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Final Report on the Safety Assessment of Glyceryl Oleate

Glyceryl Oleate, the glyceryl 1-monoester of oleic acid, is used in cosmetic products as an emulsifier at concentrations up to 5%.

Oral administration of a single 13 ml/kg dose of a sunscreen formulation containing 5% Glyceryl Oleate to rats produced no signs of toxicity and no lethality.

A single exposure of undiluted Glyceryl Oleate in animal dermal irritation studies produced only minimal irritation. Daily applicatoins of 25.0% corn oil solution of a formulation containing Glyceryl Oleate for 20 days produced severe dermal irritation in rabbits. In a 4-week dermal toxicity/phototoxicity study, product formulations containing up to 5% Glyceryl Oleate produced slight reversible dermal irritation. Subchronic and chronic toxicity data from studies with animals and humans that were used in the safety assessment of glycerides, glycerol, oleic acid, and sodium oleate are presented.

Minimal to moderate eye irritation was produced by undiluted Glyceryl Oleate in rabbits.

Glyceryl Oleate administration was associated with development of a small number of brain tumors in a two-generation study in mice. Digestive tract tumors were found in mide fed 200 mg/mouse per day Glyceryl Oleate for four–seven generations. The results of these studies were considered equivocal. Doses of 1.5 and 6.0 mg/mouse per day of Glyceryl Oleate in saline increased the survival period of mice with implanted Ehrlich ascites tumors; the higher dose inhibited tumor growth.

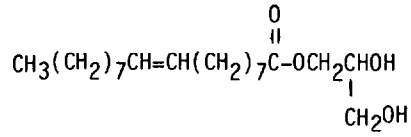
Formulations containing 5% Glyceryl Oleate were nonirritating in a human cumulative occlusive patch test and in repeat insult patch testing at 15%. Glyceryl Oleate in formulations is not phototoxic.

It is concluded that Glyceryl Oleate is safe as a cosmetic ingredient in the present practices of use and concentration.

CHEMISTRY

Chemical and Physical Properties

Glyceryl Oleate (CAS 111-03-5; 25496-72-4) is the glyceryl 1-monoester of oleic acid (*cis*-9-octadecenoic acid). The structural formula of Glyceryl Oleate is as follows[1]:



Glyceryl Oleate occurs as off-white to yellow flakes or as a soft semisolid. It is dispersible in water and soluble in acetone, methanol, ethanol, cottonseed oil, and mineral oil.[2] Glyceryl Oleate is also known as Monoolein, Glyceryl Monooleate, and Glycerol Monooleate.

A summary of the properties of Glyceryl Oleate appears in Table 1. In addition, the emulsifying and physicochemical properties of several monoglycerides have been measured in a Russian study.[3]

TABLE 1. Chemical and Physical Properties[2,9,10]

	Glyceryl Oleate
Molecular weight	365.55
Melting point (°C)	35
Boiling point (°C)	238–240
Density	0.9420
Acid value	5 max
Saponification value	155–170
Iodine value	48–80

Analytical Methods

Gas chromatography has been used to isolate and identify monoglycerides (via comparison with standard retention values).[4] Several other procedures have been coupled with gas chromatography for the determination of the separated monoglycerides or their hydrolysis products (hydrolysis products of Glyceryl Oleate are glycerol and oleic acids). These methods are nuclear magnetic resonance spectrometry[5] and a battery of spectrophotometric analyses. The most widely used chemical assay for the quantitation of glycerol or its 1-monoglycerides involves periodate or lead tetraacetate oxidation of these compounds' primary alcohol groups.[6,7] Qualitative chemical tests to assay for the presence of glycerol involve formation of colored derivatives.[4,6] Infrared spectrometry may also be used for functional group identification or for fingerprinting upon comparison with stock standards.[4]

Method of Manufacture

"Monoglycerides do not occur naturally in appreciable quantities, except in fats and oils that have undergone partial hydrolysis."[7] The most important method of monoglyceride preparation is the glycerolysis of fats and oils. Depending on the molar ratios of the reactants, this transesterification reaction can yield product mixtures containing varying quantities of monoglycerides, commercially noted as "40 percent monos" and "60 percent monos."[7]

Separation of the monoglycerides from di- and triglycerides is usually achieved by molecular distillation of the glycerolysis product mixture, resulting in the "90 percent mono" mixture used by the cosmetic industry. These commercial 90% monoglyceride mixtures predominantly consist of α-monoglycerides; β-monoglycerides are present in smaller quantities. Isomerization of β-monoglycerides to the more stable α-isomers occurs readily.[7]

The Glyceryl Oleate used by the cosmetic industry may be manufactured by the glycerolysis (glycerol is normally obtained from the triglycerides of oil and fats)[8] of oils containing high concentrations of oleic acid: olive oil (80% oleic acid), peanut oil (60% oleic acid), teaseed oil (85% oleic acid), or pecan oil (85% oleic acid). The Glyceryl Oleate could then be distilled from the resulting product mixture (vapor pressure of Glyceryl Oleate at 186°C is 0.2 mm).[7]

Impurities

Glyceryl Oleate used by the cosmetic industry is a mixture of monoglycerides consisting mainly of the compound, glyceryl α-monooleate.[2] The stated 90% minimum monoester content as written includes both α- and β-monoglycerides of oleic acid and glycerol and may also include glycerol monoesters containing other fatty acids depending on the method of manufacture (e.g., sources of reactants).

Constituents, such as free fatty acids and glycerol, may also exist in the Glyceryl Oleate preparation at maximal concentrations of 2.5% and 1.0%, respectively.[2]

USE

Purpose, Scope, and Extent of Use in Cosmetics

Glyceryl Oleate is used primarily as an emulsifier in cosmetic products. It has been reported to the Food and Drug Administration (FDA) that Glyceryl Oleate is an ingredient in 716 cosmetic formulations. Reported concentrations ranged from $\leq$0.1% to 5%. The concentrations of Glyceryl Oleate in 455 of the 716 cosmetic formulations were not reported to FDA. Cosmetic formulations containing Glyceryl Oleate are predominantly lipsticks, eye shadows, makeup bases, and skin care preparations.[11]

The cosmetic product formulation listing that is made available by FDA is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[12] Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic

ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. See Table 2 for a list of cosmetic products containing Glyceryl Oleate.

Surfaces, Frequency, and Duration of Contact

Cosmetics containing these ingredients are applied to all areas of the skin and mucous membranes. These cosmetics are frequently applied to the face and have the potential for contacting the eye or being ingested from the lips. Products containing these ingredients are applied up to several times a day and can remain in contact with the skin for long periods of time.

Noncosmetic Use

Monoglycerides consisting of a mixture of glyceryl mono- and diesters, and minor amounts of triesters, that are prepared from fats or oils or fat-forming acids derived from edible sources[13] are affirmed as generally recognized as safe (GRAS) substances (21 CFR 182.4505, 182.90)[12] and indirect food additives (21 CFR 175.105, 176.210)[12] for human consumption without restriction on their concentration (at concentrations not to exceed good manufacturing practice, GMP). Federal regulations allow the use of Glyceryl Oleate as a prior-sanctioned food ingredient (21 CFR 181.27)[12] and as both an indirect (21 CFR 175.300, 175.320)[12] and direct (21 CFR 172.515)[12] food additive. These regulatory decisions were based on a review of data in the following areas: subchronic[14-16] and chronic (multigeneration reproduction)[17] feeding studies using Glyceryl Oleate or monoglyceride mixtures derived from oils; subchronic[18,19] and chronic[20] feeding studies of similar glycerides; studies on the absorption and storage of Glyceryl Oleate and other monoglycerides[17,18,21]; and the well-documented metabolic fate of glycerides in the human body. Studies on the metabolites of Glyceryl Oleate, glycerol, and oleic acid as they appear in reviews used by the FDA in the regulation of glycerol, glycerides, and oleic acid are summarized in this report.

The FDA proposed affirmation of GRAS status of Glyceryl Oleate (Proposed issuance of 21 CFR 184.1323) and monoglycerides (proposed issuance of 21 CFR 184.1505) for several additional purposes in human food and concurrent deletion of its listing as a direct food additive (amendment of 21 CFR 172.515).[22] The listing of the most prevalent fatty acids occurring in monoglycerides in Section 184.1505 included oleic acid.[13]

Glyceryl Oleate is used by the pharmaceutical industry as a carrier compound,[23] in mixed micellar form with bile salts for the enhancement of intestinal drug absorption,[24] and for the encapsulation and/or solubilization of partic-

TABLE 2. Product Formulation Data[11]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)						
			Unreported concentration	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Glyceryl Oleate									
Baby lotions, oils, powders, and creams	56	3	3	–	–	–	–	–	–
Other bath preparations	132	1	1	–	–	–	–	–	–
Eye shadow	2582	26	15	–	–	–	10	1	
Mascara	397	3	–	–	–	–	–	3	
Other eye makeup preparations	230	2	1	–	–	–	–	–	1
Hair conditioners	478	5	3	–	–	–	–	–	2
Hair shampoos (noncoloring)	909	2	1	–	–	–	–	–	1
Tonics, dressings, and other hair grooming aids	290	1	–	–	–	–	–	–	1
Blushers (all types)	819	9	8	–	–	–	1	–	–
Makeup foundations	740	8	8	–	–	–	–	–	–
Lipstick	3319	570	355	–	–	–	–	–	215
Makeup bases	831	25	24	–	–	–	–	–	1
Rouges	211	2	2	–	–	–	–	–	–
Other makeup preparations (not eye)	530	7	–	–	–	–	–	–	7
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	8	5	–	–	–	1	1	1
Face, body, and hand skin care preparations (excluding shaving preparations)	832	12	9	–	–	–	2	–	1
Hormone skin care preparations	10	1	–	–	–	–	–	–	1
Moisturizing skin care preparations	747	14	7	–	–	–	3	3	1
Night skin care preparations	219	5	2	–	–	–	1	2	–
Paste masks (mud packs)	171	1	–	–	–	–	–	–	1
Wrinkle smoothers (removers)	38	1	1	–	–	–	–	–	–
Suntan gels, creams, and liquids	164	7	7	–	–	–	–	–	–
Other suntan preparations	28	3	3	–	–	–	–	–	–
1981 TOTALS		716	455	0	0	0	18	10	233

ular drugs.[25-27] Glyceryl Oleate is often used in controlled studies on the physiology and biophysics of laboratory-constructed lipid membranes.[28] The use of Glyceryl Oleate as a fusogen in heterokaryon formation is reported for the study of cell differentiation and genetics.[29]

BIOLOGY

Absorption, Distribution, and Metabolism

Monoglycerides are metabolized by the same mechanisms as are the triglycerides of the diet.[30] Their digestion, intestinal absorption, and transport have been reviewed.[31-37]

The catabolic fate of the glycerol and fatty acid components of glycerides is well documented.[35,37-39] Glycerol, phosphorylated and oxidized, enters the glycolytic pathway as dihydroxyacetone phosphate, and fatty acids primarily undergo β-oxidative degradation to form acetyl-CoA.

Oleic acid, a monoenoic acid, requires an isomerase after partial cleavage to catalyze the isomerization and shifting of the *cis* double bond before β-oxidation continues. Oleic Acid is currently being reviewed by Cosmetic Ingredient Review.[40]

The monoglyceride, Glyceryl Oleate, as well as its components, glycerol and oleic acid, are common intermediates in both lipid oxidation and synthesis.

General Effects

Addition of 1 mM Glyceryl Oleate plus 3 mM oleic acid to an incubation of the conjugated bile salt, sodium taurodeoxycholate, with segments of everted jejunal intestine from Sprague-Dawley rats diminished the tissue's permeability observed with the bile salt alone.[41] The mixture also prevented changes in the gross appearance of the intestinal mucosa that were found with the bile salt alone.

Weanling rats were fed a diet of 25% tristearin supplemented with 5% Glyceryl Oleate or with 2.5% Glyceryl Oleate plus 2.5% oleic acid. The absorption of tristearin, calcium, magnesium, and phosphorus was not altered.[42]

The presence of Glyceryl Oleate within the intestinal lumen enhanced the intestinal absorption of macromolecules. Glyceryl Oleate–bile salt mixed micellar solutions were necessary adjuvants to potentiate heparin absorption.[43-44]

The use of Glyceryl Oleate as a micelle promoter in chickens alleviated the toxic effects of T-2 toxin, a secondary metabolite of several species of the genus *Fusarium*.[45] Mixed micellar solutions containing taurocholate and Glyceryl Oleate prevented deoxycholate-induced malabsorption in the rat jejunum.[46]

Micellar fat containing Glyceryl Oleate decreased the contractility of canine gastric muscles after stimulation with acetylcholine or 5-hydroxytryptophan.[47] A volume of 10 ml of micellar fat consisting of 0.25 mM Glyceryl Oleate, 0.5 mM oleic acid, and dog bile diluted by a salt solution was instilled into the duodena of dogs following intravenous injections of the following gastric stimuli: food, acetylcholine, or 5-hydroxytryptophan. Bile alone and saline did not produce these responses.

Glyceryl Oleate was a minor component (1.3%–6.7%) in Fruend water-in-oil adjuvant mixtures that were used to sensitize mice to a protein antigen. Although the protein in emulsions containing Glyceryl Oleate succeeded in producing Arthus reactions and delayed hypersensitivies, no conclusion could be reached on the potential adjuvant properties of Glyceryl Oleate as an individual ingredient.[48]

Inhibition of cow's milk lipoprotein lipase by a human plasma apolipoprotein was reversed by the addition of Glyceryl Oleate to the reaction mixture.[49]

The addition of Glyceryl Oleate (1 w/v %) to a culture of the fungus, *Candida paralipolytica*, increased the lipase activity.[50] The free fatty acids tested did not significantly increase lipase activity over controls.

Glyceryl Oleate prevented the fusion of chicken myoblasts in vitro at concentrations ranging from 40 to 70 μg/ml under conditions that have been reported for erythrocytic fusion.[51] Concentrations above 80 μg/ml were toxic to the myoblastic cultures.

The interaction of fusogenic lipids, such as Glyceryl Oleate, with erythrocyte ghosts was studied using fluorescence probes.[52] Changes in the quantum yield, fluorescence intensity, and emission wavelength of the probe in the presence of Glyceryl Oleate were due to the production of a less ordered, functionally fluid membrane structure. The chemically related nonfusogenic lipid, glyceryl monostearate, had no effect on the observed fluorescence parameters.

The ability of Glyceryl Oleate to inhibit the antimicrobial activity of two imidazole antimycotic drugs against *Candida* was evaluated using an agar diffusion procedure.[53] Glyceryl Oleate decreased the diameter of the inhibition zone at a concentration of 0.25 mM. No decrease was observed at the lower concentrations of 0.13 mM and 0.06 mM.

The antimicrobial activity of Glyceryl Oleate and other polyhydric alcohols was assessed.[54] Glyceryl Oleate had slight activity, causing inhibition of growth of *Corynebacterium* sp. at concentrations above 1.40 μmol/ml. Other microorganisms, such as *Streptococcus pyogenes*, *Nocardia asteroides*, and *Staphylococcus aureus*, were not inhibited up to the highest concentration tested, 2.81 μmol/ml.

Glyceryl Oleate induced aggregation of nematodes (*Bursaphelenchus lignicolus*) as compared with untreated controls.[55]

ANIMAL TOXICOLOGY

Acute Oral Toxicity

A sunscreen formulation containing Glyceryl Oleate (at 5%) was evaluated for acute toxicity upon oral administration to 10 Fischer rats.[56] After a 14-day observation period for signs of toxicity, the study directors concluded that the single 13 ml/kg dose was not lethal in rats.

Skin Irritation

Five studies using the single insult occlusive patch test were performed to evaluate the primary dermal irritation potential of Glyceryl Oleate at two concentrations.[57–61] A volume of 0.5 ml was placed on the clipped dorsal skin of

nine rabbits. Sites were graded for erythema and edema 2 and 24 h after exposure (maximum score for either erythema or edema = 4). In the three studies with undiluted Glyceryl Oleate, it was concluded that it had minimal skin irritation potential; erythema scores ranged from 0.5 to 1.[57-59] Similar results and conclusions were reported in the two studies using 50% Glyceryl Oleate in corn oil[60-61] (Table 3).

The dermal toxicity of a sunscreen formulation containing 5% Glyceryl Oleate was evaluated using three New Zealand White (NZW) rabbits.[56] Volumes of 0.5 ml were applied to the animals' clipped dorsal skin once daily for 4 days. After a 7-day assessment period for dermal irritation, which was characterized by well-defined to moderate erythema, slight edema, and subsequent slight desquamation, the resultant irritation index was 3.0 (max = 8.0) (Table 3).

Ocular Irritation

Glyceryl Oleate was evaluated for ocular irritation in six rabbits using the Draize Eye Test. Undiluted and 50.0% in corn oil preparations were administered at a volume of 0.1 ml. The Draize system,[62] which has a calculated maxi-

TABLE 3. Primary Skin Irritation and Dermal Toxicity of Glyceryl Oleate

Material tested	*No. of rabbits*	*Method*	*Conclusion*	*Reference*
Glyceryl Oleate undiluted	9	SIPT[a]–occlusive	Minimal skin irritation PII[b] = 0.72	57
Glyceryl Oleate undiluted	9	SIPT–occlusive	Minimal skin irritation PII = 0.67	58
Glyceryl Oleate undiluted	9	SIPT–occlusive	Minimal skin irritation PII = 0.67	59
Glyceryl Oleate 50% in corn oil	9	SIPT–occlusive	Minimal skin irritation PII = 1.00	60
Glyceryl Oleate 50% in corn oil	9	SIPT–occlusive	Practically nonexistent skin irritation PII = 0.33	61
Glyceryl Oleate 5% in sunscreen formulation	3	Dermal toxicity of 0.5 ml applied to clipped dorsal skin once daily for 4 days	Mild dermal irritation PII = 3.0	56
Glyceryl Oleate at unspecified concentration in cosmetic formulation	10	Subchronic dermal toxicity (28 days). 25.0% w/v formulation in corn oil applied to shaved abraded and intact skin 5 days per week for 4 weeks	Severe irritation at application site of treated rabbits; gross and microscopic alterations noted	66

[a]SIPT, single insult patch test.
[b]PII, primary irritation index. Maximum possible score = 8.00.

mum irritation score of 110, was used to score the extent of irritation. In the two studies using undiluted Glyceryl Oleate, results were similar after 2 days of observation; mean scores were 0 and 1 in 110. Glyceryl Oleate produced minimal eye irritation.[63,64] The 50.0% Glyceryl Oleate preparation was also minimally irritating, and the mean scores were 1 and 2 for Days 1 and 2, respectively[65] (Table 4).

A fragrance preparation containing Glyceryl Oleate at 19.0% concentration was tested in rabbits with the standard Draize Test. The total mean score of 12 on Day 1 decreased to 8 on Day 2, 6 on Day 4, and 2 on Day 7. Individual mean scores for two of the six rabbits tested were in the 25 to 35 range on the first day, decreasing to approximately 18 by Day 4 and to 7 by Day 7. All other rabbits had negative to transient minimal responses. The formulation produced moderate eye irritation[67] (Table 4).

A 0.1 ml volume of a sunscreen formulation containing 5% Glyceryl Oleate was evaluated for eye irritation in six NZW rabbits.[56] Scoring was performed 1 h after treatment and on Days 1, 2, 3, and 7. Slight conjunctivitis was observed after 1 h, clearing within 24 h, and no signs of irritation to other tissues were noted (Table 4).

Subchronic Dermal Toxicity and Phototoxicity

A 28-day subchronic dermal toxicity study assessed the safety of a cosmetic formulation containing Glyceryl Oleate (at an unspecified concentration) in 10 albino rabbits.[66] A 25.0% (w/v) solution of the formulation in corn oil was applied to shaved skin that had been either abraded or left intact. The 2.0 ml/kg

TABLE 4. Ocular Irritation of Glyceryl Oleate

Material tested	*No. of rabbits*	*Results*	*Reference*[a]
Glyceryl Oleate undiluted	6	Minimal eye irritation; mean score = 1 (max score = 110) on Day 1 following treatment	63
Glyceryl Oleate undiluted	6	Minimal eye irritation; mean score = 1 on Day 1	64
Glyceryl Oleate 50% in corn oil	6	Minimal eye irritation; mean score = 1 on Day 1	65
Glyceryl Oleate 19.0% in fragrance preparation	6	Moderate eye irritation; mean score = 12 on Day 1, 8 on Days 2 and 3, 6 on Day 4, 2 on Day 7	67
Glyceryl Oleate 5% in sunscreen formulation	6	Slight conjunctivitis 1 h after treatment; cleared within 24 h	56

[a]All studies followed methods of Draize.[62]

dose was left in contact with the skin for an indefinite period of time. The rabbits were treated 5 days per week for a period of 4 weeks. The major response to repeated administration of this formulation was "severe irritation" of the skin at the site of application. Alterations included erythema, severe edema, and desquamation, fissures, hemorrhages, and pustules. Microscopic changes included acanthosis, hyperkeratosis, focal epidermal ulceration, focal dermal inflammation, abscess formation, and/or focal escharosis at some of the treated sites. No skin reactions were noted in controls. Other results (e.g., mortality, gross behavior/appearance, and results of hematological, clinical chemistry, and urine analyses) were negative or not treatment-related (Table 3).

Three formulations containing two sunscreen ingredients (maximum concentrations 2.0% and 4.0%) were evaluated in a 28-day subchronic dermal toxicity/phototoxicity study in NZW rabbits.[68] The sunscreens contained Glyceryl Oleate at a 5% concentration. Topical applications of 6 mg cream per cm^2 to clipped dorsal intact and abraded skin sites of the animals (four animals per group) were followed by a 4-minute exposure (at one-half the minimum erythemal dose) to UV radiation (Westinghouse FS-20 sunlamp) and a 6-h occlusion of the test sites. This treatment was repeated 5 days each week followed by 2 nontreatment days for 4 weeks. Animals were then observed for 2 weeks before necropsy. The four deaths (one control, three treated) were reportedly due to naturally occurring chronic enteritis. Body weights, mean group feed consumption, and hematological and urinalysis data from treated animals reflected normal variability. The organ:body weight disparity of some treated animals with controls was not considered toxicologically significant. All three formulations caused slight dermal irritation during the first week of treatment that was similar to that observed in several control animals exposed to UV light alone. Maximal irritation during the second week, which was sustained through the remainder of the treatment period, was characterized by slight to moderate erythema, slight edema, and scaly desquamation. The severity of dermal irritation was equivalent at both abraded and intact sites. Normal healing occurred during the 2-week observation period following treatment.

Subchronic and Chronic Toxicity of Glycerol and Oleic Acid

Toxicological data on glycerol and oleic acid, metabolic products of Glyceryl Oleate, were obtained from subchronic and chronic ingestion studies used to regulate these GRAS substances.[30,69-73]

Subchronic Oral Toxicity of Glycerol

Rats fed glycerol at concentrations up to 20% in their diets or by stomach tube for periods of 4–11 weeks had no adverse effects that could be attributed to glycerol consumption.[74-79] Criteria, such as body weight gain, food and water intake, resistance to cold, mortality, behavior, blood chemistry, hematology, and gross and microscopic features of major internal organs and tissues, were observed.

Oral doses of up to 3 g of undiluted glycerol given three times per day for a total of eight doses resulted in hyperemia, petechial hemorrhages, and erosion of the gastrointestinal mucosa of rats and dogs.[80]

Volumes greater than 5 ml of a 50% aqueous saline solution of glycerol administered to guinea pigs by stomach tube or from a drinking cup daily for a period of 30–40 days produced signs of acute toxicity and death.[81] Doses of 10 ml of the 50% solution for 30–40 days were well tolerated by rabbits.[81] The red blood cell count of the treated guinea pigs had decreased. No gross pathological changes and no glycerol-related changes in plasma or erythrocytic cholesterol concentrations were found in either species.

Three-month administration of up to 20% solutions of glycerol to rats as drinking water resulted in the death of 2/12 rats receiving the highest concentration and temporary impairment in the development of the remaining rats.[77] Growth of rats was normal at concentrations of glycerol of less than or equal to 10%. Temporary growth impairment was observed in rats administered 20% glycerol solutions for 3 months.[82]

After the oral administration of 2.0 ml/kg doses of glycerol to two dogs twice weekly for 4 months, growth was normal and no abnormalities were found in urine and the internal organs.[83]

The feeding of glycerol to rats at concentrations up to 41% (as a dietary supplement) for 21–25 weeks did not produce changes in growth or in the liver, kidneys, or intestines of these animals.[74] In another study, subnormal growth was found in rats fed diets containing greater than 30% glycerol for 20 weeks.[84] Pathological changes were observed in rats fed diets containing glycerol at concentrations greater than 10%. The most marked changes were hydropic and fatty changes of hepatocytes.

Subchronic Dermal Toxicity of Glycerol

Doses of 0.5–4.0 ml (0.6–5 g) per kg natural or synthetic glycerol were applied to the shaved dorsal skin of 24 albino rabbits for an 8-h exposure, 5 days per week, for 18 weeks.[85] No evidence of skin irritation was observed; no abnormalities were found in urine or blood or after gross and microscopic examinations of internal organs.

Chronic Oral Toxicity of Glycerol

The only untoward effect in a 6-month study of rats given 5% solutions of either synthetic or natural glycerol as drinking water was calcified masses in the renal tubules of 6/10 rats.[86] Administration of 1.0 ml/kg of a 50% aqueous glycerol solution to 60 rats for 6 months had no adverse effects on development, survival, internal organs, skeletal system, or hepatic glycogen.[77]

Three dogs fed glycerol at a concentration of 35% (as a dietary supplement) for 31 weeks had normal growth.[74] In the 14-week period following a reduction in feed consumption, treated dogs lost an average of 16% of their previously attained weight; control dogs maintained their weight. Diuresis was observed in treated dogs, but no hemoglobinuria, albuminuria, liver degeneration, or gross or microscopic abnormalities of internal organs were found.

Growth impairment, reduced activity, and dull coats were observed in rats fed 61% glycerol substituted for starch for 40 weeks. These changes were considered due to a lack of starch rather than to glycerol toxicity. Rats fed 20% and 40% glycerol diets for 40 weeks had normal growth.[74]

In 2-year toxicity studies using rats and dogs fed 0, 5, 10, and 20% glycerol, no treatment-related adverse effects were found.[85,87] Although Hine et al.[85] observed high incidences of albuminuria and glycosuria in treated rats and high liver:body weight ratios in females fed diets with 20% glycerol, they concluded that glycerol at concentrations below 20% would not cause untoward effects in rats.

Subchronic Oral Toxicity of Oleic Acid

A volume of 10 ml of oleic acid (approximate dose 2 g/kg) administered to four albino rabbits by stomach tube every other day for 4 days resulted in the death of one of the four rabbits.[88] Other signs included hair loss and seborrheic lesions on the rabbits' ears. No adverse effects were observed after administration of a volume of 2.5 ml (approximate dose 0.6 g/kg).

Feeding of a 5% oleic acid diet (approximate dose 6 g/kg daily) to chicks for 4 weeks had no adverse effect.[89]

Chronic Toxicity of Oleic Acid

The growth rates of albino mice receiving weekly subcutaneous injections of 0.25 ml and 0.5 ml of a 5% oleic acid emulsion (approximate dose 12–15 g/kg) for 15 months were normal.[90]

Rats fed a 15% Oleic Acid diet for 5 months had normal development and good general health.[91] A progressive reduction in spermatogenesis and prolonged estrus cycles (although most females bore living young) were noted; these signs were considered typical of animals fed diets deficient in essential fatty acids.

Carcinogenicity

Several egg lipids were examined for their potential to produce brain tumors in mice of the T.M. strain.[92] Purina mice chow, which was fed to controls ad libitum, corn oil, cholesterol, Glyceryl Oleate, corn oil plus cholesterol, or Glyceryl Oleate plus cholesterol were mixed with sugar and presented to mice once a day. Doses of these supplements were 50–100 mg/mouse per day Glyceryl Oleate, 4–5 mg/mouse per day cholesterol, and 100–150 mg/mouse per day corn oil; the purity of these supplements was not stated. Four-week-old mice were fed these diets and then bred within the same group. Their offspring were maintained on the same diets as their parents from birth "until they died or became moribund and were killed." Survival rates for the individual groups were not provided. The incidence of brain tumors in treated mice is shown in Table 5. The report contained general histopathological descriptions of the tumors; however, no specific tumor type induced by Glyceryl Oleate was described. The diets supplemented with lecithin, cholesterol, and cholesterol, in combination with any other lipid, induced brain tumors in the largest number of mice.

In a similar experiment, the carcinogenicity of Glyceryl Oleate was evaluated in T.M. strain mice that were fed Purina Chow supplemented with refined corn oil (Group 2), crude corn oil (Group 3), refined corn oil plus up to 1.5% free fatty acids, oleic and linoleic acids (Group 4), and Glyceryl Oleate (Group 5) at concentrations of 200 mg/mouse per day.[93] Controls (Group 1) were fed

TABLE 5. Incidence of Brain Tumors in Mice Fed Various Egg Lipids[92]

Diet supplement	*Total no. of mice treated*	*No. of mice examined*[a]	*No. of mice with brain tumors*
Control, no supplement	360	188	0
Corn oil	159	11	1
Cholesterol	212	80	20
Glyceryl Oleate	144	63	3
Corn oil and cholesterol	106	22	7
Glyceryl Oleate and cholesterol	158	64	7

[a]It was not stated whether or not the mice that were not examined within each group died, and, if they died, whether or not their deaths were associated with their respective dietary supplements.

Purina Chow alone. Offspring of the intragroup bred mice were maintained on the same diets for a total of four–seven generations of mice. Mice were killed when they were observed to lose weight rapidly. Three of the 195 control mice in Group 1 developed gastric papillomas and squamous cell carcinomas, and none developed pyloric or intestinal tumors. Gastric papillomas were also found in 6/209 mice of Group 2, 49/196 mice of Group 3, 87/328 mice of Group 4, and 31/166 mice of Group 5 (Glyceryl Oleate-supplemented diet). Fewer squamous cell carcinomas were observed in all treatment groups: Group 2, 1/209; Group 3, 6/196; Group 4, 10/328; Group 5, 6/166. Pyloric tumors were also recorded for all treatment groups at the following frequencies: Group 2, 2/209; Group 3, 9/196; Group 4, 41/328; Group 5, 31/166. Free fatty acids in the preparations fed to the mice that developed gastric tumors were considered the cause of the tumors; however, the relative purity of the Glyceryl Oleate was not detailed. Detailed gross and microscopic descriptions of the tumors were recorded.

Antitumorigenicity

The in vivo antitumor activity of Glyceryl Oleate was studied using implanted Ehrlich ascites tumors in mice.[94] Saline solutions at two doses (6.0 and 1.5 mg/mouse per day) of Glyceryl Oleate were administered once daily for 5 successive days to two mice per dose. Tumor growth and body weight gain after 7 days and life spans were recorded. Whereas control mice died within 17 days, both doses of Glyceryl Oleate prolonged the survival period of the mice (>30 days at 6.0 mg and an average of 24 days at 1.5 mg). Although both doses resulted in an increase in body weight over 7 days, inhibition of tumor growth was observed in mice only at the higher dose. Moderate tumor growth occurred at the lower dose.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

Glyceryl Oleate, used in hand cream at 1.5%, was evaluated for primary dermal irritation in 15 and 30% aqueous preparations.[95] Twenty subjects participated in the single insult occlusive patch test using the Draize-Shelanski tech-

nique. The 15% concentration yielded 18 negative responses; the remaining 2 subjects had scores of 0.5 and 1 (max = 3). Seventeen individuals had negative responses, and 3 had scores of 1 after treatment with the 30% solution (Table 6).

A single insult occlusive patch test was performed using 20 panelists by applying a fragrance preparation that contained 19.0% Glyceryl Oleate.[96] Negative results were found in 17 of 20 subjects (doubtful reactions were observed in 3 of 20 subjects), and the formulation's skin irritation potential was "practically nonexistent" (Table 6).

Cumulative Dermal Irritation

The Lanman-Maibach test[97,98] was used to assess the cumulative irritation potential of two sunscreen formulations containing 5% Glyceryl Oleate.[99] A dose of 50 $\mu l/cm^2$ was administered to the backs of 10 subjects under 23-h closed patches for a total of 21 consecutive applications. Sites were cleaned before scoring and at reapplication at the 24th hour. The total converted numerical scores for all applications and subjects of the two formulations were 23 and 38 (maximum score = 630), ranking them as mild materials causing no experimental irritation. Positive responses to both formulations were not observed until at least the 12th application in most subjects. Most of the points for the cumulative total scores were contributed by 1 subject alone (22/23 points, 26/38 points), whereas the remaining 9 subjects had individual scores of 0–3 (Table 6).

Sensitization

A repeated insult patch test (RIPT) using 200 people was used to evaluate a 15% aqueous solution of Glyceryl Oleate as a primary irritant, fatiguing agent, and/or sensitizer.[100] Sixteen 24-h occlusive patches were applied to the upper arm on Mondays, Wednesdays, and Fridays. Nontreatment periods were stated to be the days between alternate day applications and on weekends. No signs of skin irritation were observed after exposure to Glyceryl Oleate in any of the applications (Table 6).

An RIPT with a sunscreen formulation containing 5% Glyceryl Oleate was conducted using an occlusive patch technique.[101] Ten 24-h induction patches on Tuesdays, Thursdays, and Saturdays (sites were evaluated after removal of each patch) were followed by a 12–16-day nontreatment period and a 24-h challenge patch at an adjacent site. These challenge sites were then evaluated immediately after patch removal and 24 h later. None of the 15 subjects participating in this study alone had positive reactions during the induction phase or when challenged. Of the 37 others who were being tested simultaneously for photoallergic and phototoxic responses to treatment, 2 subjects had transient reactions of slight erythema (scores of 1 on scale of 0–4) to induction patches, and all subjects had no reaction to the challenge patch (Table 6).

Photoallergy and Phototoxicity

The potential of a sunscreen formulation containing 5% Glyceryl Oleate for inducing photoallergy and phototoxicity in humans was evaluated by modifications of an RIPT.[101] Approximately 200 mg of the formulation was applied under an occlusive patch to the inner forearms of 29 subjects for the photoal-

lergy test and of 10 subjects for the phototoxicity test. After a 24-h exposure period, the contact sites were evaluated after patch removal and irradiated with UVA light (15 minutes at 4400 $\mu W/cm^2$). The sites of subjects in the phototoxicity test were then evaluated immediately following irradiation and 24 h and 48 h later. The 24-h patch application and irradiation were repeated 10 times for subjects in the photoallergy test on Mondays, Wednesdays, and Thursdays. After a 12–16 day nontreatment period, 24-h challenge patches were applied to adjacent sites. Photoallergy test sites were evaluated before and after irradiation upon patch removal in both induction and challenge phases. Scoring was performed at 48 and 72 h after application of challenge patches. No skin reactions were observed in the 10 subjects participating in the phototoxicity test, and only 1 photoallergy test subject ($n = 29$) had a grade 1 reaction (scale 0–4) to the sixth induction patch at the nonirradiated control site. No positive reactions to induction or challenge patches were observed at any irradiated site (Table 6).

Oral Exposure to Glycerol

Data from subchronic human studies on the oral administration of glycerol, a metabolic product of Glyceryl Oleate, were used in the safety assessment process of glycerol for the federal regulation of GRAS substances.[30,69]

SUMMARY

Glyceryl Oleate, the glyceryl 1-monoester of oleic acid, is dispersible in water and soluble in acetone, simple alcohols, and cottonseed oil. Glyceryl Oleate is manufactured by the partial hydrolysis of corresponding tri- and diglycerides, by esterification of glycerol with oleic acid, or by glycerolysis of common fats and oils.

Glyceryl Oleate is used primarily in cosmetic products as an emulsifier and was listed as an ingredient in 716 of the cosmetic formulations reported to the FDA in 1981. The FDA table had Glyceryl Oleate concentrations ranging from ≤ 0.1 to 5% in formulations that were predominantly lipsticks, eye shadows, makeup bases, and skin care preparations.

Monoglycerides of edible fats or oils are considered GRAS and indirect food additives for human consumption by the FDA. Glyceryl Oleate can be used as a prior-sanctioned food ingredient and as a direct and indirect food additive. The pharmaceutical industry uses Glyceryl Oleate as an inert carrier compound and to enhance intestinal drug absorption.

Oral administration of a single 13 ml/kg dose of a sunscreen formulation containing 5% Glyceryl Oleate to rats produced no signs of toxicity and no lethality.

Undiluted and 50% in corn oil concentrations of Glyceryl Oleate used in dermal irritation studies with rabbits were found to be minimally irritating. A volume of 0.5 ml of a sunscreen formulation containing 5% Glyceryl Oleate produced erythema and slight edema in rabbits.

Minimal to moderate eye irritation was produced by undiluted Glyceryl Oleate, 50% Glyceryl Oleate in corn oil, and a fragrance preparation containing

TABLE 6. Clinical Assessment of Safety of Glyceryl Oleate

Material tested	*Glyceryl Oleate concentration*	*Type of test*	*No. of humans*	*Results/Comments*	*Reference*
Glyceryl Oleate	15% aqueous	Test for skin irritation by Draize-Shelanski SIOPT[a]	20	18/20 had score of 0 1/20 had score of 1/2 1/20 had score of 1 (max = 3)	95
Glyceryl Oleate	30% aqueous	Test for skin irritation by Draize-Shelanski SIOPT	20	17/20 had score of 0 3/20 had score of 1 (max = 3)	95
Glyceryl Oleate	15% aqueous	RIPT[b] (16 patches, Mon., Wed., Fri.)	200	No signs of skin irritation observed during induction or challenge (weekends considered nontreatment period)	100
Fragrance preparation	19.0%	Test for skin irritation by SIOPT	20	17/20 had score of 0 3/20 had score of ± (max = 4)	96
Sunscreen formulation	5%	21-day Cumulative Irritancy Test	10	Total converted numerical score of 23 (max = 630); mild material causing no irritation	99

Sunscreen formulation	5%	21-day Cumulative Irritancy Test	10	Total converted numerical score of 38 (max = 630); mild material causing no irritation	99
Sunscreen formulation	5%	RIPT	52	15/52 were involved in RIPT alone; none of the 15 had positive reactions; 37/52 were involved in simultaneous photoallergy and phototoxicity testing; 2/37 had transient, slight erythema to induction patches; no reactions to challenge patches observed	101
Sunscreen formulation	5%	Photoallergy test by RIPT + UVA irradiation	29	One subject had a score of 1 to the sixth induction patch at a nonirradiated control site (max = 4); no positive reactions to induction or challenge patches at any irradiated site	101
Sunscreen formulation	5%	Phototoxicity test single patch test + UVA irradiation	10	No skin reactions observed	101

[a]SIOPT, single insult occlusive patch test.
[b]RIPT, repeated insult patch test.

19.0% Glyceryl Oleate when administered to rabbits. A formulation containing 5% Glyceryl Oleate administered at a 0.1 ml dose to rabbit eyes induced slight conjunctivitis.

Daily applications of 2.0 ml/kg of a 25.0% corn oil solution of a formulation containing Glyceryl Oleate for 20 days produced severe dermal irritation in rabbits. In another 4-week dermal toxicity/phototoxicity study, product formulations containing varying concentrations of two sunscreen ingredients produced slight, reversible dermal irritation. Each sunscreen ingredient contained 5% Glyceryl Oleate.

Glyceryl Oleate administration was associated with development of a few brain tumors (3 tumors in 63 mice) in a two-generation study in mice of the T.M. strain whose feed was supplemented with 50–100 mg/mouse per day Glyceryl Oleate. Digestive tract tumors were found in T.M. strain mice fed 200 mg/mouse per day Glyceryl Oleate (feed supplement) for four–seven generations and were considered due to free fatty acid impurities. The Expert Panel found the results of these studies equivocal.

Doses of 1.5 and 6.0 mg/mouse per day of Glyceryl Oleate in saline increased the survival period of mice with implanted Ehrlich ascites tumors; the higher dose inhibited tumor growth.

Two aqueous Glyceryl Oleate preparations (15% and 30% concentrations) and a fragrance preparation containing 19.0% Glyceryl Oleate were negative for cutaneous irritation when tested on human skin using single insult occlusive patch tests.

Two sunscreen formulations containing 5% Glyceryl Oleate were considered mild compounds and caused no irritation in a cumulative occlusive patch test using human subjects.

No signs of irritation or sensitization were observed in humans after repeated insult patch testing of a 15% aqueous Glyceryl Oleate preparation and a sunscreen formulation containing 5% Glyceryl Oleate. A few subjects involved in simultaneous photoallergy and phototoxicity tests had slight, transient erythematous responses. No positive reactions were observed at any irradiated site during induction and challenge phases of the photoallergy test.

The metabolic products of Glyceryl Oleate are glycerol and oleic acid. The use of these compounds in and for foods is regulated by the FDA. Subchronic and chronic toxicity data from studies with animals and humans that were used in the safety assessment of glycerides, glycerol, oleic acid and sodium oleate are presented in this report.

CONCLUSION

Based on the data from animal and human studies included in this report, the CIR Expert Panel concludes that Glyceryl Oleate is safe as a cosmetic ingredient in the present practices of use and concentration.

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