Conc of Use (%)[10]	# of Uses[9]	Max Conc of Use (%)[10]	# of Uses[9]	Max Conc of Use (%)[10]
	Glycereth-7		**Glycereth-12**		**Glycereth-18**	
Totals*	**80**	**1 - 2**	**6**	**0.09 - 0.35**	**21**	**0.019 - 0.32**
Duration of Use						
Leave-On	*76*	*1*	*6*	*0.21 - 0.35*	8	*0.019 - 0.3*
Rinse-Off	*4*	*2*	*NR*	*0.09*	13	*0.3 - 0.32*
Diluted for (Bath) Use	*0*	*NR*	*NR*	*NR*	NR	*NR*
Exposure Type						
Eye Area	NR	NR	3	0.09-0.35	NR	0.019-0.036
Incidental Ingestion	67	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	6[a]; 2[b]	NR	2[b]	NR	5[a]; 1[b]	NR
Incidental Inhalation-Powder	2[b]	NR	2[b]	NR	1[b]	0.3[c]
Dermal Contact	13	1- 2	4	0.09- 0.21	21	0.036-0.32
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	68	NR	NR	NR	9	0.3
Baby Products	NR	NR	NR	NR	NR	NR

	Glycereth-20		**Glycereth-26**		
Totals*	**3**	**NR**	**437**	**0.3 - 39.5**	
Duration of Use					
Leave-On	*3*	*NR*	338	*0.3 - 6*	
Rinse Off	*NR*	*NR*	99	*0.9 - 39.5*	
Diluted for (Bath) Use	*NR*	*NR*	NR	*NR*	
Exposure Type					
Eye Area	NR	NR	18	2-6	
Incidental Ingestion	NR	NR	NR	NR	
Incidental Inhalation-Spray	2[a]; 1[b]	NR	5; 128[a]; 138[b]	1; 0.3-2[a]	
Incidental Inhalation-Powder	1[b]	NR	138[b]	1[c]	
Dermal Contact	2	NR	385	1-39.5	
Deodorant (underarm)	NR	NR	NR	NR	
Hair - Non-Coloring	NR	NR	50	0.3-1	
Hair-Coloring	NR	NR	1	NR	
Nail	NR	NR	NR	NR	
Mucous Membrane	NR	NR	35	NR	
Baby Products	NR	NR	NR	NR	

NR = Not reported.

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

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

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

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

Table 5. Acute toxicity studies

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

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