Final Safety Assessment

On the Safety Assessment of Alkyl Glyceryl Ethers As Used in Cosmetics

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ABSTRACT Alkyl glyceryl ethers function mostly as skin conditioning agents in cosmetic products. Based on the available animal toxicity and clinical data, including the low dermal absorption, the CIR Expert Panel concluded that the alkyl glyceryl ethers are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The safety of the following ingredients in cosmetics is reviewed in this report:

- Ethylhexylglycerin
- Caprylyl Glyceryl Ether
- Glyceryl Capryl Ether
- Cetyl Glyceryl Ether/Chimyl Alcohol
- Batyl Alcohol
- Glyceryl Allyl Ether
- Glyceryl Lauryl Ether
- Isodecyl Glyceryl Ether
- Isostearyl Glyceryl Ether
- Oleyl Glyceryl Ether

These ingredients function mostly as surfactants or skin conditioning agents in cosmetic products. Cetyl glyceryl ether and chimyl alcohol are listed in The International Cosmetic Ingredient Dictionary and Handbook[1] as discrete chemicals. However, these two ingredients are identical chemicals. Accordingly, there are eleveningredients listed in this review, but two of them represent the same entity. Since chimyl alcohol was the ingredient name first assigned in the International Cosmetic Ingredient Dictionary and Handbook, cetyl glyceryl ether will be referred to as chimyl alcohol throughout the report text.

CHEMISTRY

Definition and Structure

These ingredients are alkyl glyceryl ethers. Structurally, this means that an alkyl or alkenyl chain is terminated with glycerin at one end via an ether linkage. For example, caprylyl glyceryl ether is an 8-carbon, alkyl chain terminated with glycerin (Figure 1).

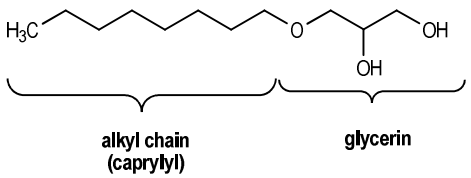


Figure 1. Caprylyl Glyceryl Ether

Substances with a similar structure, alkoxylipids, are widely distributed in human and animal tissue and occur as neutral alkoxylipids and ionic alkoxylipids.[2,3]

The ingredients reviewed in this safety assessment vary only by alkyl chain length, degree of chain branching, or the degree of unsaturation. Their gross structural characteristics are typical of a surfactant, that is, they contain a hydrophilic head group (i.e., glycerin) and a hydrophobic tail (i.e., the alkyl chain). The definitions, structures, and functions of these alkyl glyceryl ethers are included Table 1.[1]

Physical and Chemical Properties

Chemical and physical properties of 6 of the 10 alkyl glyceryl ethers are included in Table 2. In general, these ingredients are solids at room temperature and have molecular weights that are < 400 g/mol. As would be expected, increased chain length translates into greater hydrophobicity. Ethylhexylglycerin, specifically, has "limited solubility in water (≈ 0.1%), is highly soluble in organic solvents," and has an estimated octanol/water partition coefficient of Log P_{ow} = 2.4.

Method of Manufacture

The manufacture of alkyl glyceryl ethers can be accomplished by traditional etherification techniques. For example, one method of synthesis of chimyl alcohol involves reacting the sodium salt of acetone glycerol (a form of glycerin wherein 2 of the hydroxyl groups are protected and the third is activated as the sodium salt) with hexadecyl iodide in boiling glycol dimethyl ether, yielding the acetone compound of α-hexadecyl glycerol. Hydrolysis of the protecting group with acetic acid results in the formation of chimyl alcohol.[4]

Alternatively, these ingredients can be produced by the reduction of triglycerides. For example, long-chain alkyl glyceryl ethers can be synthesized via the treatment of a triglyceride with lithium aluminum hydride (LAH) + boron trifluoride etherate (BFE), followed by LAH hydrogenolysis.[5] The major reaction products are the glyceryl monoether, glyceryl triether, and free alkanol.

One method for the synthesis of ethylhexylglycerin is via the catalytic splitting of ethylhexylglycidyl ether, followed by the addition of water.[6] The product can then be purified by vacuum distillation.

Impurities

Sensiva® SC50 is one of the trade names under which ethylhexylglycerin is being marketed. According to Schülke and Mayr GmbH, Sensiva® SC 50 contains > 99% ethylhexylglycerin.[6] Sensiva® SC 50 also contains a small amount of α-tocopherol, added to stabilize the molecule, and the impurities 2-ethylhexyl-glycidylether and water.[7]

Chimyl alcohol is approximately 98% pure and also contains approximately 2% batyl alcohol as an impurity. It has an acid value of approximately 0.001, which means that fatty acids are not present.[8]

USE

Cosmetic

These ingredients function mostly as surfactants or skin conditioning agents in cosmetic products.[1] These and additional functions are included in Table 1. Ethylhexylglycerin (Sensiva® SC 50) reportedly inhibits the growth and multiplication of odor-causing bacteria and enhances the efficacy of cosmetic preservatives, such as phenoxyethanol, methylisothiazolinone, or methylparaben. Preservatives defined as Sensiva® SC 50 + phenoxyethanol and Sensiva® SC 50 + methylisothiazolinone are being marketed.[9]

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), reported in 2011 FDA database, the following 4 ingredients were being used in personal care products: ethylhexylglycerin, glyceryl lauryl ether, chimyl alcohol, and isostearyl glyceryl ether.[10] These data are summarized in Table 3. Surveys of ingredient use concentrations conducted by the Personal Care Products Council (also included in Table 3) provided use concentrations for these 5 ingredients: ethylhexylglycerin (up to 8% [maximum in rinse-off products]), chimyl alcohol (up to 0.5% [maximum in leave-on products]), batyl alcohol (up to 3% [maximum in leave-on products]), glyceryl lauryl ether (7% [in rinse-off products]), and isostearyl glyceryl ether (up to 0.02% [maximum in leave-on products]).[11,12,13] Except for the use concentration data on glyceryl lauryl ether and batyl alcohol (collected in 2011), the data on these ingredients were collected in 2010.

Ethylhexylglycerin was reported as being used in 3 baby products in the VCRP, but use concentration data were not reported in the Council survey.[11]

No uses of the remaining 5 ingredients reviewed in this safety assessment were reported in the VCRP database or in the Council survey.[10,11]

Cosmetic products containing these ingredients may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Ethylhexylglycerin is used in hair sprays and, body and hand sprays, and effects on the lungs that may be induced by aerosolized products containing this ingredient are of concern. In practice, 95% to 99% of the aerosols released from cosmetic sprays have aerodynamic equivalent diameters in the 10 to 110 μm range.[14,15] 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., able to enter the lungs) to any appreciable amount.[16,17] However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions may cause toxic effects, depending on their chemical and other properties.

Noncosmetic

The use of ethylhexylglycerin as an emollient in an alcohol-based surgical hand disinfectant (Surgicept™) has been reported.[18]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Oral Studies

Chimyl Alcohol

The absorption and metabolism of chimyl alcohol was evaluated using adult male rats.[19] (1-^{14}C)-Chimyl alcohol (5 mg) in 0.5 ml olive oil was administered via stomach tube. Feces were collected in 24 h portions. The amount of chimyl alcohol absorbed was calculated as the difference between the amount of radioactivity administered and the amount recovered from the feces. The amount of [^{14}C]-labeled chimyl alcohol absorbed after feeding was 95%, and the remainder was recovered in the unsaponifiable fraction of fecal lipids. The percentage of total absorbed activity (whole body) that was recovered in the lymph lipids was 45% (1 rat) and 59% (1 rat). The distribution of the activity between the different fractions in the lymph lipids was phospholipid fatty acids (3% and 4%) and glyceride fatty acids (45% and 51%). Also, in the lymph lipids, 45% and 51% of the activity was present as chimyl alcohol, of which free chimyl alcohol accounted for more than half. The remainder was esterified.

A similar study on the absorption and metabolism of chimyl alcohol using rats (strain not stated) was performed. α-(1-C^{14})-Chimyl alcohol was fed, by stomach tube, as free alcohol or as chimyl dioleate (in olive oil).[20] In one series of experiments, intestinal contents were analyzed during the absorption phase, 2-4 h after administration. In another series, the distribution of activity in expired CO_2 was determined at 24 h post-administration. In other experiments, the distribution of activity in lymph lipids was monitored after chimyl dioleate (in olive oil) was fed to rats with a thoracic duct fistula (for lymph collection). Results for dosing with free chimyl alcohol indicated the incorporation of free fatty acids into chimyl alcohol, with the formation of alkoxydiglycerides in lymph lipids. The results of analyses of intestinal contents together with lymph analyses clearly indicated the dynamic situation in the intestine. In the intestinal lumen, the ether linkage was intact during the entire absorption process, but, once absorbed into the intestinal mucosa, more than 50% of the compound was rapidly converted into palmitic acid.

Following administration of ^{14}C-chimyl dioleate (chimyl alcohol esterified with oleic acid) in olive oil to rats by stomach tube, 8% of the total administered radioactivity was excreted as exhaled $^{14}CO_2$ in 24 h. Results also indicated that fatty acids in both the 1- and 2-position in the alkoxydiglyceride molecule were exchanged during hydrolysis by pancreatic enzymes *in vivo*. Apparently an equilibrium between the synthesis and hydrolysis of mono- and di-esterified chimyl alcohol and free chimyl alcohol was reached. Approximately 75% of radioactivity in the lymph was present as glyceride fatty acids and, approximately 2%, as phospholipid fatty acids. Approximately 25% of lymph activity was present as chimyl alcohol, of which more than two-thirds was present as esterified chimyl alcohol. More than half the radioactivity was associated with palmitic acid, indicating a splitting of the ether bond in mucosal cells. It was concluded that chimyl alcohol can be absorbed unchanged, but that it is already extensively metabolized in the mucosal cells, whether it is fed as free chimyl alcohol or as an alkoxydiglyceride.[20]

Parenteral Studies

Chimyl Alcohol

The intravenous injection of ^{14}C-chimyl alcohol (dose not stated) into rats of an unspecified strain resulted in excretion of 24% of the administered radioactivity as $^{14}CO_2$ in 24 h.[20]

Male albino Sprague-Dawley rats (total of 40 used) were injected i.p. with 2-^{3}H-α-1-^{14}C-α-1-^{14}C-2-^{3}H-chimyl alcohol (5.60 mg) or β1-^{14}C-chimyl alcohol (6.30 mg).[21] After dosing, the animals were killed and the entire liver and small intestine removed. Lipids were then extracted. The purpose of these timed experiments (4h or 8 h post-injection) was to

determine if these alcohols would be converted directly to alkyl glyceryl ether phospholipids in the liver and small intestines. Both labeled glyceryl ethers were converted to alkaline stable glyceryl ether phospholipids in the intestine. The β-ether was not incorporated into the glyceryl ether phospholipids as rapidly, when compared to the α-ether. This difference in incorporation of the β-glyceryl ethers might be explained by the fact that, in most acyl phospholipids, the fatty acid that is attached to the secondary carbon of glycerol is usually unsaturated.

For both the α- and β-chimyl alcohols, phosphatidyl choline was the major labeled intestinal fraction. For any of the liver lipid extracts, < 1% of alkaline stable glyceryl ether phospholipids was detected. In each experiment examining the metabolism of labeled glyceryl ethers, < 1% of the radioactivity was detected in each of the following: free fatty acids, long-chain alcohols, cholesterol esters, monoglycerides, and long-chain aldehydes. To substantiate that the glyceryl ether was converted to the glyceryl ether phospholipids, the rats were injected i.p. with double-labeled α-chimyl alcohol. At 4 h post-injection, very little tritium was detected in the total liver lipids, but was present in substantial quantities in the intestine. This finding was attributed to the degree of cleavage of the linkage in the liver and small intestines.[21]

The metabolism of chimyl alcohol was evaluated using 6 female rats of the Carworth Farm Nelson strain. ^{14}C-chimyl alcohol was injected i.v. (10 µCi/100g body weight) as a fat emulsion.[22,22] Approximately 28% of the ^{14}C from chimyl alcohol was eliminated as $^{14}CO_2$ within 6 h post-injection. During the same period of time, the urine contained 1% of the ^{14}C from chimyl alcohol. Approximately 6 to 13% of the radioactivity was accounted for as lipid in the liver, and the remainder was associated with adipose tissue or transferred into a nonlipid metabolic pool. These *in vivo* results were confirmed in the *in vitro* liver slice system, in that the ^{14}C from chimyl alcohol was found in triglycerides, free fatty acids, fatty alcohols, glyceryl ether monoesters, lecithin, and cephalin. Less than 2% of the chimyl alcohol was oxidized to $^{14}CO_2$ duirng the 3-h incubation period. When bone marrow cells and spleen slices were studied *in vitro*, the bone marrow cells were less active in metabolizing the labeled chimyl alcohol. Less than 6% of the ^{14}C from ^{14}C-chimyl alcohol was incorporated into phospholipids by bone marrow cells or spleen slices during the 3-h incubation period.

The metabolism of chimyl alcohol and phosphatidylethanolamine (PE) in the brain was studied using 3 groups of male Sprague-Dawley rats(18 days old).[23] Use of a control group was not mentioned. Each rat was anesthetized and given an intracerebral injection of 0.375 ml of an emulsion consisting of: 20 mg of 6 µc chimyl alcohol-^{3}H, 7.3 mg of 25µc phosphatidylethanolameine (PE)-^{14}C, and Tween 20 (36 mg/ml). The 3 groups of animals were killed after 4h, 8h, and 16 h, respectively, and brains removed. Ethanolamine phosphoglycerides were isolated and analyzed. It was evident that label from both substrates was incorporated into the brain lipids of the rats. A major portion of the ^{14}C activity (25-35%) appeared in the front fraction, defined as containing cholesterol, ceramide, cerebroside, choline phosphoglycerides, sphingomyelin and lyso phosphatidylcholine. The ^{14}C and ^{3}H activities in the dimethyl acetals derived from alkenyl acylethanolamine phosphoglycerides and in the glyceryl ethers derived from the alkyl acylethanolamine phosphoglycerides were measured. The absence of ^{14}C in the dimethyl acetals indicated that phosphatidylethanolamine was not transformed into phosphatidal ethanolamine. The increase, with time, of the ^{3}H content of the glyceryl ethers and dimethyl acetals indicated that chimyl alcohol was a precursor of both types of phospholipids.[23]

Batyl Alcohol

Male albino Sprague-Dawley rats (total of 40 used) were injected i.p. with α-1-^{14}C-batyl alcohol (7.24 mg) or β1-^{14}C-batyl alcohol (10.37 mg).[21] After dosing, the animals were killed and the entire liver and small intestine removed. Lipids were then extracted. After 8 h, 24.5% of the injected dose was present in the liver lipids. Approximately 15% of the α-1-^{14}C-batyl alcohol liver lipid label was identified as intact free glyceryl ether. All of the liver lipid label was identified as esterified fatty acid, with the exception of the remaining free glyceryl ether that had been injected. No significant free fatty acid label was observed in any of the liver lipid fractions. A different labeling pattern was found for the intestinal lipids. At 8 h post-injection of α-1-^{14}C-batyl alcohol, 65% of the intestinal lipid label was present as free glyceryl ether, and 8% of the injected dose was found in the small intestine. Only 7% of the dose was identified as esterified fatty acids. The major portion of the radioactive label in the intestine derived from α-1-^{14}C-batyl alcohol was in the phospholipids. After 8 h, approximately 18% of the total lipid label was associated with the phospholipids. β1-^{14}C-batyl alcohol was not incorporated into the glyceryl ether phospholipids as rapidly as the α-ether.

The metabolism of batyl alcohol was evaluated using 6 female rats of the Carworth Farm Nelson strain. ^{14}C-batyl alcohol was injected i.v. (10 µc/100g body weight) as a fat emulsion.[22] Approximately 13% of the ^{14}C from batyl alcohol was eliminated as $^{14}CO_2$ within 6 h post-injection. During the same period of time, the urine contained 6.5% of the ^{14}C from batyl alcohol. Approximately 6 to 13% of the radioactivity was accounted for as lipid in the liver, and the remainder was associated with adipose tissue or transferred into a nonlipid metabolic pool. These *in vivo* results were confirmed in the *in vitro* liver slice system, in that the ^{14}C from batyl alcohol was found in triglycerides, free fatty acids, fatty alcohols, glyceryl

ether monoesters, lecithin, and cephalin. Less than 0.2% of the batyl alcohol was oxidized to $^{14}CO_2$ during the 3-h incubation period.

Human Study

Chimyl Alcohol

Two adult patients (1 male, 1 female) were used to evaluate the absorption of chimyl alcohol.[24] The female patient with chyluria was maintained on a liquid formula (administered orally) 5 times per day. The formula was enriched with corn oil containing 25 mg of ^{14}C-labeled chimyl alcohol. Urine was collected at 3-h intervals over a 12-h period. The male patient (with bilateral chylothorax secondary to carcinoma) was maintained on a mixed hospital diet, and, on day 1 the chest was emptied by thoracentisis. This process was followed by feeding with bread containing ^{14}C-labeled chimyl alcohol (18 mg). A second thoracentesis was performed 48 h later, prior to the removal of chylous fluid. In the female patient, 95% of administered labeled chimyl alcohol was absorbed and approximately 40% of the dose was recovered in the urine within 12 h post-administration. This indicated that this patient shunted approximately 40% of her intestinal lymph into the urinary tract. Approximately half of the radioactivity in the lymph was identified as chimyl alcohol, and the remaining 50% had been converted to palmitic acid, found in triglycerides, phospholipids, and free fatty acids. Essentially the same results were reported for the male patient. Study results also indicated that rupture of the ether linkage of chimyl alcohol can occur in the intestinal mucosa of man, and that the palmitoyl moiety is readily oxidized to palmitic acid.

Percutaneous Absorption

In Vivo Study

Ethylhexylglycerin

An acute toxicokinetic study on ethylhexylglycerin (Sensiva® SC 50) was performed using 2 groups of 5 rabbits of an unspecified strain.[25] The test substance was applied (single application) to the 2 groups at concentrations of 1% and 5% in corn oil, respectively. Each concentration was applied at a dose of 2 g/kg body weight, spread evenly over surgical gauze (25 x 25 mm). The occlusive dressing remained in place for 4 h. There were no signs of irritation at the application site as late as 60 min post-application of either concentration. Changes in body weight were unremarkable. Ethylhexylglycerin was detected in the plasma of 3 of 5 rabbits tested with the 5% concentration. The mean absorption through skin in this group was 0.02% at approximately 2 h after the beginning of exposure. Plasma concentrations in animals treated with 1% ethylhexylglycerin were below the limit of detection. In all blood samples collected after treatment ended, the concentrations of ethylhexylglycerin were below the limit of detection (1.03 µg/ml).

In Vitro Study

Ethylhexylglycerin

The skin penetration of ^{14}C-ethylhexylglycerin (Sensiva® SC 50) was also evaluated using human skin.[25] The experiments were performed after administration of the test substance at 3 concentrations formulated as solutions in ethanol:water, 10:90 v/v, and concentrations of the test substance that were determined using quantitative radiochemical analysis. The lowest test concentration was based on dermal application of the test substance at a concentration of 2% in cream (at 1.4 mg cream/cm^2 of skin). Based on concentrations determined in the receptor fluid, mean absorption values for ^{14}C-ethylhexylglycerin at the 3 concentrations evaluated were as follows: 44.65% (at 31 µg/cm^2), 47.15% (at 60 µg/cm^2), and 54.94% (at 151 µg/cm^2). These 3 values corresponded to mean penetration rates of 2.38, 8.19, and 20.38 µg/cm^2/h, respectively. Results indicated that the lag time was essentially the same for all concentration tested. The rate at which ^{14}C-ethylhexylglycerin moved from the outer skin surface (dissolved in ethanol:water (10:90 v/v]) to the receptor fluid appeared to have been linear.

Skin Penetration Enhancement

The penetration of indomethacin (from propylene glycol solutions) through rat abdominal skin *in vitro* was substantially increased in the presence of 0.2% or 1% (w/w) α-monoisostearyl glyceryl ether.[26]

TOXICOLOGY

Acute Inhalation Toxicity

Ethylhexylglycerin

The acute inhalation toxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated in a study involving groups of 10 (5 males, 5 females/group) Sprague-Dawley rats.[25,27] The animals were exposed to the aerosolized ethylhexylglycerin (nose only, mean achieved concentrations of 1.89, 2.96, and 4.98 mg/L) for 4 h according to the OECD TG 403 test method, using a continuous flow system. After exposure, the animals were observed for 14 days. The mean diameter of the aerosol particles was between 1.2 and 1.4 µm. Clinical observations included labored and noisy respiration and occasional sneezing (frequent when noted), ataxia, and gasping respiration. The acute inhalation LC50 was 3.07 mg/L (low to moderate toxicity), and the following mortalities were reported: 4.98 mg/L (4 males, 5 females), 2.96 mg/L (3 males, 2 females), and 1.89 mg/L (1 male). Morphological findings for the lungs were described as dark or abnormally reddened appearance, pale patches, enlargement, and an isolated incidence of hemorrhage. Thus, an irritant effect on the respiratory tract was evident. An abnormally dark liver (accentuated lobular pattern) was also reported for the male in the lowest dose group that died. The lung was described as a target organ, based on rapid deaths, severe respiratory changes, and abnormal coloration and enlargement of the lungs.

Acute Oral Toxicity

Ethylhexylglycerin

In an acute toxicity study on undiluted ethylhexylglycerin (Sensiva® SC 50), 5 male and 5 female Wistar rats each received a single oral dose (2,000 mg/kg) by gavage according to the OECD TG 401 test method.[25,27] An LD50 of > 2,000 mg/kg (low toxicity, no deaths) was reported, and clinical observations included irregular respiration and hemorrhagic nasal discharge for up to 24 h post-administration. No test-substance related morphological findings were reported.

Chimyl Alcohol

The acute oral toxicity of chimyl alcohol was evaluated using 6-week-old SD rats of the Crl:CD(SD) strain (5 males, 5 females).[28] Animals received a single oral dose of chimyl alcohol in a 1 w/v% Tween 80 solution (concentration = 200 mg/ml; dose volume = 10 ml/kg). None of the animals died. Diarrhea was observed after dosing; however, body weight gain was described as normal. Necropsy findings did not reveal any abnormalities. It was included that the acute toxicity induced by chimyl alcohol was extremely low (LD_{LO} > 2,000 mg/kg).

Acute Dermal Toxicity

Ethylhexylglycerin

The acute dermal toxicity of undiluted ethylhexylglycerin (Sensiva® SC 50) was evaluated in a study involving 5 male and 5 female Wistar rats.[27,25] The undiluted test substance was applied (2.17 ml on porous gauze/elastic dressing; dose = 2,000 mg/kg) to shaved, intact skin according to the OECD TG 402 test method. The application site was defined as a 5 x 10 cm area on the back, and the occlusive dressing remained in place for 24 h. No abnormal clinical signs or signs of erythema or edema were observed during the study. None of the animals died, and an acute dermal LD50 of > 2,000 mg/kg (non-toxic) was reported. Necropsy findings were described as normal.

Acute Subcutaneous Toxicity

Batyl Alcohol

Single subcutaneous doses of batyl alcohol were administered to adult white mice (10 to 15, ages not stated), and deaths were reported at 24 h post-dosing.[29] A mean LD50 of > 8.8 mM/kg was reported. Details relating to the test protocol and study results were not included.

Repeated Dose Toxicity

Ethylhexylglycerin

The oral toxicity of ethylhexylglycerin (Sensiva® SC 50, in polyethylene glycol 400) at doses of 100, 500, and 1,500 mg/kg was evaluated in a 28-day study using groups of 10 rats of an unspecified strain. The test substance was administered at a dose volume of 5 ml/kg.[25] There were no treatment-related mortalities. Body weight development was retarded in mid- and high-dose groups, and this finding was accompanied by a non-statistically significant reduction in food intake when compared to the control (polyethylene glycol 400) group. Both eye and ear functions remained unchanged during the study, and increased salivation (dose not stated) was the only clinical symptom observed. Hematological parameters were unaffected by treatment; however, serum analyses indicated changes in aminotransferase (above normal) in high-dose rats. Urinalysis and necropsy findings were unremarkable.

Increased liver and adrenal weights were reported for high-dose rats, especially females. Microscopic findings in the liver were described as follows: slight to moderate hypertrophy (rats from all dose groups), fatty infiltration of hepatocytes (high –dose males), and necrosis of hepatocytes (1 rat each from mid- and high-dose groups). A dose of 100 mg/kg was defined as the no-observed-adverse effect-level (NOAEL), assuming that the slight hepatocyte hypertrophy observed in 5 of 10 rats in this dose group was not toxicologically significant.[25]

In a 13-week study, ethylhexylglycerin (Sensiva® SC 50, in polyethylene glycol [PEG] 400) was administered at oral doses of 0, 50, 200, and 800 mg/kg/day to groups of Sprague- Dawley rats (10 males, 10 females/group).[25,30] A fourth group (control) was dosed with PEG 400 only. Testing was done in accordance with the OECD TG 407 test method. There was no evidence of treatment-related deaths or statistically significant changes in body weight gain. Furthermore, neurotoxicology testing and ophthalmoscopic examinations revealed no test-substance-related changes. Compared to controls, statistically significant changes in some clinical parameters (e.g., statistically significant decrease in lymphocytes) were observed, but were considered toxicologically insignificant. Abnormally noisy respiration and an increased incidence of subcutaneous masses were reported for the highest dose group. Noisy respiration was also observed in some animals in the mid dose group, and the incidence increased with time in mid- as well as high-dose groups. Treatment-related macroscopic effects were not found in animals killed at the end of dosing or the 4-week recovery period or in animals that died during the study.

In males of all dose groups and high-dose females, a statistically significant increase in absolute and relative-to-body weight liver weights was observed during dosing. Relative liver weights remained increased in males at the end of the recovery period. Increased liver weight was the only toxicologically significant finding that was also observed in the low-dose group. However, this finding was not accompanied by changes in clinical parameters associated with functional impairment of this organ. Increased absolute and relative kidney weights (statistically significant) were observed in females of low- and high-dose groups, but this finding was not observed at the end of the recovery period. Microscopic examination revealed generalized hepatocytic hypertrophy in the high-dose group. When compared to controls, this finding was statistically significant in high-dose male rats. An increased incidence of renal mineralization was observed in high-dose females, but this finding was not apparent at the end of the recovery period. According to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS, Australia) summary of data from this 13-week study, it was not possible to establish a no-observed-adverse-effect level (NOAEL), in that increased liver weight was observed at all doses. The study authors considered 50 mg/kg/day to be an NOAEL, because this dose was associated with increased liver weights without any other effects.[30] In comparison, the NICNAS identified 50 mg/kg/day as a lowest observed adverse effect level (LOAEL), based on the increased liver weights reported in this study.[27]

Batyl Alcohol

The hematopoietic activity of batyl alcohol was evaluated using male guinea pigs of the Dunkin-Hartley strain (ages not stated).[31] One group of 12 guinea pigs was dosed subcutaneously (s.c.) with batyl alcohol (4 mg) in 1 ml of arachis oil on each of 5 consecutive days. The control group (10 guinea pigs) received s.c. injections of arachis oil. On day 6, the animals were killed and erythrocyte and leukocyte counts were performed on blood obtained from a small ear incision. Changes in bone marrow were also evaluated. Results suggested that batyl alcohol may be an erythropoietic stimulant. The authors suggested that batyl alcohol exerted an influence on the lymphocytic, but not the granulocytic, population of the bone marrow. The following changes were observed in the bone marrow: increased population of small lymphocytes ($p < 0.05$), increased bone marrow reticulocyte count ($p < 0.05$), increase in the number of cells intermediate between small lymphocytes and blast-like cells ($p \approx 0.05$), and an increase in the mean numbers of nucleated cells at each stage of the red cell series ($0.10 > p > 0.05$). Significant reticulocytosis ($p < 0.05$) in the blood was also observed. Stimulation of hematopoiesis was also observed in Wistar rats given 15 daily 50 mg doses of a 10% suspension of racemic batyl alcohol in distilled water,[32]

and in Wistar rats that received 20 s.c. injections of peanut oil containing 12.5 mg or 25.0 mg of racemic batyl alcohol 5 days per week over a period of 4 weeks.[33] In the latter study, the erythrocytosis and reticulocytosis were more marked and appeared earlier in rats that received the higher dose.

Ocular Irritation

Ethylhexylglycerin

Undiluted ethylhexylglycerin (Sensiva® SC 50, 0.1 ml) was instilled into the left conjunctival sac of each of 3 New Zealand White rabbits (sex not specified), and animals were observed up to day 21 post-instillation.[25,27] Right eyes served as untreated controls. Testing was in accordance with the OECD TG 405 test protocol. Conjunctival redness and chemosis were observed in all animals and irritation scores of 2 or 3 predominated. Conjunctival irritation persisted up to day 14, and, in one animal, corneal opacity persisted beyond the 21-day observation period. Thus, ethylhexylglycerin (Sensiva® SC 50) caused severe damage to the eyes of rabbits. When a 5% aqueous solution of the test substance was instilled into the eyes of 3 additional rabbits according to the same procedure, conjunctival erythema (score = 1) was observed in each animal at 1 h post-instillation. Conjunctival irritation had resolved completely within 24 h. There were no signs of irritation to the iris or cornea. Thus, the 5% aqueous solution of ethylhexylglycerin (Sensiva® SC 50) was mildly irritating to the eyes of rabbits.[25,27]

Chimyl Alcohol

In the Draize test, the ocular irritation potential of chimyl alcohol was assessed using 6 male Japanese White rabbits of the Kbl: JW, SPF strain.[34] The test substance (0.1 g) was instilled into the right eye of each animal. The eyes of 3 rabbits were rinsed after instillation. In all unrinsed eyes, conjunctival redness and chemosis (score = 1) and discharge (score = 2 or 3) were observed at 1 h post-instillation. Reactions had cleared by 48 h post-instillation. Chimyl alcohol was classified as minimally irritating in unrinsed eyes (maximum mean Draize score = 9.3). Ocular reactions were not observed in rinses eyes. Chimyl alcohol was classified as having minimal ocular irritation potential in this study.

Skin Irritation and Sensitization

Non-Human Studies

Ethylhexylglycerin

The skin irritation potential of ethylhexylglycerin (Sensiva® SC 50) was evaluated using 3 New Zealand White rabbits (sex not specified).[27] Undiluted test substance (0.5 ml) was applied to intact skin (shaved) and the test site was covered with a semi-occlusive dressing secured with elastic tape. Testing was in accordance with the OECD TG 404 test protocol. During the 4-day observation period, erythema (score = 1) was observed in 2 rabbits, but edema was not observed in any of the animals. Signs of erythema had cleared by day 4 post-application. Ethylhexylglycerin (Sensiva® SC 50) was classified as a mild skin irritant.

In another study, the skin irritation potential of undiluted ethylhexylglycerin (Sensiva® SC 50) was evaluated in 3 rabbits (strain not stated) according to the protocol stated in the preceding paragraph.[25] The test substance remained in contact with the skin for 4 h, and very slight erythema was observed in 2 of 3 rabbits at 24 h and 48 h post-application. It was concluded that ethylhexylglycerin could not be classified as a skin irritant.

In the maximization test (OECD TG 406 test method), the skin sensitization potential of ethylhexylglycerin (Sensiva® SC 50) was evaluated using 2 groups of 20 guinea pigs (10 males, 10 females/group); one of the 2 groups served as the negative control.[25,27] The induction phase involved 10 test animals with 3 pairs of injection sites on the shaved neck according to the following procedure. Starting at day 0, 0.1 ml of the test substance was injected intradermally into the neck region (2 pairs of injection sites) at concentrations of 0.5% in peanut oil and 0.5% in Freund's complete adjuvant/saline 1:1, respectively. The third pair of sites was injected with Freund's complete adjuvant/water 1:1. On day 7, the undiluted test substance was applied (under occlusive dressing) to the neck for 48 h. On day 21, the animals were challenged with the test substance (50% in peanut oil, under occlusive dressing) for 24 or 48 h. Sensitization was not observed in any of the animals tested.

The sensitization potential of ethylhexylglycerin (Sensiva® SC 50) was evaluated in the local lymph node assay at concentrations up to 50%.[25] The test substance did not induce 3-fold increases (EC_3-value) in tritiated thymidine (^{3}HTdR) incorporation at any concentration tested, and it was concluded that Ethylhexylglycerin was not a sensitizer.

Chimyl Alcohol

The skin irritation potential of chimyl alcohol was evaluated in the Draize test using 3 male Japanese White rabbits of the Kbl: JW, SPF strain (11 weeks old).[35] Chimyl alcohol (0.5 g) moistened with propylene glycol (0.5 ml) was applied to intact and abraded skin sites on each animal. Each application site was covered with an occlusive patch for 24 h. At 24 h post-application, all animals received an erythema score of 1 at intact and abraded skin sites. Reactions had cleared by 72 h post-application. Skin irritation was not observed at intact or abraded sites tested with propylene glycol (0.5 ml). Chimyl alcohol was classified as a mild irritant (primary irritation index [PII] = 0.5, intact and abraded skin).

A 14-day cumulative skin irritation study was performed using 3 male Japanese White rabbits of the Kbl: JW, SPF strain. Chimyl alcohol (10 w/v%, suspended in propylene glycol) was applied to the skin at a volume of 0.2 ml, without an occlusive patch.[36] Applications were made once daily for 14 days. Propylene glycol (solvent control) was applied to control sites. Skin irritation was not observed at sites treated with chimyl alcohol or control sites. It was concluded that chimyl alcohol did not have cumulative skin irritation potential.

Human Studies

Ethylhexylglycerin

The skin irritation and sensitization potential of a facial cream containing 0.4975% ethylhexylglycerin was evaluated in an RIPT using 600 subjects (ages not stated).[37] Occlusive patches (0.5" x 0.5") containing the test substance were applied (48 h) weekly for a total of 10 induction applications. Reactions were scored after patch removal. After a 2-week non-treatment period, challenge patches were applied for 48 h. As second challenge application (48 h) was made one week later. There was no evidence of primary irritation, skin fatiguing, or allergic eczematous dermatitis.

A foundation containing 0.4% ethylhexylglycerin was evaluated for skin irritation and sensitization potential in an RIPT involving 108 male and female (18 to 70 years old).[38] Partially-occlusive patches (2 cm x 2 cm) containing the test substance (~ 150 mg) were applied for 24 h, for a total of 9 induction applications. During the challenge phase (105 subjects), test sites were scored at the time of patch removal and 24 h and 48 h later. The induction application site and a new test site were challenged. The foundation was neither a skin irritant nor sensitizer.

A repeated insult patch test (RIPT) on a liquid eyeliner containing 0.5% ethylhexylglycerin was performed using 115 male and female subjects (16 to 79 years old).[39] Approximately 0.2 g of the test substance on a 1" x 1" semi-occlusive patch was applied (24 h) 3 times per week for a total of 9 induction applications. Reactions were scored after patch removal. After a 2-week non-treatment period, a challenge patch was applied to a new site adjacent to the original induction site. Challenge reactions were scored at 24 h and 72 h post-application. The product did not have skin irritation or allergic contact sensitization potential.

The skin irritation and sensitization potential of a makeup preparation containing 0.995% ethylhexylglycerin was studied in 111 male and female subjects (18 to 70 years old) using the same test procedure, except for the application of 100 µl of test material to the partially-occlusive patch.[40] The number of subjects who participated in the challenge phase was 108. The makeup preparation was neither a skin irritant nor sensitizer.

An RIPT on a fragranced body lotion containing 0.6965% ethylhexylglycerin was conducted using 108 subjects (between 18 and 70 years old).[41] A semi-occlusive patch containing the test substance was applied (24 h) 3 times per week for a total of 9 induction applications. Reactions were scored after patch removal. After a 2-week non-treatment period, a challenge patch was applied to a previously untreated site for 24 h. Reactions were scored at 24 h, 48 h, and 72 h. The body lotion was not a skin irritant or sensitizer.

Skin Tanning

Chimyl Alcohol

A study was performed to achieve skin whitening via the control of cytokines by coating the skin with a chemical substance and the control of melanogenesis, in which inflammation of the skin became a trigger.[42] The effect of chimyl alcohol on reduction of peroxisome proliferator activated receptor (PPAR) expression of normal human keratinocytes (NHK) by USB was evaluated in one of the experiments. The cells were cultured for 24 h in media containing chimyl alcohol at concentrations up to 10 µM, and cultures were then exposed to UVB light (5.0 mJ/cm^2). The participation of PPAR in the

control PGE_2 production due to chimyl alcohol was observed. Chimyl alcohol checked the reduction of expression of mRNA of PPARγ due to UVB. This effect of chimyl alcohol was eliminated in the presence of a PPARγ antagonist (GW9662). In another experiment, The effect on the erythema reaction caused by coating chimyl alcohol on the skin model was determined by changing the minimum erythema dose (MED), and the effect on pigmentation was visually determined. Study results suggested that chimyl alcohol had an inflammatory effect via PPARs of keratinocytes. Chimyl alcohol suppressed the production of chemical mediators of UVB-irradiated keratinocytes *in vitro*, possibly via the PPARγ pathway and erythema in human skin. It substantially suppressed UV-induced tanning in human skin. The results of this study led to the proposal of chimyl alcohol as an ingredient of a new skin whitening agent.

Phototoxicity

Ethylhexylglycerin

The phototoxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated at concentrations ranging from 25% to 100% using albino guinea pigs (number not stated).[25] Each solution was applied to the flank, after which sites were irradiated with UVA light at a dose of 20 J/cm^2. The opposite flank (control) was treated with the test substance, but not irradiated. Study results indicated no evidence of phototoxic effects.

Photoallergenicity

Ethylhexylglycerin

Tests were also performed to evaluate the photoallergenicity of ethylhexylglycerin (Sensiva® SC 50).[25] Initially, albino guinea pigs (number not stated) were pretreated with Freund's adjuvant. The animals were then treated dermally (5 times in 14 days) with the undiluted test substance and irradiated with UVA and UVB light. None of the animals had reactions during the challenge phase that followed, and it was concluded that ethylhexylglycerin was not a photosensitizer.

Case Reports

Ethylhexylglycerin

A 57-year-old female developed perioral and periocular itchy erythematosquamous edema of the eyelids after using a facial cream that contained ethylhexylglycerin.[43] Patch test results for 10% ethylhexylglycerin in petrolatum in this subject were positive (+) on days 2 and 4, but results were negative in 5 control subjects.

A 64-year-old female with chronic eczema was patch tested with ingredients provided by a product manufacturer. Reactions were scored on days 3 and 7.[44] A strong positive reaction (++,+) to 5% ethylhexylglycerin in petrolatum was reported. A repeated open application test (ROAT, 7 days) was also performed. ROAT results for 5% ethylhexylglycerin were strongly positive on day 2, after only 4 applications. The reaction spread to the entire right arm and to the face. Patch test results were negative for 5% ethylhexylglycerin in 25 consecutive controls.

Recurrent and spreading facial dermatitis was observed in a 68-year-old, non-atopic female after using a cream containing ethylhexylglycerin.[45] Occlusive patches (Finn chambers) were applied for 2 days and reactions were scored on days 3 and 7. Results were positive for 5% ethylhexylglycerin in petrolatum. Patch test results were negative in 25 consecutive controls.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Ethylhexylglycerin

The effects of ethylhexylglycerin (Sensiva® SC 50) on pregnancy and embryo-fetal development were evaluated in a prenatal developmental toxicity study involving groups of female rats of an unspecified strain (no. of animals not stated).[25] The test substance was administered by gavage at doses of 50, 200, and 800 mg/kg/day. None of the animals died. Salivation and rales were considered the most relevant signs observed in mid- and high-dose groups. There were no treatment-related effects on terminal body weight, uterine weight, or absolute weight gain. Litter data and the results of macroscopic examinations of females were also unaffected by treatment, and the malformations observed in 3 fetuses at external examination were considered incidental. The results of visceral and skeletal examinations did not reveal any changes between test and control groups that were considered treatment-related. Based on these results, the no-observed-

adverse-effect-level (NOAEL) was considered to be 800 mg/kg/day, and this was the highest dose tested in the one-generation developmental toxicity study summarized below.

The developmental toxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated in a one-generation developmental toxicity study using groups of male and female rats of an unspecified strain.[25] The test substance was administered orally at doses of 50, 200, and 800 mg/kg/day. Male rats were dosed daily for 10 weeks prior to pairing, after which dosing continued through the day before animals were killed. Female rats were dosed for 2 weeks prior to pairing and during gestation and post-partum periods; dosing ended on post-partum day 20. Treatment-related findings, rales and salivation, occurred only in males of mid- and high-dose groups. Two male rats were found dead (1 low-dose and 1 mid-dose; cause not stated) and 3 rats (2 high-dose males, 1 high-dose female) were killed for humane reasons. Necropsy findings in animals found dead or killed did not reveal any treatment-related changes in tissues/organs. On day 21 post-partum, there were 17 to 23 females per group with live pups. Twelve females did not become pregnant. Estrous cycles were comparable between groups, but the fertility index for high-dose animals was lower when compared to controls. Data on pre-birth loss and gestation length indicated no treatment-related effects on implantation. The no-observed-effect-level (NOEL) was 50 mg/kg/day for both sexes.

GENOTOXICITY

Ethylhexylglycerin

The genotoxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated in the Ames test (OECD TG 471 test method) using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 with and without metabolic activation.[25,27] The test substance was evaluated at concentrations up to 1.5 µg/plate. Toxicity was observed at the highest test concentration. Ethylhexylglycerin was not genotoxic with or without metabolic activation. Normal reversion rates were observed in negative control plates, and positive controls were genotoxic.

In another *in vitro* test (mouse lymphoma assay), the genotoxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated with and without metabolic activation using mouse lymphoma L5178Y cells.[25] Test concentrations were not stated. Negative results were reported for ethylhexylglycerin.

In the *in vivo* micronucleus assay, the genotoxicity of ethylhexylglycerin (Sensiva® SC 50) in mouse bone marrow cells was evaluated.[25,27] According the OECD TG 474 test method, 60 mice of the BOR:NMRI strain (30 males, 30 females) received single oral doses of 1,000 and 2,000 mg/kg by gavage. The examinations for cell nucleus changes in the bone marrow were performed on animals killed at 24 h and 48 h. Reduced activity, alterations in tone, and abnormal gait were among the findings observed up to 1 h post-dosing; however, none of the animals died. A statistically significant decrease in the numbers of polychromatic erythrocyte was observed in bone marrow cells from females of all dose groups. There were no statistically significant increases in micronucleated polychromatic erythrocytes at any timepoint, and it was concluded that ethylhexylglycerin was non-clastogenic.

Chimyl Alcohol

The genotoxicity of chimyl alcohol (in DMSO) was evaluated in the Ames pre-incubation test using the following bacterial strains, with and without metabolic activation:[46] *Salmonella typhimurium* strains TA100, TA 1535, TA98, and TA1537, and *Escherichia coli* strain WP2uvrA. Test concentrations up to 5,000 µg/plate were used. It was concluded that chimyl alcohol was not mutagenic to any of the strains tested. The numbers of revertant colonies in the negative (solvent) control and positive control cultures were within the acceptable ranges stipulated at the testing facility.
In the *in vitro* chromosomal aberrations assay involving CHL/IU cells (derived from female Chinese hamster lungs), the genotoxicity of chimyl alcohol was evaluated with (concentrations up to 1,000 µg/ml) and without (concentrations up to 200 µg/ml) metabolic activation in short-term assays and at concentrations up to 100 µg/ml (with metabolic activation) in the 24-h assay.[47] In all assays, the incidence of cells with chromosomal aberrations was < 5% at each concentration tested, with or without metabolic activation. It was concluded that chimyl alcohol did not have the potential to induce chromosomal aberrations under the conditions used in this study.

Batyl Alcohol

Batyl alcohol was evaluated for genotoxicity in the Ames test (reverse mutation assay) using the following *Salmonella typhimurium* strains: TA 97a, Ta 98, TA 100, TA 102, and TA 1535.[48] The test substance was evaluated with and without metabolic activation at doses up to 25 µg/plate. The following chemicals served as positive controls:

benzo[a]pyrene (with metabolic activation) and sodium azide; ICR 191; 2,4,7-trinitro-9-fluorene; and Mitomucine C (all without metabolic activation). Batyl alcohol was not genotoxic with or without metabolic activation.

Glyceryl Allyl Ether

The genotoxicity of glyceryl allyl ether was evaluated in the following battery of short-term tests: Ames test (*Salmonella typhimurium* strains TA98, TA100, and TA1538 and *Escherichia coli* strains WP_2 and WP_2 uvrA; test concentrations up to 4,000 µg/plate in plate incorporation assay, with and without metabolic activation), yeast assay for mitotic gene conversion (*Saccharomyces cerevisiae* strain JD1; 0.1 ml test substance added, with and without metabolic activation), and the rat-liver chromosome damage assay (RL_4 rat-liver cell line; tested up to 0.125 of the GI_{50} [50% growth inhibition]).[49] Glyceryl allyl ether did not induce mutations in any of the bacterial strains tested, gene conversion in yeast (*S. cerevisiae*), or chromosome damage in RL_4 cells.

CARCINOGENICITY

Studies on the carcinogenicity of the alkyl glyceryl ethers reviewed in this safety assessment were not found in the published literature.

SUMMARY

The safety of the following ingredients in cosmetics is reviewed in this safety assessment: ethylhexylglycerin, caprylyl glyceryl ether, glyceryl capryl ether, chimyl alcohol, batyl alcohol, glyceryl allyl ether, glyceryl lauryl ether, isodecyl glyceryl ether, isostearyl glyceryl ether, and oleyl glyceryl ether. These ingredients function mostly as surfactants or skin conditioning agents in cosmetic products. Together, information supplied to FDA as part of the Voluntary Cosmetic Registration Program, reported in 2011 FDA database, and the results of Personal Care Products industry surveys conducted in 2010 and 2011 indicated use of the following ingredients in cosmetics: ethylhexylglycerin (0.000001% to 8%), chimyl alcohol (0.002% to 0.5%), glyceryl lauryl ether (7%), and isostearyl glyceryl ether (0.001% to 0.02%). The concentration of use survey for batyl alcohol is still underway.

Sensiva® SC 50, one of the trade names under which ethylhexylglycerin is being marketed contains > 99% ethylhexylglycerin.[6] It also contains a small amount of α-tocopherol and the impurities, 2-ethylhexyl-glycidylether and water. Chimyl alcohol is approximately 98% pure and also contains approximately 2% batyl alcohol as an impurity.

Most of the (1-^{14}C)-chimyl alcohol administered orally to rats was absorbed in 24 h (95% absorption), and the remainder was found in fecal lipids. Other results (rats) indicated that 8% of ^{14}C-chimyl dioleate (esterified chimyl alcohol) administered orally was excreted as expired $^{14}CO_2$ in 24 h. Labeled chimyl alcohol was also detected in the lymph of rats dosed orally, and was also present in this form as well as in the form of its palmitic acid metabolite in intestinal mucosal cells. After dosing with free chimyl alcohol (rats, via stomach tube), alkoxydiglycerides resulted from the incorporation of free fatty acids into chimyl alcohol. At 8 h post-i.p. dosing of rats with α-1-^{14}C-batyl alcohol, 24.5% of the injected dose was present in the liver lipids and 8% of the injected dose was found in the small intestine; 65% of the intestinal lipid label was present as free glyceryl ether. In another study involving rats, approximately 13% of the ^{14}C from batyl alcohol was eliminated as $^{14}CO_2$ within 6 h post-injection and the urine contained 6.5% of the ^{14}C from batyl alcohol.

Following oral administration of ^{14}C-chimyl alcohol to human subjects, 95% of the labeled chimyl alcohol was absorbed, and approximately 40% of the dose was recovered in the urine within 12 h post-administration. Approximately half of the radioactivity in the lymph was identified as chimyl alcohol, and the remaining 50% had been converted to palmitic acid, found in triglycerides, phospholipids, and free fatty acids.

The i.p. dosing of rats with labeled α- and β-chimyl alcohols resulted in conversion to glyceryl ether phospholipids in the intestine. After i.v. dosing of rats with ^{14}C-chimyl alcohol, approximately 28% of the ^{14}C was eliminated as $^{14}CO_2$ within 6 h, and the urine contained 1%. Approximately 6 to 13% of the radioactivity was accounted for as lipid in the liver, and the remainder was associated with adipose tissue or transferred into a nonlipid metabolic pool. Similarly, 24% of ^{14}C-chimyl alcohol injected i.v. was excreted as expired $^{14}CO_2$ in 24 h. After dosing with free chimyl alcohol (rats, via stomach tube), alkoxydiglycerides resulted from the incorporation of free fatty acids into chimyl alcohol. The incorporation of ^{3}H-chimyl alcohol into brain lipids was apparent after intracerebral injection into rats.

In an acute toxicokinetic study *in vivo*, the mean absorption of ethylhexylglycerin through the skin of rabbits was 0.02% at approximately 2 h post-application and there were no signs of skin irritation. The quantity of ethylhexylglycerin in the plasma was below the detection limit at the end of the 4 h application period. Over a range of 3 concentrations (44.65, 47.15, and 54.94%) applied to human skin in vitro, mean penetration rates of 2.38, 8.19, and 20.38 $\mu g/cm^2/h$ were reported.

In an acute inhalation toxicity study using groups of rats exposed to ethylhexylglycerin (nose-only, mean achieved concentrations of 1.89, 2.96, and 4.98 mg/L), a concentration-related increase in mortality was observed. The lung was described as a target organ, based on rapid deaths, severe respiratory changes, and abnormal coloration and enlargement of the lungs.

No mortalities or exposure-related toxicological findings were observed in rats dosed orally with undiluted ethylhexylglycerin or chimyl alcohol. Subcutaneous administration of batyl alcohol to mice yielded an LD50 of > 8.8 mM/kg.

No mortalities or signs of skin irritation or abnormal necropsy findings were observed after undiluted ethylhexylglycerin was applied to the skin of rats. Necropsy findings were unremarkable and there were no treatment-related mortalities in rats dosed orally with ethylhexylglycerin at doses up to 1,500 mg/kg for 28 days. Increased liver and adrenal weights were observed in the highest dose group, and microscopic findings included slight to moderate liver hypertrophy in rats of all 3 dose groups. The 100 mg/kg dose was defined as the no-observed-adverse effect-level (NOAEL). Ethylhexylglycerin administered orally to rats, at doses up to 800 mg/kg/day, in a 13-week study did not result in any treatment-related deaths, macroscopic observations, or neurotoxicity. A statistically significant increase in absolute and relative-to-body weight liver weights was observed in males of all dose groups and females of the highest dose group. Generalized hepatocytic hypertrophy was observed at microscopic examination in the highest dose group, a finding that was statistically significant in males. Two summaries of this 13-week study were provided, and a dose of 50 mg/kg/day (lowest dose) was considered the lowest observed adverse effect level (LOAEL) in one summary and the NOAEL in the other summary. Batyl alcohol stimulated hematopoiesis (both red and white blood cells) in repeated dose studies involving rats and guinea pigs. In these studies, batyl alcohol (4 mg in arachis oil) was injected s.c. into guinea pigs for 5 days. Rats received 15 daily 50 mg doses of a 10% suspension of batyl alcohol in distilled water or 20 s.c. injections of 12.5 mg or 25.0 mg of batyl alcohol in peanut oil over a period of 4 weeks (5 days per week).

Undiluted ethylhexylglycerin was severely irritating , but 5% ethylhexylglycerin was mildly irritating, to the eyes of rabbits.

Undiluted ethylhexylglycerin was classified as a mild skin irritant in rabbits in one test and as a non-irritant in another test. Chimyl alcohol was classified as a mild skin irritant in rabbits after a single application, but was a non-irritating to the skin of rabbits in a cumulative skin irritation study. Skin sensitization was not observed in guinea pigs tested with 0.5% ethylhexylglycerin during induction and challenged with a higher concentration (50%) in the maximization test. Local lymph node assay results for ethylhexylglycerin at concentrations up to 50% were also negative. Products containing ethylhexylglycerin at concentrations ranging from 0.4% to ~ 1% were neither skin irritants nor sensitizers in RIPT's involving human subjects. Positive patch test results were reported for dermatitis patients patch tested with ethylhexylglycerin at concentrations up to 10%. However results were negative for control subjects.

Ethylhexylglycerin was not phototoxic or photoallergenic in guinea pigs when tested at concentrations up to 100% in the presence of UVA/UVB light. Chimyl alcohol suppressed the production of chemical mediators of UVB-irradiated keratinocytes *in vitro* and substantially suppressed UV-induced tanning in human skin. Based on these findings, a new concept for skin whitening via controlling keratinocyte function was proposed.

In a preliminary test, the results of visceral and skeletal examinations in litters of female rats given oral doses of ethylhexylglycerin (up to 800 mg/kg/day) were negative. None of the dosed animals died, and the no-observed-adverse-effect-level (NOAEL) for developmental toxicity was considered to be 800 mg/kg/day. In the one-generation developmental toxicity study (same doses) involving male and female rats, estrous cycles were comparable between groups, but the fertility index for rats of the highest dose group was lower when compared to controls. There were no treatment-related effects on implantation. Necropsy findings in dosed rats found dead or killed did not indicate any treatment-related changes. The no-observed-effect-level (NOEL) for developmental toxicity in both sexes was 50/mg/kg/day.

Ethylhexylglycerin was non-genotoxic in the Ames test (Salmonella typhimurium strains)and in the mouse lymphoma assay in vitro, both with and without metabolic activation. It was also non-clastogenic in the micronucleus assay in vivo. Chimyl alcohol was non-genotoxic (with and without metabolic activation) in the Ames test and in the chromosomal aberrations assay involving Chinese hamster lung cells. Batyl alcohol also was not genotoxic in the Ames test, with and without metabolic activation. Glyceryl Allyl Ether was non-genotoxic (with and without metabolic activation) in the Ames

test (Salmonella typhimurium and E. coli strains) and yeast assay for mitotic gene conversion (Saccharomyces cerevisiae). Results were also negative in the rat-liver chromosome damage assay (RL_4 rat-liver cell line). Studies on the carcinogenicity of the alkyl glyceryl ethers reviewed in this safety assessment were not found in the published literature.

DISCUSSION

The CIR Expert Panel considered the evidence of minimal percutaneous absorption of ethylhexylglycerin through rabbit skin *in vivo* and the relevance of such data to the entire group of ingredients. The Panel determined that the similar chemical structures of these alkyl glyceryl ethers and the similar ways in which they are used in cosmetics suggested that all of these ingredients would have minimal dermal penetration. Furthermore, a review of the available data on toxicity revealed: an absence of genotoxicity in studies using ethylhexylglycerin, chimyl alcohol, batyl alcohol, and glyceryl allyl ether; an absence of reproductive and developmental toxicity in oral studies using ethylhexylglycerin; negative skin irritation/sensitization data in studies using ethylhexylglycerin and chimyl alcohol; and negative phototoxicity/photoallergenicity data in studies using ethylhexylglycerin. Overall, the available toxicity data, coupled with the limited dermal penetration, suggested that these ingredients could be used safely in the present practices of used and concentration.

However, the Panel did note the skin penetration enhancement effect of isostearyl glyceryl ether, and emphasized that this should be taken into consideration when formulating cosmetic products that contain alkyl glyceryl ethers.

Because ethylhexylglycerin (up to 2%) can be used in cosmetics that may be sprayed, the Panel discussed the issue of incidental inhalation exposure. In the absence of sufficient inhalation data, the Panel considered that the available data from other routes of exposure that suggested an absence of genotoxicity, reproductive and developmental toxicity, dermal irritation and sensitization, and phototoxicity/photoallergenicity for this entire group of ingredients. The Panel noted that 95 – 99% of the droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

CONCLUSION

The CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment:

- Ethylhexylglycerin
- Caprylyl Glyceryl Ether*
- Glyceryl Capryl Ether*
- Cetyl Glyceryl Ether/Chimyl Alcohol
- Batyl Alcohol
- Glyceryl Allyl Ether*
- Glyceryl Lauryl Ether
- Isodecyl Glyceryl Ether*
- Isostearyl Glyceryl Ether
- Oleyl Glyceryl Ether*

Were ingredients in this group not in current use to be in the future (indicated by *), the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

Table 1. Definitions, functions, and structures of alkyl glycerin ether ingredients in this safety assessment.[1]

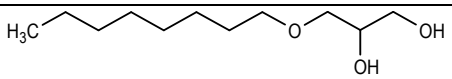
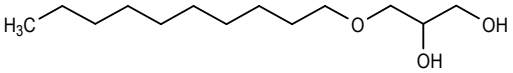
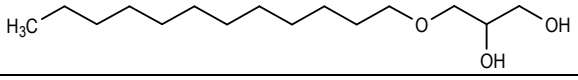
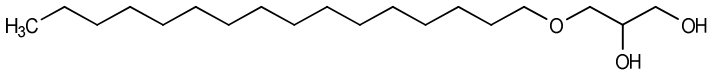
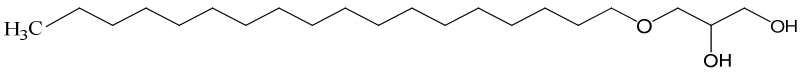
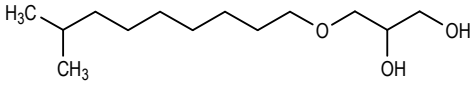
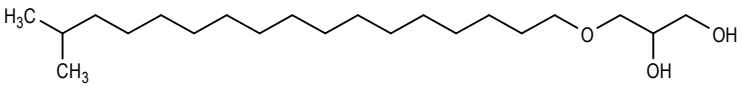
Ingredient CAS No.	Definition	Function(s)	Formula/structure
-Straight chain			
Caprylyl Glyceryl Ether 10438-94-5	Caprylyl Glyceryl Ether is the condensation product of octanol and glycerin.	Surfactants - Cleansing Agents; Surfactants - Foam Boosters	
Glyceryl Capryl Ether 10430-97-4 [current per CAS]	Glyceryl Capryl Ether is the condensation product of decanol and glycerin.	Surfactants - Cleansing Agents; Surfactants - Emulsifying Agents; Surfactants - Foam Boosters	
Glyceryl Lauryl Ether 1561-07-5 [current per CAS]	Glyceryl Lauryl Ether is the condensation product of dodecanol and glycerin.	Surfactants - Emulsifying Agents	
Chimyl Alcohol 506-03-6 [*S* isomer] 6145-69-3	Chimyl Alcohol is the condensation product of cetyl alcohol and glycerin. Chimyl Alcohol is synonymous with Cetyl Glyceryl Ether.	Skin-Conditioning Agents – Emollient	
Batyl Alcohol 544-62-7	Batyl Alcohol is the monooctadecyl ether of glycerin. Batyl alcohol is synonymous with 3-(Octadecyloxy)-1,2-Propanediol	Emulsion stabilizers; Skin-conditioning agents - occlusive	
-Branched			
Isodecyl Glyceryl Ether 84083-82-9 [current per CAS]	Isodecyl Glyceryl Ether is the condensation product of isodecanol and glycerin.	Surfactants - Foam Boosters	 one example of an "iso"
Isostearyl Glyceryl Ether 78145-84-3 [current per CAS]	Isostearyl Glyceryl Ether is the condensation product of isostearyl alcohol and glycerin.	Skin-Conditioning Agents - Emollient	 one example of an "iso"

Table 1. Definitions, functions, and structures of alkyl glycerin ether ingredients in this safety assessment.[1]

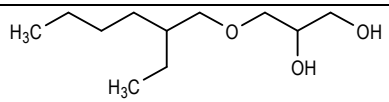
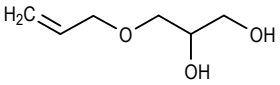
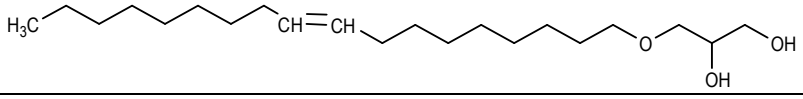
-Branched			
Ethylhexylglycerin 70445-33-9	Ethylhexylglycerin is the condensation product of 2-ethylhexanol and glycerin.	Deodorant Agents; Skin-Conditioning Agents – Miscellaneous	
-Unsaturated			
Glyceryl Allyl Ether 123-34-2 [current per CAS]	Glyceryl Allyl Ether is the condensation product of propenol and glycerin.	Skin-Conditioning Agents - Humectant	
Oleyl Glyceryl Ether [30524-89-1 per CAS]	Oleyl Glyceryl Ether is the condensation product of oleyl alcohol and glycerin.	Skin-Conditioning Agents - Emollient	

Table 2. Properties of Alkyl Glyceryl Ethers

Chemical	Molecular Weight	logP	Specific Gravity (SG)/Density (D)	Solubility	Boiling Point	Melting Point
Caprylyl Glyceryl Ether	204.31[50]	2.6 +/- 0.5[50]	0.9923 g/cm^3 (D)[51]		135 to 136ºC (@ 0.85 Torr)[51]	68.5 to 69.5ºC[51]
Glyceryl Capryl Ether	232.36[50]	3.6 +/- 0.5[50]			361.7 +/- 22ºC (@ 760 Torr)[50]	77 to 77.5ºC[52]
Glyceryl Lauryl Ether	260.41[50]	4.6 +/- 0.5[50]	0.937 +/- 0.06 cm^3 (D)[50]		390.5 +/- 22.0ºC (@ 760 Torr)[50]	62 to 63ºC[53]
Chimyl Alcohol (S isomer, CAS No. 506-03-6)	316.52[50]	6.7 +/- 0.5[50]	0.920 +/- 0.06 g/cm^3 (D)[50]	Solubility in acetone, hexane, and chloroform[54]	445.2 +/- 25ºC (@ 760 Torr)[50]	65 to 66ºC[55]
Chimyl Alcohol (CAS No. 6145-69-3)	316.52[50]	6.7 +/- 0.5[50]	0.920 +/- 0.06 g/cm^3 (D)[50]		445.2 +/- 25ºC (@ 760 Torr)[50]	64 to 66ºC[56]
Batyl Alcohol (CAS No. 544-62-7	344.57[50]	7.7 +/- 0.5[50]	0.914 +/- 0.06 g/cm^3 (D)[50]	Sparingly soluble in unbuffered water[50]	471.1 +/- 25ºC (@ 760 Torr)[50]	68 to 69ºC[57]
Ethylhexylglycerin	204.31[50]	2.4 +/- 0.5[50]	~0.95 g/cm^3 (D)[50]	limited solubility in water (≈ 0.1%); highly soluble in organic solvents, such as alcohols, glycols, and glycol ethers[9]	145ºC (@ 9 h Pa)[9]	
Glyceryl Allyl Ether	132.16[50]	- 0.1 +/- 0.5[50]	1.0841 g/cm^3 (D)[58]		142ºC (@ 28 Torr)[59]	-100ºC to 90ºC[58]

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2011[10-13]

	Ethylhexylglycerin		**Chimyl Alcohol**		**Batyl Alcohol**		**Glyceryl Lauryl Ether**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type								
Eye Area	102	0.02 to 1	1	NR	26	0.5 to 1	NR	NR
Incidental Ingestion	23	0.08 to 0.5	NR	NR	6	0.5	NR	NR
Incidental Inhalation-sprays	114	0.01 to 2	NR	NR	1	NR	NR	NR
Incidental Inhalation-powders	11	0.2 to 0.5	NR	NR	NR	NR	NR	NR
Dermal Contact	952	0.000001 to 8	5	0.002 to 0.5	108	0.4 to 3	NR	NR
Deodorant (underarm)	89	0.04 to 2	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	63	0.0003 to 2	NR	NR	2	0.03 to 1	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	44	7
Nail	3	0.1	NR	NR	NR	NR	NR	NR
Mucous Membrane	63	0.000001 to 0.5	NR	NR	6	0.5	NR	NR
Baby Products	7	NR	NR	NR	NR	NR	NR	NR
Duration of Use								
Leave-On	891	0.002 to 2	5	0.02 to 0.5	116	0.4 to 3	NR	NR
Rinse off	169	0.000001 to 8	NR	0.002	8	0.03 to 1	44	7
Diluted for (bath) use	6	0.1	NR	NR	NR	NR	NR	NR
Totals/Conc. Range	1066	0.000001 to 8	5	0.002 to 5	124	0.03 to 3	44	7

	Isostearyl Glyceryl Ether	
	# of Uses	Conc. (%)
Exposure Type		
Eye Area	NR	NR
Incidental Ingestion	NR	NR
Incidental Inhalation-sprays	NR	NR
Incidental Inhalation-powders	NR	NR
Dermal Contact	5	0.001 to 0.02
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	1	NR
Baby products	NR	NR
Duration of Use		
Leave-On	4	0.01 to 0.02
Rinse off	1	0.001
Diluted for (bath) use	NR	NR
Totals/Conc. Range	5	0.001 to 0.02

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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