Safety Assessment of Propylene Glycol Esters as Used in Cosmetics

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety assessment of propylene glycol esters. These ingredients mostly function as skin-conditioning agents-emollient and as surfactants – emulsifying agent. The Panel reviewed relevant animal and human data related to the ingredient. The similar structure, properties, functions and uses of these ingredients enabled grouping them and using the available toxicological data to assess the safety of the entire group. The Panel mostly relied on data on the component moieties. The Panel concluded that these propylene glycol esters were safe as cosmetic ingredients in the practices of use and concentration of this safety assessment.

INTRODUCTION

This is a safety assessment of propylene glycol esters (PG esters) as used in cosmetics using the available relevant scientific literature and unpublished data provided by industry. The PG esters in this report are listed in Table 1. These ingredients mostly function as skin-conditioning agents-emollient and as surfactants – emulsifying agent.[1]

In 1999, a safety assessment of 13 PG esters was published by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) with a conclusion of safe as used.[2] These were:

propylene glycol dicaprate
propylene glycol dicaprylate
propylene glycol dicaprylate/dicaprate
propylene glycol dicocoate
propylene glycol diisostearate
propylene glycol dilaurate
propylene glycol dioleate
propylene glycol dipelargonate
propylene glycol isostearate
propylene glycol laurate
propylene glycol myristate
propylene glycol oleate
propylene glycol oleate SE (self-emulsifying)

Additional PG esters have been reviewed by the Panel and are included in this safety assessment: propylene glycol stearate, propylene glycol stearate SE, and propylene glycol diisononanoate.[3-6] The Panel concluded that these ingredients were safe as used. Other ingredients that have not been reviewed by the Panel have also been added to this safety assessment:

propylene glycol behenate
propylene glycol caprylate
propylene glycol cocoate
propylene glycol dicaproate
propylene glycol diethylhexanoate
propylene glycol distearate
propylene glycol behenate
propylene glycol caprylate
propylene glycol cocoate
propylene glycol dicaproate
propylene glycol diethylhexanoate
propylene glycol distearate
almond oil propylene glycol esters
apricot kernel oil propylene glycol esters
avocado oil propylene glycol esters
olive oil propylene glycol esters
soybean oil propylene glycol esters

Because of their structural and functional similarities, these 31 ingredients are being grouped together as PG esters. The similar chemical structures, physicochemical properties, and functions and concentrations in cosmetics enable grouping these ingredients and reading across the available toxicological data to support the safety assessment of the entire group. Table 2 lists previous safety assessments of the ingredients in this safety assessment that have been separately reviewed by the Panel. The summaries of these reports are provided below.

Because data obtained on radiolabeled PG stearate showed that it can almost certainly be converted at varying rates (dependent on the particular fatty acid and the route of exposure) to propylene glycol and the component fatty acid, the safety of the component submoieties will thus be relevant to the safety of the PG esters. The safety assessments of related ingredients (ie, propylene glycol and the acids from which these esters are the products) are also listed in Table 2. The table indicates the conclusions reported previously for those individual components. These ingredients are representative of the starting materials of these PG esters. Coconut acid, pelargonic (nonanoic) acid, isostearic acid, oleic acid, lauric acid, myristic acid, stearic acid, almond oil propylene glycol esters, apricot kernel oil propylene glycol esters, avocado oil propylene glycol esters, olive oil propylene glycol esters, and glycine soja (soybean) oil were found to be safe as used. Propylene glycol and alkyl ethylhexanoates were found to be safe as used when formulated to be non-irritating. Behenic acid, capric acid, caproic acid, caprylic acid, diheptanoates, linoleic acid, undecanoic acid, and potassium oleate have not been reviewed. Heptanoic acid is not a cosmetic ingredient. To provide additional information on the unreviewed moieties, summary safety information on undecanoic acid and heptanoic acid are provided in Table 3. The data from the existing safety assessments included in Table 2 are already published; only new data will be included in the body of this safety assessment.

SUMMARIES OF REPORTS THAT INCLUDE PG ESTERS

Propylene Glycol Esters and Diesters (1999)

The limited information on chemical properties of Propylene Glycol esters and diesters indicates that, generally, these ingredients are soluble in most organic solvents.[2] Methods of production that have been reported for some of the esters and diesters included in this review are as follows: Propylene Glycol Oleate is produced via the acylation of propylene glycol with oleic anhydride, and the dioleate is a product of the reaction of propylene glycol with oleic acid chloride. Propylene Glycol Dicaprate is a product of the reaction of decanoic acid with propane-1,3-diol. Similarly, Propylene Glycol Dicaprylate is produced by reacting propane-1,2-diol and octanoyl chloride with pyridine. Pyridine is also used in the production of Propylene Glycol Dipelargonate and Propylene Glycol Dilaurate. Propylene Glycol is a product of the reaction of nonanoyl chloride and C12H2403 with pyridine, and, Propylene Glycol Dilaurate, a product of the reaction of lauroyl chloride and propylene glycol [in the presence of] *pyridine.*

Cosmetic uses of Propylene Glycol esters and diesters include skin-conditioning agent-occlusive, viscosity increasing agent-nonaqueous, skin conditioning agent-emollients, and surfactant-emulsifying agents. These ingredients are used widely in a variety of rinse-off and leave-on cosmetics products. Data submitted to CIR by the cosmetics industry in 1995 indicated that Propylene Glycol diesters were used at concentrations up to 51.7%, and, Propylene Glycol esters, at concentrations up to 22%.

Propylene Glycol Dicaprylate/Dicaprate and Propylene Glycol Dipelargonate promoted the percutaneous penetration of drugs across excised human skin/hairless mouse skin in vitro. Propylene Glycol Laurate was classified as practically nontoxic (LD_{50} > 34.6 g/kg) when administered orally to rats.

In two skin irritation studies involving rabbits, Propylene Glycol Dicaprylate/Dicaprate and Propylene Glycol Laurate were classified as minimally irritating and slightly irritating, respectively. Propylene Glycol Dicaprylate/Dicaprate was also classified as an insignificant comedogen in rabbits.

Antitumor activity (in vivo) in ddY mice was observed following the intraperitoneal injection of Propylene Glycol Myristate, but not Propylene Glycol Oleate. Skin irritation was not observed in either of the three subjects patch tested with a 95% ethanol:Propylene Glycol Dicaprylate/Dicaprate mixture (20:80). Patches were removed at 24 hours postapplication. Similar results were reported for a fourth subject patch tested with a 95% ethanol:Propylene Glycol Dicaprylate/Dicaprate mixture (40:60).

Propylene Glycol Stearate and Propylene Glycol Stearate SE (1983)

Propylene Glycol Stearate (PGS) is a mixture of the mono- and diesters of triple-pressed stearic acid and propylene glycol.[4] Propylene Glycol Stearate SE (PGS-SE) is a self-emulsifying grade of PGS that contains an additional 5%-6% potassium stearate and 7%-10% free stearic acid. They are used in a wide variety of cosmetic products at concentrations of up to 25% for PGS and up to 10% for PGS-SE (1979 data). PGS is also approved for a variety of pharmaceutical uses and is considered Generally Recognized as Safe (GRAS) for food use.

Studies with ^{14}C-labeled PGS show that it is readily metabolized following ingestion. In rats, the acute oral LD_{50} has been shown to be approximately 25.8 g/kg. The raw ingredient produced no significant dermal toxicity, skin irritation, or eye irritation in acute tests with rabbits. Subchronic animal studies produced no evidence of oral or dermal toxicity. A chronic six-month feeding study showed no signs of toxicity when a mixture containing 17% propylene glycol monostearate was incorporated at 10% into the diets of rats and dogs. Propylene glycol monostearate was negative in in vitro microbial assays for mutagenicity.

Although PGS-SE has not been tested as extensively as PGS, it produced no apparent significantly different results in any of the animal tests. The acute oral LD_{50} in rats is estimated to be greater than 32 g/kg. The ingredient per se produced no significant skin or eye irritation in Draize rabbit irritation tests, and it was not a sensitizer in a guinea pig sensitization test. No other subchronic or chronic studies were available.

In clinical studies, PGS produced no significant skin irritation at concentrations up to 55% in 24-hour single insult skin patch tests. A 28-day controlled use test on a product containing 2.5% PGS demonstrated no cumulative irritation with normal product use but mild to moderate irritation with a challenge skin patch; the offending ingredient was not identified. Several skin sensitization tests on product formulations containing 1.5%-2.5% PGS showed no evidence of sensitization reactions in a total subject population of 4084. Two photo-contact allergenicity tests on product formulations containing 1.5% PGS were negative.

No clinical data were available for PGS-SE. However, the chemical components of PGS-SE that distinguish it from PGS have been considered previously to be safe, and the information generally applicable to PGS is considered applicable to PGS-SE.

Propylene Glycol Myristate (2010)

The report includes no specific data about propylene glycol myristate. The safe conclusion is based on data the related compounds.

Propylene Glycol Diisononanoate (2011)

Information not relevant to propylene glycol diisononanoate has been removed.

Pelargonic acid and nonanoate esters are cosmetic ingredients that function as skin-conditioning agents in cosmetics.[5]

Straight-chain pelargonic acid esters are likely hydrolyzed to component alcohols and pelargonic acid, which is further metabolized by β-oxidation. Iso-fatty acids and straight-chain fatty acids both are metabolized at the β-carbon to yield 2-carbon fractions by mitochondrial and microsomal fractions of rat liver homogenate. Additionally, iso-fatty acids are oxidized at the ω carbon to ultimately form 3-carbon dicarboxylic acids. The enzymes catalyzing the ω-hydroxylation are present in the mitochondrial and microsomal fractions, whereas the enzymes catalyzing further oxidation into carboxylic acids are in the soluble fractions of rat liver homogenate. With the exception of pelargonic acid and ethyl pelargonate, specific information relating to the metabolism of the remaining ingredients reviewed in this safety assessment was not identified in the published literature. Branched-chain fatty acid metabolism involves initial α-oxidation, which is followed by the β-oxidation pathway.

Octanol-water partition coefficient (logP) and mw data included in the safety assessment may be used to predict the skin penetration potential of pelargonic acid and its esters/ester moieties. Most of the ingredients reviewed in this safety assessment have a logP of >5 and a mw of <500. Compounds with a LogP of >5 and a mw of [>]*500 are less likely to penetrate the skin. For example, cholesteryl nonanoate has a logP of 10 and a mw of >500, suggesting that dermal absorption is unlikely. The skin penetration enhancement effect of pelargonic acid on other chemicals has been demonstrated in vitro using human stratum corneum and hairless rat skin.*

CHEMISTRY

The PG esters are the esters and diesters of propylene glycol and the corresponding acid or acids. Propylene glycol dicaprylate/dicaprate, propylene glycol dipelargonate, propylene glycol laurate, propylene glycol dilaurate, propylene glycol oleate, propylene glycol dicaprylate/dicaprate, and propylene glycol laurate are liquids that are either clear or yellowish.[2] Structures are provided in Table 1.

Impurities

No additional impurity data were discovered in the literature other than what has already been reported in previous reports.

USE

Cosmetic

The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category through the Voluntary Cosmetic Registration Program (VCRP). A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group (Tables 4-6).[7,8] Both historical and current use data are provided in Table 4.

In 2014, propylene glycol dicaprylate/dicaprate was reported to have the greatest number of uses reported to the VCRP at 525, which is an increase from 202 in 1995.[2,7] This ingredient had reported uses in all exposure types. Propylene glycol dicaprylate also increased in reported uses from 1 in 1995 to 102 in 2014. The other previously reviewed ingredients (propylene glycol dicaprate, propylene glycol dicaprylate/dicaprate, propylene glycol dioleate, propylene glycol dipelargonate, propylene glycol isostearate, propylene glycol laurate, propylene glycol myristate, propylene glycol oleate, propylene glycol stearate, and propylene glycol stearate SE) have decreased in the number of reported uses; these are mostly reported to be used in dermal products, in the eye area, and in lipsticks. Of the ingredients being reviewed for the first time in this safety assessment, only propylene glycol diethylhexanoate has uses reported to the VCRP, 28 uses (Tables 4 and 5).[2,6,7,9]

Propylene glycol dipelargonate was reported to be used at the highest concentration of 60% in perfumes; an increase from a highest concentration of use 33.796% in hair preparations in 1995. This was followed by propylene glycol dicaprylate/dicaprate at 51.8% in blushers, an increase from a highest concentration of use from 45% in a blush. The rest of the ingredients with current reported concentrations of use were 22% or less.[2,6,8,9] PG esters with no reported uses in either the VCRP or by the Council survey are listed in Table 6.

In some cases, reports of uses were not received in the VCRP, but concentrations of use data were available. For example, propylene glycol dicaprylate/dicaprate was reported to be used in a baby lotions, oils and creams formulations at 2.5%, but there were no data reported for any baby products in the VCRP. In other cases, use was reported in the VCRP, but a use concentration was not provided in the industry survey. For example, Propylene glycol dicaprylate/dicaprate was reported to be used in a deodorant in the VCRP, but the industry survey did not report any concentrations of use in that category.[7,8]

PG esters were reported to be used in hair sprays (propylene glycol dicaprylate/dicaprate up to 0.13%) and in spray face and neck skin care products (propylene glycol diethylhexanoate up to 2%) and could possibly be inhaled. Propylene glycol dicaprylate/dicaprate and propylene glycol diethylhexanoate were reported to be used in deodorants, which may or may not be aerosols or sprays. Propylene glycol esters are also reported to be used in face powders (eg, propylene glycol dicaprylate/dicaprate up to 38%). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[10-13] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[10,13] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[10] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Non-Cosmetic

The mono and diesters of propylene glycol are permitted as direct and secondary food additives (Table 7). [21CFR172.856, 21CFR173.340] Propylene glycol esters are permitted as indirect food additives for adhesives and components of coatings for packaging that comes in contact with food. [21CFR175.105, 21CFR175.300, 21CFR176.170, 21CFR176.210, 21 CFR177.2800, 40 CFR180.1250]

TOXICOKINETICS

Penetration Enhancement

In multiple in vitro experiments, several PG esters enhanced the permeability of drugs through human and animal skin (Table 8). Propylene glycol caprylate increased the dermal penetration of diclofenac through rat abdominal skin.[14] Propylene glycol oleate, propylene glycol dioleate, propylene glycol linoleate, propylene glycol dilinoleate, propylene glycol linolenate, and propylene glycol dilinolenate (1%) enhanced the dermal penetration of lidocaine (1% in tetraglycol-distilled water 1:1 w/w) through pig ear skin using a Franz cell by ratios of 1.91, 2.11, 1.68, 1.44, 1.70, and 1.37, respectively, when compared to controls.[15] Propylene glycol dipelargonate increased the dermal penetration of [^{3}H(G)] heparin sodium salt, thiocolchicoside, and caffeine but not testosterone.[16-18] A saturated solution of propylene glycol dipelargonate increased the dermal penetration of methyl nicotinate.[19] A mixture of propylene glycol dilaurate/propylene glycol laurate in combination with ethoxydiglycol (50:50) enhanced the dermal penetration of carbenoxolone.[20] Propylene glycol dicaprylate did not increase the penetration of water-soluble drugs.[21] Propylene glycol caprylate and propylene glycol laurate did not enhance the dermal penetration of Loxoprofen.[22]

Propylene glycol diperlargonate (estimated by staff to be 0.8%; 1 g added to the approximately 9.45 g base formulation; however, due to incomplete information, assumptions were made for density of the foam and how much test material was added), with 20 g of ethanol, in an aqueous foam formulation enhanced the dermal penetration of thiocolchicoside through fresh, clipped rat skin using Franz cell.[23]

Propylene glycol caprylate increased the permeability of 5-fluorouracil (5-FU) in multiple transdermal formulations through fresh abdominal skin from male hairless HWY rats using Franz cells.[24] Adding propylene glycol caprylate (5%) to the hydrotropic formulations of sodium salicylate (30% w/v in water) and sodium benzoate (43% w/v in water) increased the enhancement factor from 3.85 and 2.74 to 1250 and 1115, respectively. Adding propylene glycol caprylate (5%) to the co-solvent formulations of ethanol (50% v/v in water) and propylene glycol (80% v/v in water) increased the enhancement factor from 2.65 and 0.58 to 273 and 441, respectively. Adding propylene glycol caprylate (5%) to the mixed micelle formulation increased the enhancement factor from 3.15 to 13. The mixed micelle formulation consisted of 2% Tween 80/Span 83 (73:27) in water. 5-FU was added at a slight excess and agitated for 12 h, and then filtered.

TOXICOLOGICAL STUDIES

Acute Toxicity

New data on acute toxicity of PG esters were not found in the published literature nor were unpublished data provided.

Repeated Dose Toxicity

PROPYLENE GLYCOL DICAPRYLATE/DICAPRATE

The oral administration of propylene glycol dicaprylate/dicaprate, up to 1000 mg/kg/d for 90 days, led to no adverse effects in male and female Wistar rats.[25] The NOAEL was set to 1000 mg/kg/day. No adverse effects were observed for clinical signs, mortality, body weight, feed consumption, ophthalmoscopic examination, hematology, clinical chemistry, gross pathology, organ weights, and histopathology. The rats (n=10, 15/sex) were orally administered propylene glycol dicaprylate/dicaprate (0, 100, 300, 1000 mg/kg/d in peanut oil) by gavage 5 days per week. The control group and the high-dose groups were observed for an additional 34 days.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

PROPYLENE GLYCOL DICAPRYLATE/DICAPRATE

The oral administration of propylene glycol dicaprylate/dicaprate (0, 100, 300 or 1000 mg/kg/d in arachidis oil) on days 6-15 of gestation, was not embryotoxic and there were no effects observed in the dams.[25] The NOAEL was set to >1000 mg/kg/day. There were no differences in implantations, number of live or dead fetuses, sex ratio, fetus body weights, number of litters, or fetus malformations between the treatment and control groups. The dams were killed and necropsied on gestation day 20.

GENOTOXICITY

New data on the genotoxicity of PG esters were not found in the published literature nor were unpublished data provided.

CARCINOGENICITY

Studies

New data on the carcinogenicity of PG esters were not found in the published literature nor were unpublished data provided.

IRRITATION AND SENSITIZATION

Irritation

Dermal-Animal

PROPYLENE GLYCOL STEARATE, PROPYLENE GLYCOL OLEATE, PROPYLENE GLYCOL LINOLEATE

In a primary skin irritation test using male albino rabbits (n=3), dermal administration of propylene glycol stearate (1% in tetraglycol:distilled water 1:1, with and without 1% lidocaine) did not result in irritation; propylene glycol oleate (1% in tetraglycol:distilled water 1:1, with and without 1% lidocaine) and propylene glycol linoleate (1% in tetraglycol:distilled water 1:1, with and without 1% lidocaine) showed mild erythema.[15] No edema was observed during the 7 days of observation after treatment by any of the 3 PG esters. The test substances were administered to the backs (clipped of hair) of the rabbits in adhesive plasters with an exposure area diameter of 1.5 cm^2. The test sites were kept under occlusion except when the dressing was removed on days 1, 3, 5, and 7 only long enough for observation. Then sterile pads were changed and the rabbits' backs re-occluded.

Dermal-Human

PROPYLENE GLYCOL DICAPRYLATE/DICAPRATE

There were no adverse effects reported, including irritation, in a skin test (n=5) of a sunless tanning preparation containing propylene glycol dicaprylate/dicaprate administered to humans.[26] The exact concentration was not specified but was part of a blend of dimethylacrylamide/ethyltrimonium chloride methacrylate copolymer, propylene glycol dicaprylate/dicaprate, PPG-1 trideceth-6, and C10-11 isoparaffin that was present in the product at 3%. The test substance (0.1 g) was administered to the volar part of the forearms over a 50 cm^2 area for a dermal dose of 2 mg/cm^2. The test sites were examined at 24, 48, and 120 h. The subjects were to continue their normal routine of bathing, etc.

Sensitization

New data on the dermal sensitization of PG esters were not found in the published literature nor were unpublished data provided.

Phototoxicity

New data on the phototoxicity of PG esters were not found in the published literature nor were unpublished data provided.

SUMMARY OF NEW DATA

This is a safety assessment of PG esters as used in cosmetics using the available relevant scientific literature and unpublished data provided by industry. The PG esters are the esters and diesters of propylene glycol and the corresponding acid or acids. These ingredients mostly function as skin-conditioning agents-emollient and as surfactants – emulsifying agent. A safety assessment of 13 of these PG esters was published by CIR with a conclusion of safe as used. Other safety assessments that included PG esters have also been published with conclusions of safe as used. This re-review combines previously reviewed and newly reviewed ingredients into one report as PG ester ingredients. Since this is a re-review of this group, only new data will be summarized here.

In 2014, propylene glycol dicaprylate/dicaprate was reported to have the greatest number of uses reported to the VCRP at 525, which is an increase from 202 in 1995. This ingredient is reported to be used in all exposure types. Propylene glycol dicaprylate also increased in reported uses from 1 in 1995 to 102 in 2014. The other previously reviewed ingredients have decreased in the number of reported uses; these are mostly reported to be used in dermal products, in the eye area, and in lipsticks. Of the ingredients being reviewed for the first time in this safety assessment, only propylene glycol dicaprylate and propylene glycol diethylhexanoate have uses reported to the VCRP, 49 and 28 uses, respectively.

Propylene glycol dipelargonate was reported to be used at the highest concentration of 60% in perfumes; an increase from a highest concentration of use 33.796% in hair preparations in 1995. This was followed by propylene glycol dicaprylate/dicaprate at 51.8% in blushers, an increase in the highest concentration of use from 45%. The rest of the ingredients with current reported concentrations of use were 22% or less.

In multiple in vitro experiments, several PG esters enhanced the permeability of drugs through human and animal skin. Propylene glycol caprylate increased the dermal penetration of diclofenac through rat abdominal skin. Propylene glycol oleate, propylene glycol dioleate, propylene glycol linoleate, propylene glycol linolenate, and propylene glycol dilinolenate enhanced the dermal penetration of lidocaine through pig ear skin. Propylene glycol dipelargonate increased the dermal penetration of [^{3}H(G)] heparin sodium salt, thiocolchicoside, and caffeine, but not testosterone. A saturated solution of propylene glycol dipelargonate increased the dermal penetration of methyl nicotinate. A mixture of propylene glycol dilaurate/propylene glycol laurate in combination with Transcutol™ enhanced the dermal penetration of carbenoxolone. Propylene glycol dicaprylate did not increase the penetration of water-soluble drugs. Propylene glycol caprylate and propylene glycol laurate did not enhance the dermal penetration of Loxoprofen.

The oral administration of propylene glycol dicaprylate/dicaprate, up to 1000 mg/kg/d for 90 days, led to no adverse effects in male and female rats.

The oral administration of propylene glycol dicaprylate/dicaprate, up to 1000 mg/kg/d, to pregnant rats on gestation days 6-15 was not embryotoxic and there were no effects observed in the dams.

There were no adverse effects reported in a human skin test of a sunless tanning preparation containing propylene glycol dicaprylate/dicaprate.

In a primary skin irritation test using rabbits, propylene glycol stearate at 1%, with and without lidocaine was not an irritant. Administration of propylene glycol oleate at 1%, with and without 1% lidocaine, and propylene glycol linoleate at 1%, with and without lidocaine, to the backs of rabbits produced mild erythema.

DISCUSSION

The Panel supported combining the previously reviewed ingredients and the unreviewed ingredients into one safety assessment. Although there are data gaps, the similar chemical structures, physicochemical properties, and functions and concentrations in cosmetics allow grouping these ingredients and using the available toxicological data to support the safety of some ingredients in the group.

The Panel acknowledged that the original safety assessment relied upon data based on the safety of the component moieties of most of these ingredients (eg, propylene glycol and the acids of the esters). The Panel agreed that this approach was still acceptable for the PG esters in this safety assessment.

The Expert Panel recognized that PG esters can enhance the penetration of other ingredients through the skin as demonstrated by the penetration enhancement of other chemicals (eg, diclofenac, lidocaine, thiocolchicoside, and caffeine). The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The Panel discussed the issue of incidental inhalation exposure from use in hair sprays spray face and neck skin care products. Propylene glycol esters are also reported to be used in face powders. There were no inhalation toxicity data available. However, the Expert Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics.

These ingredients are reportedly used at concentrations up to 2% in cosmetic products that may be aerosolized and up to 38% in other products that may become airborne. The Panel noted that 95%–99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on the properties of the PG esters and on data that shows that these ingredients are not irritants. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

To evaluate incidental inhalation, the Panel considered other data available to characterize the potential for PG esters to cause systemic toxicity, irritation, sensitization, and genotoxicity in this and in previous safety assessments. They noted the lack of systemic toxicity at high doses in several acute and subchronic oral and dermal exposure studies, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, the absence of genotoxicity in Ames. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

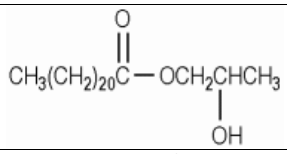
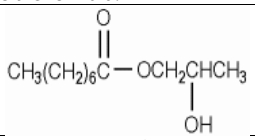
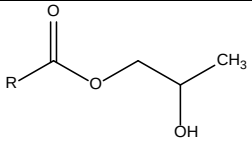
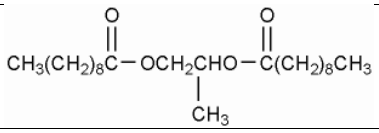
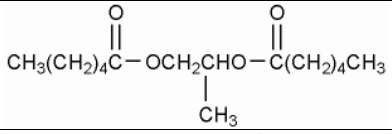
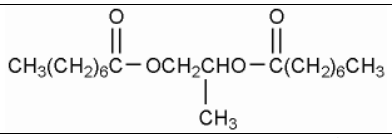
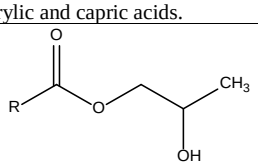
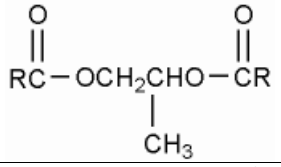
The CIR Expert Panel concluded that the following ingredients are safe in the present practices of use and concentration described in this safety assessment in cosmetics:

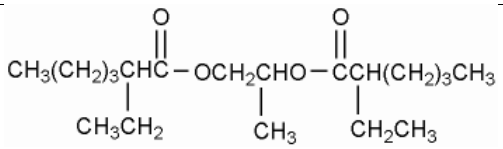
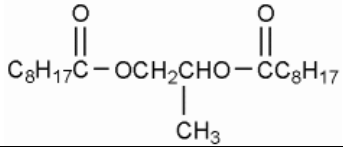
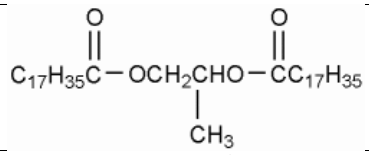
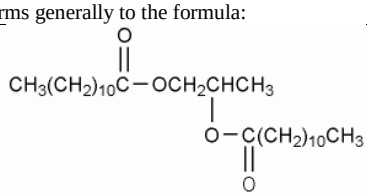
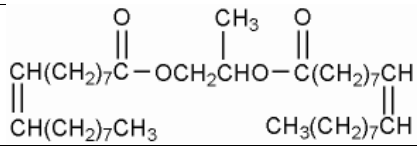
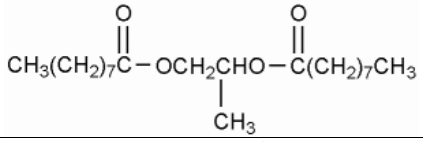
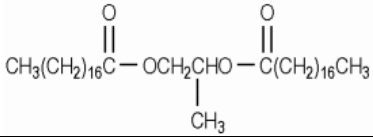
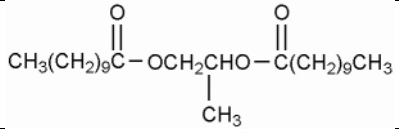
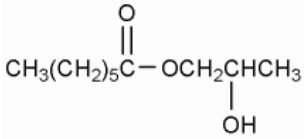
propylene glycol behenate*
propylene glycol caprylate*
propylene glycol cocoate*
propylene glycol dicaprate
propylene glycol dicaproate
propylene glycol dicaprylate
propylene glycol dicaprylate/dicaprate
propylene glycol dicocoate*
propylene glycol diethylhexanoate
propylene glycol diisononanoate*
propylene glycol diisostearate*
propylene glycol dilaurate*
propylene glycol dioleate
propylene glycol dipelargonate
propylene glycol distearate*
propylene glycol diundecanoate*
propylene glycol heptanoate*
propylene glycol linoleate*
propylene glycol linolenate*
propylene glycol isostearate
propylene glycol laurate
propylene glycol myristate
propylene glycol oleate
propylene glycol oleate SE (self-emulsifying)*
propylene glycol stearate
propylene glycol stearate SE
soybean oil propylene glycol esters*
almond oil propylene glycol esters*
apricot kernel oil propylene glycol esters*
avocado oil propylene glycol esters*
olive oil propylene glycol esters*

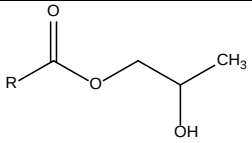
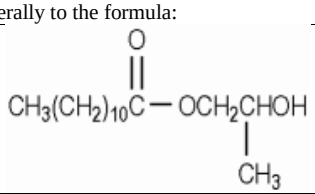
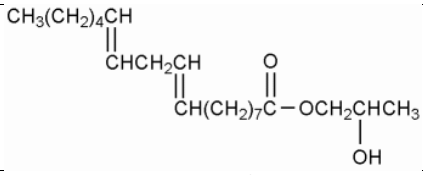
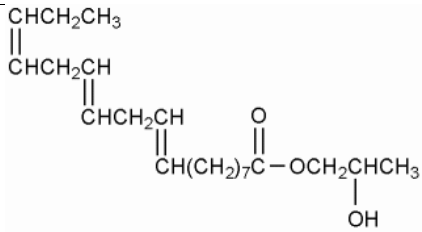
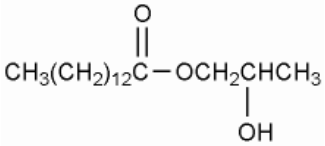
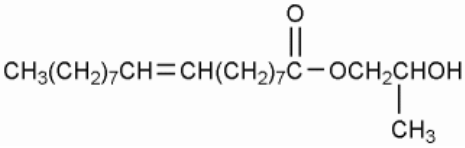
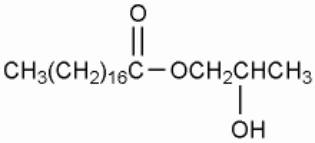
*Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

TABLES AND FIGURES

Table 1. Ingredient names, CAS nos., definitions, and functions of PG esters used in cosmetics.[1]

Ingredient CAS No.	Definition	Function
Propylene glycol behenate No CAS no.	Propylene glycol behenate is the ester of propylene glycol and behenic acid. 	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol caprylate 31565-12-5 68332-79-6	Propylene glycol caprylate is the ester of caprylic acid and propylene glycol that conforms to the formula: 	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol cocoate No CAS no.	Propylene glycol cocoate is the ester of propylene glycol and coconut acid.  Wherein RC(O) represents the fatty acid residues of coconut acid	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol dicaprate 53824-77-4 56519-72-3	Propylene glycol dicaprate is the diester of propylene glycol and capric acid. 	Skin-conditioning agent-occlusive; surfactant – emulsifying agent
Propylene glycol dicaproate 50343-36-7	Propylene glycol dicaproate is the diester of propylene glycol and caproic acid. 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol dicaprylate 7384-98-7	Propylene glycol dicaprylate is the diester of propylene glycol and caprylic acid that conforms generally to the formula: 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol dicaprylate/ dicaprate 58748-27-9 68583-51-7 68988-72-7	Propylene glycol dicaprylate/dicaprate is a mixture of the propylene glycol diesters of caprylic and capric acids.  Wherein RC(O) represents the residues of caprylic and capric acids.	Skin-conditioning agent - occlusive
Propylene glycol dicocoate 68953-19-5	Propylene glycol dicocoate is the diester of propylene glycol and coconut acid. It conforms to the formula: where RCO- represents the fatty acids derived from coconut oil. 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol diethylhexanoate 93981-97-6	Propylene glycol diethylhexanoate is the diester of propylene glycol and 2-ethylhexanoic acid.	Skin-conditioning agent – occlusive

		
Propylene glycol diisononanoate 125804-17-3	Propylene glycol diisononanoate is the diester of propylene glycol and branched chain nonanoic acids. 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol diisostearate 68958-54-3	Propylene glycol diisostearate is the diester of propylene glycol and isostearic acid. 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol dilaurate 22788-19-8	Propylene glycol dilaurate is the diester of propylene glycol and lauric acid that conforms generally to the formula: 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol dioleate 105-62-4	Propylene glycol dioleate is the diester of propylene glycol and oleic acid. 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol dipelargonate 41395-83-9	Propylene glycol dipelargonate is the diester of propylene glycol and pelargonic acid that conforms generally to the formula: 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol distearate 6182-11-2	Propylene glycol distearate is the diester of propylene glycol and stearic acid. 	Opacifying agent; skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol diundecanoate 68227-47-4	Propylene glycol diundecanoate is the diester of propylene glycol and undecanoic acid. 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Propylene glycol heptanoate 7249-54-9	Propylene glycol heptanoate is the ester of propylene glycol and heptanoic acid that conforms to the formula: 	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol isostearate 63799-53-1	Propylene glycol isostearate is the ester of propylene glycol and isostearic acid.	Skin-conditioning agent-emollient; surfactant –

68171-38-0	 Wherein RC(O) represents the fatty acid residues of isostearic acid.	emulsifying agent
Propylene glycol laurate 142-55-2 199282-83-2 27194-74-7 37321-62-3	Propylene glycol laurate is the ester of propylene glycol and lauric acid that conforms generally to the formula: 	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol linoleate No CAS no.	Propylene glycol linoleate is the ester of propylene glycol and linoleic acid that conforms to the formula: 	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol linolenate No CAS no.	Propylene glycol linolenate is the ester of propylene glycol and linolenic acid that conforms to the formula: 	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol myristate 29059-24-3	Propylene glycol myristate is the ester of propylene glycol and myristic acid that conforms generally to the formula: 	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol oleate 1330-80-9	Propylene glycol oleate is the ester of propylene glycol and oleic acid. 	Skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol oleate SE 1330-80-9	Propylene glycol oleate SE is a self-emulsifying grade of propylene glycol oleate that contains some sodium and/or potassium oleate.	surfactant – emulsifying agent
Propylene glycol stearate 1323-39-3 142-75-6	Propylene glycol stearate is the ester of propylene glycol and stearic acid that conforms generally to the formula: 	Fragrance ingredient; skin-conditioning agent-emollient; surfactant – emulsifying agent
Propylene glycol stearate SE 1323-39-3	Propylene glycol stearate SE is a self-emulsifying grade of propylene glycol stearate that contains some sodium and/or potassium stearate.	Surfactant – emulsifying agent
Almond oil propylene glycol esters No CAS no.	The product obtained by the transesterification of prunus amygdalus dulcis (sweet almond) oil and propylene glycol.	Skin-conditioning agent-emollient
Apricot kernel oil propylene glycol esters No CAS no.	The product obtained by the transesterification of prunus armeniaca (apricot) kernel oil with propylene glycol.	Skin-conditioning agent-miscellaneous
Avocado oil propylene glycol esters No CAS no.	The product obtained from the transesterification of persea gratissima (avocado) oil and propylene glycol.	Skin-conditioning agent-emollient; surfactant-emulsifying agent
Olive oil propylene glycol esters 84012-27-1 8001-25-0	The product obtained by the transesterification of olea europaea (olive) fruit oil	Skin-conditioning agent-emollient
Soybean oil propylene glycol esters	Soybean oil propylene glycol esters is the product obtained by the transesterification of glycine soja (soybean) oil with propylene glycol.	Skin-conditioning agent-emollient

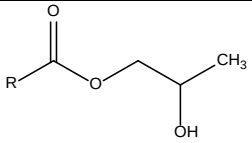
No CAS no.	 Wherein RC(O) represents the fatty acid residues of glycine soja (soybean) oil.

Table 2. Safety assessments by CIR of ingredients relevant to this safety assessment. These include previous safety assessments of ingredients in this report as well as ingredients related to or component parts of ingredients in this report.

Ingredient(s)	Results	Maximum concentration (%)	Reference
Previous safety assessments of ingredients			
Propylene glycol esters and diesters	Safe as used.	51.730	[2]
Propylene glycol stearate and propylene glycol stearate SE	Safe as used.	>10-25	[3,4]
Propylene glycol diisononanoate, Pelargonic (nonanoic) acid and esters	Safe as used.	74	[5]
Propylene glycol myristate	Safe as used.	82	[6]
Safety assessments of components			
Propylene glycol	Safe as used when formulated to be non-irritating.	40; 99 in bath products diluted for the bath.	[27,28]
Caprylic/capric triglyceride	Safe as used.	>50	[4,29]
Coconut acid, *Cocos nucifera* (coconut) oil and related ingredients	Safe as used.	80	[30,31]
Alkyl ethylhexanoates	Safe as used when formulated to be non-irritating.	77.3	[32]
Isostearic acid	Safe as used.	26	[3,33]
Oleic acid, lauric acid, myristic acid, and stearic acid	Safe as used.	11	[9,34]
Stearyl heptanoate and cetyl and alkyl esters	Safe as used when formulated to be non-irritating.	78	[35-37]
Sweet almond oil	Safe as used.	100	[3,38,39]
Prunus ameniaca (apricot) kernel oil	Safe as used.	100	[38]
Olea europaea (olive) fruit oil	Safe as used.	100	[38]
Glycine soja (soybean) oil	Safe as used.	100	[38]

Table 3. Toxicity data for heptonic acid and undecanoic acid, moieties of Propylene glycol heptanoate and Propylene glycol diundecanoate.

Ingredient	Study/assay	Results	Reference
Dermal effects			
Undeconoic acid	Penetration enhancement	Did not increase the dermal penetration enhancement of hexyl nicotinate using	[40]
Heptonic acid (0.16 M in propylene glycol)	Penetration enhancement	Enhancement ratio of *p*-aminobenzoic acid (PABA)=1.6. Stratum corneum sheets were pretreated with test substance (300 µL) for 24 h. PABA (25 g/L in the test solution was placed in the donor cell for 20 h.	[41]
Undecanoic acid (300 µL)	Penetration enhancement	Enhancement ratio= 25.1. Stratum corneum sheets were pretreated with test substance for 24 h. PABA (25 g/L in the test solution was placed in the donor cell for 20 h.	[41]
Acute toxicity			
Heptonic acid	IV in mice	LD_{50} = 1200 ± 56 mg/kg	[42]
Undecanoic acid	IV in mice	LD_{50} = 140 ± 4.2 mg/kg	[42]

Table 3. Toxicity data for heptonic acid and undecanoic acid, moieties of Propylene glycol heptanoate and Propylene glycol diundecanoate.

Ingredient	Study/assay	Results	Reference
Dermal irritation – in vitro			
Heptonic acid	EpiDerm assay	Heptanoic acid had no effect on the tissue viability up to and including 0.5%. There was reduced cell viability to 38.5%, 13.9%, and 9.7% of control at 1%, 2% and 4%, respectively. Heptanoic acid also induced IL-1a release, more than the lactic acid. The lowest concentration of heptanoic acid, 0.1% induced a release of 76.3 pg/mL IL-1a, compared to 17.0 pg/mL for the negative control PBS*. This release increased steadily as the concentration increased until 4%, where it decreased, likely due to rapid cell death. The NOAEL was 0.5%; the EC_{50} value was 0.85% for heptanoic acid in sesame oil.	[43]
Heptanoic acid (100%)	SkinEthic-direct topical application test	Predicted to be a dermal irritant due to cell viability score ~2 (MTT reduction assay, <50% viability); but not for IL-1α release, score ~5 (did not meet >30 pg/mL).	[44]
Heptanoic acid (100%)	In vitro patch test	Predicted to be a dermal irritant due to cell viability score ~5 (MTT reduction assay, criteria for irritation: <50% viability); IL-1α release score ~110 (criteria for irritation: >105 pg/mL); histological observation score ~0 (criteria for irritation: score < 75).	[44]
Heptanoic acid (0.1%, 0.25%, 0.5%,1%, 2% and 4% in sesame oil)	EpiDerm assay	No effect on tissue viability up to and including 0.5%. Heptanoic acid reduced cell viability to 38.5%, 13.9% and 9.7% of control at 1%, 2% and 4%, respectively. Heptanoic acid also induced IL-1α release. 0.1% induced a release of 76.3 pg/mL IL-1α, compared to 17.0 pg/mL for the negative control PBS. This release increased as heptanoic acid increased until 4%, then it dropped off, likely due to rapid cell death. NOAEL=0.5%. EC_{50}=0.85%.	[43]
Undecanoic acid (80 µL/0.78 cm^2)	Artificial skin (fibroblast-populated collagen gel)	Not predicted to be irritating. No morphology changes. No effect to IL0-α and IL-8 levels.	[40]
Dermal irritation – in vivo			
Undecanoic acid	Patch test using Hill-Top chamber. 0.16 M on the forearm (n=5). Control – propylene glycol	Irritation index=approximately 1; enhancement ratio of TEWL=approximately 1. The test substance administered to the forearm for 3 h	[40]
Undecanoic acid (30% in ethanol)	Modified Draize test using New Zealand White rabbits (n=4)	Draize scores were: 2.12, 1.62, and 1.06; average 1.60. The test substance was rated as mildly irritating. Contact maintained under occlusion for 24 h. Sites read at 30 min, and 48 h. Study conducted 3 times.	[45]
Undecanoic acid (30% in ethanol)	Modified Draize test using human males (n=4)	Draize scores were 0. Contact maintained under occlusion for 24 h. Sites read at 30 min, and 48 h.	[45]
Undecanoic acid (1%, 10%, 20%, and 40% in ethanol; 0.2 mL)	21-day continuous closed patch test (n=2)	Cumulative irritation index=0, 38.5, 50.5, and 69, respectively. Patches were left in place on the forearm for 23.5 h, removed, read at 30 min, then a new patch placed.	[45]
Undecanoic acid (10%, in ethanol; 0.2 mL)	21-day continuous closed patch test (n=8)	Cumulative irritation index=0. Patches were left in place on the forearm for 23.5 h, removed, read at 30 min, then a new patch placed.	[45]
Undecanoic acid (10%, 20%, 40% and 60% in ethanol; 0.2 mL)	21-day continuous open patch test (n=1 or 2)	Cumulative irritation index=0 for all concentrations. Patches were left in place on the forearm for 23.5 h, removed, read at 30 min, then a new patch placed.	[45]
Other assessment			
Heptanoic acid	Safety assessment for use as an additive in animal feed.	Safe for all animal species at 5 mg/kg complete feed with a margin of safety between 1 and 120. No direct data, conclusion was based on read across from data on acetaldehyde, butanol, and octanol.	[46]

PBS=phosphate buffered saline; TEWL=transdermal water loss

Table 4. Current and historical frequency and concentration of use of PG esters according to duration and exposure.[7,8] The Council is conducting a survey on the plant-derived PG esters added to this report.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Propylene glycol dicaprate				**Propylene glycol dicaprylate**			
	2014	**1995**	**2014**	**1995****	**2014**	**1995****	**2014**	**1995****
Totals	**102**	**1**	**0.025-0.76**	**NR**	49	**1**	**0.0042-1.2**	NR
Duration of Use								
Leave-On	91	*1*	0.025-0.76	NR	48	*1*	0.0042-1.2	NR
Rinse-Off	11	NR	0.11-0.16	NR	1	*NR*	0.084	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type*								
Eye Area	13	NR	0.3-0.55	NR	7	NR	NR	NR
Incidental Ingestion	3	NR	0.025-0.76	NR	16	NR	NR	NR
Incidental Inhalation-Spray	47[a]; 18[c]	1[a]	NR	NR	25[a]	1[b]	NR	NR
Incidental Inhalation-Powder	46[b]; 18[c]	NR	NR	NR	24[b]	1[b]	NR	NR
Dermal Contact	99	NR	0.1-0.55	NR	40	1	0.0042-1.2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	5	NR	NR	NR
Mucous Membrane	3	NR	0.25-0.76	NR	9	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Propylene glycol dicaprylate/dicaprate				**Propylene glycol dioleate**			
	2014	**1995**	**2014**	**1995****	**2014**	**1995****	**2014**	**1995****
Totals*	**525**	**202**	**0.045-51.8**	**7-45**	**1**	NR	**15.8**	NR
Duration of Use								
Leave-On	417	*183*	0.1-51.8	*7-45*	NR	NR	NR	NR
Rinse-Off	106	*19*	0.045-14.4	NR	1	NR	15.8	NR
Diluted for (Bath) Use	2	NR	0.045	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	32	14	1.5-41	7-19	NR	NR	NR	NR
Incidental Ingestion	16	24	8-38	10	NR	NR	NR	NR
Incidental Inhalation-Spray	180[a]; 108[c]	78[a]; 21[c]	0.13[b]; 0.13	16-24[a]	NR	NR	NR	NR
Incidental Inhalation-Powder	126[b]; 108[c]	57[b]; 21[c]	0.1-38[c]; 0.1-38	16[b]	NR	NR	NR	NR
Dermal Contact	371	174	0.045-51.8	7-45	1	NR	15.8	NR
Deodorant (underarm)	1[b]	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	120	NR	0.13-2	NR	NR	NR	NR	NR
Hair-Coloring	11	NR	0.075-0.63	NR	NR	NR	NR	NR
Nail	5	4	3.5-21.6	NR	NR	NR	NR	NR
Mucous Membrane	39	24	0.045-38	10	NR	NR	NR	NR
Baby Products	NR	1	2.5	NR	NR	NR	NR	NR

	Propylene glycol dipelargonate				**Propylene glycol isostearate**			
	2014	**1995**	**2014**	**1995****	**2014**	**1995**	**2014**	**1995****
Totals*	**42**	**82**	**0.71-60**	**1-33.796**	**19**	**22**	**0.3-15**	**1.4**
Duration of Use								
Leave-On	36	*72*	0.71-60	*1-33.796*	10	*7*	15	NR
Rinse-Off	6	*9*	5-6	*5*	9	*15*	0.3-1	*1.4*
Diluted for (Bath) Use	NR	*1*	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	2	2	NR	NR	1	1	NR	NR
Incidental Ingestion	9	8	NR	NR	1	1	NR	NR
Incidental Inhalation-Spray	7[a]; 14[c]	17[c]	60[a]	1[a]; 4[c]	6[a]	2	NR	NR
Incidental Inhalation-Powder	7[b]; 14[c]	16[c]	NR	1[a]; 4[c]	6[b]	1	NR	NR
Dermal Contact	33	74	0.71-60	1-9.3	18	21	1-15	1.4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	33.796	NR	NR	NR	NR
Nail	NR	NR	5	5	NR	NR	0.3	NR
Mucous Membrane	9	10	NR	NR	1	1	NR	NR
Baby Products	NR	1	NR	NR	NR	NR	NR	NR

Table 4. Current and historical frequency and concentration of use of PG esters according to duration and exposure.[7,8] The Council is conducting a survey on the plant-derived PG esters added to this report.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Propylene glycol laurate				**Propylene glycol myristate**			
	2014	**1995**	**2014**	**1995****	**2014**	**2006**	**2014**	**2006**
Totals*	**67**	**87**	**0.005-5**	**1-22**	**5**	**15**	**4**	**4-6**
Duration of Use								
Leave-On	62	73	0.005-5	1-22	5	*15*	4	*4-6*
Rinse-Off	5	13	0.05-2.3	1.25	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	12	6	0.005-5	1-1.3	1	1	NR	NR
Incidental Ingestion	3	7	NR	9	1	2	4	5
Incidental Inhalation-Spray	13[a]; 5[c]	22[a]; 9[c]	NR	6[a]	3[b]	3[a]; 4[c]	NR	4-6[a]; 4[c]
Incidental Inhalation-Powder	12[b]; 5[c]	4[b]; 9[c]	NR	NR	1[b]	1[b]; 4[c]	NR	4[b]
Dermal Contact	54	69	0.005-5	1.3-6	4	13	NR	4-6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	7	2.3	1.25-22	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	1	NR	NR	NR	NR	NR	NR
Mucous Membrane	3	8	NR	9	1	2	4	5
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Propylene glycol oleate				**Propylene glycol stearate**			
	2014	**1996**	**2014**	**1995****	**2002**	**2002**	**2014**	**2002**
Totals*	**NR**	**6**	**0.48-1**	**NR**	**NR**	**60**	**1-1.4**	**NR**
Duration of Use								
Leave-On	NR	*6*	NR	NR	NR	59	1	NR
Rinse-Off	NR	NR	0.48-1	NR	NR	1	1.4	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	1	NR	NR	NR	5	1	NR
Incidental Ingestion	NR	NR	NR	NR	NR	1	NR	NR
Incidental Inhalation-Spray	NR	3[c]	NR	NR	NR	12[a]; 4[c]	NR	NR
Incidental Inhalation-Powder	NR	3[c]	NR	NR	NR	12[b]; 4[c]	NR	NR
Dermal Contact	NR	6	1	NR	NR	56	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	0.48	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	1.4	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	NR	NR	1	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Propylene glycol stearate SE			
	2014	**2002**	**2014**	**2002**
Totals*	**34**	**60**	**1-1.4**	**NR**
Duration of Use				
Leave-On	33	59	1	NR
Rinse-Off	1	1	1.4	NR
Diluted for (Bath) Use	NR	NR	NR	NR
Exposure Type				
Eye Area	14	5	1	NR
Incidental Ingestion	NR	1	NR	NR
Incidental Inhalation-Spray	14[a]	12[a]; 4[c]	NR	NR
Incidental Inhalation-Powder	14[b]	12[b]; 4[c]	NR	NR
Dermal Contact	30	56	1	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR
Hair-Coloring	NR	NR	1.4	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	1	NR	NR
Baby Products	NR	NR	NR	NR

Table 5. Frequency of use and concentration according to duration and exposure of PG esters.[7,8]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Propylene glycol diethylhexanoate							
Total/range	**28**	**0.000099-2**						
Duration of use								
Leave-on	26	0.000099-2						
Rinse-off	2	NR						
Diluted for (bath) use	NR	NR						
Exposure type[a]								
Eye area	3	0.0008-0.5						
Incidental ingestion	NR	NR						
Incidental Inhalation-sprays	18	0.0008[b]; 2						
Incidental inhalation-powders	15	NR						
Dermal contact	28	0.000099-2						
Deodorant (underarm)	1[b]	NR						
Hair-noncoloring	NR	NR						
Hair-coloring	NR	NR						
Nail	NR	NR						
Mucous Membrane	1	NR						
Baby	NR	NR						

NR=Not Reported; NS=Not Surveyed; Totals=Rinse-off + Leave-on Product Uses.

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

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

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

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

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

Table 6. There were no current reported uses or concentrations of use reported for these PG esters.[7,8]

Propylene glycol behenate	Propylene glycol dilaurate
Propylene glycol cocoate	Propylene glycol diundecanoate
Propylene glycol dicocoate	Propylene glycol linoleate
Propylene glycol diisostearate	Propylene glycol oleate SE
Propylene glycol distearate	Almond oil propyene glycol esters*
Propylene glycol heptanoate	Apricot kernel oil propylene glycol esters*
Propylene glycol linolenate	Avocado oil propylene glycol esters*
Propylene glycol caprylate	Olive oil propylene glycol esters*
Propylene glycol dicaproate	Soybean oil propylene glycol esters
Propylene glycol diisononanoate	

* VCRP only. The Council is conducting a concentration of use survey of these ingredients.

Table 7. Code of Federal Regulations that pertain to PG esters ingredients.

Ingredient(s)	Rule	Citation
Propylene glycol mono- and diesters of fats and fatty acids	TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart I--Multipurpose Additives Sec. 172.856 Propylene glycol mono- and diesters of fats and fatty acids. Propylene glycol mono- and diesters of fats and fatty acids may be safely used in food, subject to the following prescribed conditions: (a) They are produced from edible fats and/or fatty acids in compliance with 172.860 and/or oleic acid derived from tall oil fatty acids in compliance with 172.862. (b) They are used in food in amounts not in excess of that reasonably required to produce their intended effect.	21CFR172.856
Propylene glycol mono- and diesters of fats and fatty acids	PART 173 -- SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN CONSUMPTION Subpart D--Specific Usage Additives Sec. 173.340 Defoaming agents. Defoaming agents may be safely used in processing foods, in accordance with the following conditions: (a) They consist of one or more of the following: (1) Substances generally recognized by qualified experts as safe in food or covered by prior sanctions for the use prescribed by this section. (2) Substances listed in this paragraph (a)(2) of this section, subject to any limitations imposed: (3) Substances listed in this paragraph (a)(3), provided they are components of defoaming agents limited to use in processing beet sugar and yeast, and subject to any limitations imposed: Propylene glycol mono- and diesters of fats and fatty acids: As defined in 172.856 of this chapter.	21CFR173.340
Propylene glycol esters of coconut fatty acids, propylene glycol monolaurate, propylene glycol monostearate	PART 175 -- INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS Subpart B--Substances for Use Only as Components of Adhesives Sec. 175.105 Adhesives. (a) Adhesives may be safely used as components of articles intended for use in packaging, transporting, or holding food in accordance with the following prescribed conditions: (1) The adhesive is prepared from one or more of the optional substances named in paragraph (c) of this section, subject to any prescribed limitations.	21CFR175.105
Propylene glycol esters	PART 175 -- INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS Subpart C--Substances for Use as Components of Coatings Sec. 175.300 Resinous and polymeric coatings. Resinous and polymeric coatings may be safely used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, in accordance with the following prescribed conditions: (a) The coating is applied as a continuous film or enamel over a metal substrate, or the coating is intended for repeated food-contact use and is applied to any suitable substrate as a continuous film or enamel that serves as a functional barrier between the food and the substrate. The coating is characterized by one or more of the following descriptions: (1) Coatings cured by oxidation. (2) Coatings cured by polymerization, condensation, and/or cross-linking without oxidation. (3) Coatings prepared from prepolymerized substances. (b) The coatings are formulated from optional substances that may include: (1) Substances generally recognized as safe in food. (2) Substances the use of which is permitted by regulations in this part or which are permitted by prior sanction or approval and employed under the specific conditions, if any, of the prior sanction or approval. The oils may be raw, heat-bodied, or blown. They may be refined by filtration, degumming, acid or alkali washing, bleaching, distillation, partial dehydration, partial polymerization, or solvent extraction, or modified by combination with maleic anhydride. (ii) Reconstituted oils from triglycerides or fatty acids derived from the oils listed in paragraph (b)(3)(i) of this section to form esters with: Propylene glycol (vii) Polyester resins (including alkyd-type), as the basic polymers, formed as esters of acids listed in paragraph (b)(3)(vii) (*a*) and (*b*) of this section by reaction with alcohols in paragraph (b)(3)(vii) (*c*) and (*d*) of this section. (*c*) Polyhydric alcohols: Propylene glycol (xxii) Driers made by reaction of a metal from paragraph (b)(3)(xxii)(*a*) of this section with acid, to form the salt listed in paragraph (b)(3)(xxii)(*b*) of this section: Propylene Glycol	21CFR175.300
Propylene glycol mono- and diesters of fats and fatty acids	PART 176 -- INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS Subpart B--Substances for Use Only as Components of Paper and Paperboard Sec. 176.170 Components of paper and paperboard in contact with aqueous and fatty foods. Substances identified in this section may be safely used as components of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty	21CFR176.170

	foods, subject to the provisions of this section. Components of paper and paperboard in contact with dry food of the type identified under Type VIII of table 1 in paragraph (c) of this section are subject to the provisions of 176.180. (a) Substances identified in paragraph (a) (1) through (5) of this section may be used as components of the food-contact surface of paper and paperboard. Paper and paperboard products shall be exempted from compliance with the extractives limitations prescribed in paragraph (c) of this section:*Provided,* That the components of the food-contact surface consist entirely of one or more of the substances identified in this paragraph:*And provided further,* That if the paper or paperboard when extracted under the conditions prescribed in paragraph (c) of this section exceeds the limitations on extractives contained in paragraph (c) of this section, information shall be available from manufacturing records from which it is possible to determine that only substances identified in this paragraph (a) are present in the food-contact surface of such paper or paperboard. (1) Substances generally recognized as safe in food. (2) Substances generally recognized as safe for their intended use in paper and paperboard products used in food packaging. (3) Substances used in accordance with a prior sanction or approval. (4) Substances that by regulation in parts 170 through 189 of this chapter may be safely used without extractives limitations as components of the uncoated or coated food-contact surface of paper and paperboard in contact with aqueous or fatty food, subject to the provisions of such regulation.	
Propylene glycol esters	PART 176 -- INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS Subpart B--Substances for Use Only as Components of Paper and Paperboard Sec. 176.210 Defoaming agents used in the manufacture of paper and paperboard. Defoaming agents may be safely used in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food in accordance with the following prescribed conditions: (a) The defoaming agents are prepared from one or more of the substances named in paragraph (d) of this section, subject to any prescribed limitations. (b) The defoaming agents are used to prevent or control the formation of foam during the manufacture of paper and paperboard prior to and during the sheet-forming process. (c) The quantity of defoaming agent or agents added during the manufacturing process shall not exceed the amount necessary to accomplish the intended technical effect. (d) Substances permitted to be used in the formulation of defoaming agents include substances subject to prior sanctions or approval for such use and employed subject to the conditions of such sanctions or approvals, substances generally recognized as safe for use in food, substances generally recognized as safe for use in paper and paperboard, and substances listed in this paragraph, subject to the limitations, if any, prescribed. (2) Fatty triglycerides, and marine oils, and the fatty acids and alcohols derived therefrom (paragraph (d)(1) of this section) reacted with one or more of the following, with or without dehydration, to form chemicals of the category indicated in parentheses: Propylene glycol (esters)	21CFR176.210
Propylene glycol esters	PART 177 -- INDIRECT FOOD ADDITIVES: POLYMERS Subpart C--Substances for Use Only as Components of Articles Intended for Repeated Use Sec. 177.2800 Textiles and textile fibers. Textiles and textile fibers may safely be used as articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, subject to the provisions of this section. (a) The textiles and textile fibers are prepared from one or more of the fibers identified in paragraph (d) of this section and from certain other adjuvant substances required in the production of the textiles or textile fibers or added to impart desired properties. (b) The quantity of any adjuvant substance employed in the production of textiles or textile fibers does not exceed the amount reasonably required to accomplish the intended physical or technical effect or any limitation further provided. (c) Any substance employed in the production of textiles or textile fibers that is the subject of a regulation in parts 174, 175, 176, 177, 178 and 179.45 of this chapter conforms with any specification in such regulation. (d) Substances employed in the production of or added to textiles and textile fibers may include: (1) Substances generally recognized as safe in food. (2) Substances subject to prior sanction or approval for use in textiles and textile fibers and used in accordance with such sanction or approval. (3) Substances generally recognized as safe for use in cotton and cotton fabrics used in dry-food packaging. (4) Substances that by regulation in this part may safely be used in the production of or as a component of textiles or textile fibers and subject to provisions of such regulation. (5) Substances identified in this paragraph (d)(5), subject to such limitations as are provided: Fats, oils, fatty acids, and fatty alcohols described in the preceding item reacted with one or more of the following substances: Propylene glycol	21CFR177.2800
Propylene glycol caprylate, propylene glycol caprate, and propylene glycol laurate	TITLE 40—Protection of Environment CHAPTER I—ENVIRONMENTAL PROTECTION AGENCY SUBCHAPTER E—PESTICIDE PROGRAMS PART 180—TOLERANCES AND EXEMPTIONS FOR PESTICIDE CHEMICAL RESIDUES IN FOOD C8, C10, and C12 fatty acid monoesters of glycerol and propylene glycol; exemption from the requirement of a tolerance. The C8, C10, and C12 straight-chain fatty acid monoesters of glycerol (glycerol monocaprylate,	40CFR180.1250

	glycerol monocaprate, and glycerol monolaurate) and propylene glycol (propylene glycol monocaprylate, propylene glycol monocaprate, and propylene glycol monolaurate) are exempt from the requirement of a tolerance in or on all food commodities when used in accordance with approved label rates and good agricultural practice.

Table 8. Penetration enhancement studies of PG esters.

Ingredient(s); concentration (%)	Experiment/results	Reference
Propylene glycol caprylate (10)	Did not increase the dermal penetration of Loxoprofen through guinea pig abdominal skin when added to a PSA using horizontal diffusion cells (effect area 3.14 cm^2). Samples were collected every 2 h for 24 h.	[22]
Propylene glycol caprylate (5, 10, 20, 40, 60, 100)	Increased the dermal penetration of diclofenac through rat abdominal skin using Franz cells (effective area 0.785 cm^2). Samples were collected for 24 h. The permeability indexes were calculated to be 9.08±0.90, 9.82±1.85, 6.56±0.46, 4.34±0.86, 3.86±0.37, and 5.46±1.12 cm/h for 5%, 10%, 20%, 40%, 60%, and 100% propylene glycol caprylate, respectively.	[14]
Propylene glycol dicaprylate (5)	Increased the dermal penetration of diclofenac through rat abdominal skin using Franz cells (effective area 0.785 cm^2). Samples were collected for 24 h. The permeability index was calculated to be 0.32±0.06 cm/h.	[14]
Propylene glycol caprylate (10)	Increased the dermal penetration of diclofenac through the shaved skin of male Wistar rats (n=4). The area under the curve (AUC_{0-8}) and maximum concentration (C_{max}) were 65.0±8.0 µg h/mL and 10.5±1.5 µg/mL at 4.3±1.3 h (t_{max}) compared to 1.9±0.3 µg h/mL and 0.25±0.05 10.5±1.5 µg/mL at 5.0±1.7 h for water. The test substance (1 g) was placed in a columnar cylinder (15 mm diameter) glued to the abdomen of the sedated rats. Blood samples were taken from the jugular vein periodically for 8 h.	[14]
Propylene glycol dicaprylate (not clear)	Did not increase the dermal penetration of the water-soluble drugs levodopa, dopamine HCl, and isoproterenol HCl. 2.0 mL of drug in lactate buffer with and without propylene glycol dicaprylate in diffusion cells using abdominal skin of hairless mice. Effective diffusion area 1.13 cm^2.	[21]
Propylene glycol oleate, propylene glycol dioleate, propylene glycol linoleate, propylene glycol dilinoleate, propylene glycol linolenate, and propylene glycol dilinolenate;(1)	Enhanced the dermal penetration of lidocaine (1% in tetraglycol-distilled water 1:1 w/w) through pig ear skin using a Franz cell by ratios of 1.91, 2.11, 1.68, 1.44, 1.70, and 1.37, respectively, when compared to controls. However, there was no increase in penetration using propylene glycol mono-γ-linolenate and propylene glycol di-γ-linolenate. The skin from freshly killed pigs was trimmed of hair and frozen for less than 2 weeks before use. The lidocaine solution (200 µL) was placed in the donor cell (n≥4) with or without the test substance. Samples (2 mL) were collected and replenished every hour from the receptor cell for 8 h. Samples were analyzed by high-performance liquid chromatography (HPLC).	[15]
Propylene glycol dipelargonate (5)	Increased the dermal penetration of [^{3}H(G)] heparin sodium salt (0.49 n/ci/mg) through human skin using Franz cells, with an enhancement factor of 4.57, compared to controls. The skin was obtained from 3 different donors having breast reduction surgeries. The available surface area in the cells was 0.75 cm^2. The gel was placed in the donor cell and the receptor cell was sampled periodically over 24 h.	[16]
Propylene glycol dipelargonate (100 µL)	When skin from the same source was pretreated with propylene glycol dipelargonate (100 µL) for 12 h, there was increase dermal penetration of [^{3}H(G)] heparin sodium salt with an enhancement factor of 10.06. The test substance was wiped off then the heparin sodium salt (400 µL) was placed in the donor cell of the Franz cells. The receptor cell was sampled periodically over 24 h	[16]
Propylene glycol diperlargonate (1%)	Increased the dermal penetration of thiocolchicoside through human skin using Franz cells, with an enhancement factor of 3.20 compared to a thiogel ointment. The authors suggested that the enhanced flux of thiocolchicoside was probably due to propylene glycol diperlargonate's very low polarity enabling the thiocolchicoside to penetrate into the stratum corneum and interact with the lipid bilayers, thus increasing their fluidity. The skin was obtained from breast reduction surgeries from 6 different donors. Subcutaneous fat, stratum corneum, and epidermis were removed. The available surface area in the cells was 0.75 cm^2. The gel (300 mg) was placed in the donor cell and the receptor cell, containing a water:ethanol solution (50: 50), was sampled periodically over 24 h. Samples were analyzed by HPLC.	[17]
Propylene glycol dipelargonate (saturation)	Increased dermal penetration of caffeine (hydrophilic) but not testosterone (lipophilic) through human skin from breast reduction surgeries using Franz cells. Suspensions of caffeine or testosterone saturated with propylene glycol dipelargonate were administered to the skin. Saline in the receptor cell was sampled periodically for 24 h. The flux values were 2.278±0.353 and 0.079±0.080, respectively. The experiment was repeated with a 50:50 mix of propylene glycol dipelargonate and propylene glycol. The flux values were 2.193±0.174 and 1.226±0.121, respectively.	[18]
Propylene glycol diperlargonate	The concentration of propylene glycol dipelargonate with 20 g of ethanol in the foam test substance was estimated by staff to be 0.8% using the provided data (1 g added to the approximately 9.45 g base formulation; however, due to incomplete information, assumptions were made for density of the foam and how much test material was added). The aqueous foam formulation enhanced the dermal penetration of thiocolchicoside through fresh, clipped rat skin using Franz cell. The enhancement factor was 3.58. The dorsal hair of Sprague-Dawley rats was	[23]

Table 8. Penetration enhancement studies of PG esters.

Ingredient(s); concentration (%)	Experiment/results	Reference
	clipped. The skin was excised and placed immediately into the Franz cells. The test formulation (1 g) was placed in the donor cell and covered to prevent evaporation. Samples were collected and the phosphate buffer in the receptor cell was replaced at 4, 7, 24, and 30 h. Samples were analyzed by HPLC. This experiment was repeated with a hydroalcoholic solution with the same amount of propylene glycol diperlargonate. There was no difference in dermal penetration between the 2 tests.	
Propylene glycol dilaurate/propylene glycol laurate (described as 45%-70% propylene glycol laurate and the rest as propylene glycol dilaurate)	In a saturated solution of carbenoxolone, a mixture of propylene glycol dilaurate/propylene glycol laurate in combination with Transcutol™ (50:50) enhanced the dermal penetration of carbenoxolone through human abdominal skin using Franz cells. The k_p was 6.75. The test substance was administered as infinite doses (1 mL) to the donor cell and permeation values were cumulative. Thawed, female, abdominal, full thickness skin was used. A similar test substance containing only propylene glycol laurate did not enhance dermal penetration of carbenoxolone (k_p=1.23).	[20]
Propylene glycol Laurate (10)	Did not increase the dermal penetration of Loxoprofen through guinea pig abdominal skin when added to a PSA using horizontal diffusion cells (effect area 3.14 cm^2). Samples were collected every 2 h for 24 h.	[22]
Propylene glycol laurate/propylene glycol dilaurate (50% in a saturated solution)	Propylene glycol laurate/propylene glycol dilaurate (45%-70% propylene glycol laurate) in combination with Transcutol™ (50:50) increased the dermal penetration of carbenoxolone through female abdominal full thickness cadaver skin using Franz cell. There were infinite doses of 1 mL over 48 h.	[20]
Propylene glycol dipelargonate (saturated solution)	Increased the dermal penetration of methyl nicotinate through the abdominal skin of hairless rats using glass static diffusion cells (effective skin surface area 2.54 cm^2). The steady-state flux was 3.56. The test substance was 2 g propylene glycol dipelargonate containing 537 mg/g methyl nicotinate (120% of solubility saturation). Samples were taken for 4 h and analyzed by HPLC.	[19]

PSA – pressure sensitive adhesive

REFERENCES

1. Nikitakis, J and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 15 *ed*. Washington, DC: Personal Care Products Council, 2014.

2. Andersen, FA. Final report on the safety assessment of propylene glycol (PG) dicaprylate, PG dicaprylate/dicaprate, PG dicocoate, PG dipelargonate, PG isostearate, PG Laurate, PG myristate, PG oleate, PG oleate SE, PG dioleate, PG dicaprate,PG diisostearate, and PG dilaruate. *International Journal of Toxicology*. 1999;18(Suppl. 2):35-52.

3. Andersen, FA. Annual review of cosmetic ingredient safety assessments 2002/2003. *International Journal of Toxicology*. 2005;24(Suppl. 1):1-102.

4. Elder, RL. Final report on the safety assessment of propylene glycol stearate and propylene glycol stearate self-emulsifying. *Journal of the American College of Toxicology*. 1983;2(5):101-124.

5. Johnson Jr, W, Heldreth, B, Bergfeld, WF, Belsito, DV, Klaassen, CD, Hill, RA, Liebler, D, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, and Andersen, FA. Final report of the Cosmetic Ingredient Revew Expert Panel on the safety assessment of pelargonic acid (nonanoic acid) and nonanoate esters. *International Journal of Toxicology*. 2011;30(Suppl. 3):228S-269S.

6. Becker, LC, Bergfeld, WF, Belsito, DV, Hill, RA, Klaassen, CD, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, and Andersen, FA. Final report of the amended safety assessment of myristic acid and its salts and esters as used in cosmetics. *International Journal of Toxicology*. 2010;29(Suppl. 3):162S-186S.

7. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2014. Washington, DC: FDA.

8. Personal Care Products Council. 6-18-2014. Concentration of Use Information: Propylene Glycol Esters. Unpublished data submitted by Personal Care Products Council.

9. Andersen, FA. Annual review of cosmetic ingredient safety assessments - 2004/2005. *International Journal of Toxicology*. 2006;26(Suppl. 2):1-89.

10. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

11. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27.

12. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.

13. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett.* 8-28-2011;205(2):97-104.

14. Takahashi, K, Matsumoto, T, Kimura, T, Sakano, H, Mizuno, N, and Yata, N. Effect of polyol fatty acid esters on diclofenac permeation through rat skin. *Biological & Pharmaceutical Bulletin*. 1996;19(6):893-896.

15. Ben-Shabat, S, Baruch, N, and Sintov, AC. Conjugates of unsaturated fatty acids with propylene glycol as potentially less-irritant skin penetration enhancers. *Drug Development and Industrial Pharmacy*. 2007;33(11):1169-1175.

16. Bonina, FP and Montenegro, L. Effects of some non-toxic penetration enhancers on in vitro heparinskin permiation from gel vehicles. *International Journal of Pharmaceutics*. 1994;111(2):191-196.

17. Bonnina, F, Puglia, C, Trombetta, D, Dragani, MC, Gentile, MM, and Clavenna, G. Vehicle effects on *in vitro* skin permeation of thiocolchicocide. *Pharmazie*. 2002;57(11):750-752.

18. Bonnina, F, Carelli, V, Di Colo, G, Montenegro, L, and Nannipieri, E. Vehicle effects on in vitro skin permeation of and stratum corneum affinity for model drugs caffeine and testosterone. *International Journal of Parmaceutics.* 1993;100:41-47.

19. Lafforgue, C, Eynard, I, Falson, F, Watkinson, AC, and Hadgraft, J. Percutaneous absorption of methyl nicotinate. *International Journal of Parmaceutics.* 1995;121(1):89-93.

20. Hirata, K, Helal, F, Hadgraft, J, and Lane, ME. Formulation of carbenoxolone for deliver to the skin. *International Journal of Pharmaceutics.* 2013;448:360-365.

21. Okumura, M, Sugibayashi, K, and Morimoto, Y. Effects of several enhancers on the skin penetration of water-soluble drugs. *Chemical and Pharmaceutical Bulletin*. 1989;37(5):1375-1378.

22. Kawahara, K and Tojo, K. Skin irritation in transdermal drug delivery systems: A strategy for its reduction. *Parmaceutical Research*. 2007;24(2):399-408.

23. Ceschel, GC and Maffei, P. In vitro permieation screening of a new formulation of thiocolchicoside containing various enhancers. *Drug Delivery*. 2002;9:259-263.

24. Takahashi, K, Komai, M, Kinoshita, N, Nakamura, E, Hou, X-L, Takatani-Nakase, T, and Kawase, M. Application of hydrotropy to transdermal formulations: Hydrotropic solubilization of polyol fatty acid monoesters in water and enhancement effect on skin permeation of 5-FU. *Journal of Pharmacy and Pharmacology*. 2011;63:1008-1014.

25. European Chemicals Agency. ECHA - European Chemicals Agency (68583-51-7; Decanoic acid, mixed diesters with octanoic acid and propylene glycol). http://echa.europa.eu/.

26. Dueva-Koganov, OV, Mandalia, Y, Brito, J, Rocafort, C, Orofino, S, and Vazquez, G. *In vitro*/*in vivo* and analytical evaluation of sunless tanning formulations containing different rheology modifiers. *Journal of Cosmetic Science*. 2010;61:73-83.

27. Andersen, FA. Final report on the safety assessment of propylene glycol and polypropylene glycols. *Journal of the American College of Toxicology*. 1994;13(6):437-491.

28. Fiume, MM, Bergfeld, WF, Belsito, DV, Hill, RA, Klaassen, CD, Liebler, D, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, and Andersen FA. Safety assessment of propylene glycol, tripropylene glycol, and PPGs as used in cosmetics. *International Journal of Toxicology*. 2012;31(Suppl. 2):2455-2605.

29. Andersen, FA. Annual review of cosmetic ingredient safety assessments - 2001/2002. *International Journal of Toxicology*. 2003;22(Suppl. 1):1-35.

30. Elder, RL. Final report on the safety assessment of coconut oil, coconut acid, hydrogenated coconut acid, and hydrogenated coconut oil. *Journal of the American College of Toxicology*. 1986;5(3):103-121.

31. Burnett, CL, Bergfeld, WF, Belsito, DV, Klaassen, CD, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, and Andersen FA. Final report on the safety assessment of *Cocos nucifera* (coconut) oil and related ingredients. *International Journal of Toxicology*. 2011;30(Suppl 1):55-165.

32. Fiume, MM, Bergfeld, WF, Belsito, DV, Hill, RA, Klaassen, CD, Liebler, D, Marks Jr, JG, Shank, RC, Slaga, TJ, and Snyder, PW. Amended safety assessment of alkyl ethylhexanoates as used in cosmetics. Washington, DC, Cosmetic Ingredient Review. 2013. pp. 1-16.

33. Elder, RL. Report on the safety assessment of isostearic acid. *Journal of the American College of Toxicology*. 1984;2(7):61-74.

34. Elder, RL. Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myrisitic acid, and stearic acid. *Journal of the American College of Toxicology*. 1987;6(3):321-401.

35. Elder, RL. Final report on the safety assessment of stearyl heptanoate. *Journal of the American College of Toxicology*. 1995;14(6):498-510.

36. Fiume, MM, Bergfeld, WF, Belsito, DV, Hill, RA, Klaassen, CD, Liebler, D, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, and Andersen, FA. Safety assessment of stearyl heptanoate and related stearyl alkanoates as used in cosmetics. *International Journal of Toxicology*. 2012;31(Suppl. 2):141S-146S.

37. Fiume, MM, Belsito, DV, Hill, RA, Klaassen, CD, Liebler, D, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, Andersen, FA, and Heldreth, B. Amended safety assessment of alkyl esters as used in cosmetics. Washington, DC, Cosmetic Ingredient Review. 2013. pp. 1-82.

38. Burnett, CL, Fiume, MM, Bergfeld, WF, Belsito, DV, Hill, RA, Klaassen, CD, Liebler, D, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, and Andersen, FA. Final Report - Plant-derived fatty acid oils as used in cosmetics. Washington, DC, Cosmetic Ingredient Review. 2011. pp. 1-100.

39. Elder, RL. Final report on the safety assessment of sweet almond oil and almond meal. *Journal of the American College of Toxicology*. 1983;2(5):85-99.

40. Boelsma, E, Tanojo, H, Boddé, HE, and Ponec, M. An *in vivo-in vitro* study of the use of a human skin equivalent for irritancy screening of fatty acids. *Toxicology in Vitro*. 1997;11(4):365-376.

41. Tanojo, H and Junginger, HE. Skin permeation enhancement by fatty acids. *Journal of Dispersion Science and Technology*. 1999;20(1-2):127-138.

42. Orö, L and Wretlind, A. Pharmacological effects of fatty acids, triolein and cottonseed oil. *Acta Pharmacologica et Toxicologica*. 1961;18(2):141-152.

43. Casas, JW, Lewerenz, GM, Rankin, EA, Willoughby Sr, JA, Blakeman, LC, McKim Jr, JM, and Coleman, KP. *In vitro* human skin irritation test for evaluation of medical device extracts. *Toxicology in Vitro*. 2013;27(8):2175-2183.

44. Tornier, C, Rosdy, M, and Maibach, HI. In vitro skin irritation testing on reconstituted human epidermis: Reproducibility for 50 chamical tested with two protocols. *Toxicology in Vitro*. 2006;20(4):401-416.

45. Phillips II, L, Steinberg, M, Maibach, HI, and Akers, WA. A comparison of rabbit and human skin response to certain irritants. *Toxicology and Applied Pharmacology*. 1972;21(3):369-382.

46. European Food Safety Authority (EFSA). Scientific Opinion on the safety and efficacy of straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters with esters containing saturated alcohols and acetals containing saturated aldehydes (chemical group 1) when used as flavourings for all animal species. *European Food Safety Authority Journal*. 2013;11(4):3169-3204.