

---

# Safety Assessment of Propylene Glycol Esters as Used in Cosmetics

---

Status: Final Amended Report  
Release Date: January 15, 2015  
Panel Meeting Date: December 8-9, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, 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.

---

© Cosmetic Ingredient Review

1620 L Street, NW, Suite 1200 √ Washington, DC 20036-4702 √ ph 202.331.0651 √ fax 202.331.0088 √ [cirinfo@cir-safety.org](mailto:cirinfo@cir-safety.org)

## ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of propylene glycol esters (PG esters) as used in cosmetics. These ingredients mostly function as skin-conditioning agents-emollient and as surfactants – emulsifying agent. The Panel reviewed relevant animal and human data related to these ingredients. 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 chemical components of these ingredients. The Panel concluded that these propylene glycol esters were safe as cosmetic ingredients in the practices of use and concentration described in this safety assessment.

## INTRODUCTION

This is a safety assessment of PG esters as used in cosmetics based on the relevant published scientific literature and unpublished data. 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.<sup>1</sup>

This safety assessment is a re-review of several PG esters from previous reports. In 1999, a safety assessment of 13 PG esters was published by the CIR Panel with a conclusion of safe as used.<sup>2</sup> These were:

propylene glycol dicaprate	propylene glycol dipelargonate
propylene glycol dicaprylate	propylene glycol isostearate
propylene glycol dicaprylate/dicaprate	propylene glycol laurate
propylene glycol dicocoate	propylene glycol myristate
propylene glycol diisostearate	propylene glycol oleate
propylene glycol dilaurate	propylene glycol oleate SE
propylene glycol dioleate	

Three additional PG esters included in this safety assessment previously have been reviewed by the Panel and were found to be safe as used:

propylene glycol stearate
propylene glycol stearate SE
propylene glycol diisononanoate <sup>3-6</sup>

Further, the Panel determined that it was appropriate to include the following 16 ingredients that had not yet been reviewed by the Panel in this safety assessment:

propylene glycol behenate	propylene glycol linolenate
propylene glycol caprylate	propylene glycol distearate
propylene glycol cocoate	propylene glycol soyate
propylene glycol dicaproate	almond oil propylene glycol esters
propylene glycol diethylhexanoate	apricot kernel oil propylene glycol esters
propylene glycol diundecanoate	avocado oil propylene glycol esters
propylene glycol heptanoate	olive oil propylene glycol esters
propylene glycol linoleate	soybean oil propylene glycol esters

These 32 ingredients are grouped together in this safety assessment because of their chemical structures and functional similarities. The similar physicochemical properties and concentrations used in cosmetics help to justify grouping these ingredients and extrapolating the available toxicological data to support the safety assessment of the entire group. Table 2 lists the previous CIR safety assessments of ingredients named in this report. The summaries of these reports are provided below.

Data obtained from studies using radiolabeled PG stearate showed that PG stearate can be converted to propylene glycol and fatty acid components at rates that depend on the fatty acid moiety and the exposure route. Thus, the safety of the component moieties of the PG esters is relevant for assessing the safety of the PG esters. The safety assessments of related ingredients (ie, the propylene glycol and the fatty acids from which the esters are produced) are also listed in Table 2. The table presents the conclusions reported previously for the relevant propylene glycol and fatty acid ingredients, which are the starting materials for, and potential metabolites of the PG esters. In summary, coconut acid, pelargonic (nonanoic) acid, isostearic acid, oleic acid, lauric acid, myristic acid, stearic acid, almond oil, apricot kernel oil, avocado oil, olive oil, and 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 by the Panel. Heptanoic acid is not a cosmetic ingredient. Summary safety information on undecanoic acid and heptanoic acid are provided in Table 3 to provide additional information on the moieties of the PG esters that have not been reviewed by the Panel. Because the data from the existing safety

assessments included in Table 2 have been published, only new data (and pertinent excerpts from previous reports) 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.<sup>2</sup> 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 C<sub>12</sub>H<sub>24</sub>O<sub>3</sub> 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/Dicaprante 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<sub>50</sub> > 34.6 g/kg) when administered orally to rats.

In two skin irritation studies involving rabbits, Propylene Glycol Dicaprylate/Dicaprante and Propylene Glycol Laurate were classified as minimally irritating and slightly irritating, respectively. Propylene Glycol Dicaprylate/Dicaprante 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/Dicaprante mixture (20:80). Patches were removed at 24 hours post application. Similar results were reported for a fourth subject patch tested with a 95% ethanol:Propylene Glycol Dicaprylate/Dicaprante 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.<sup>4</sup> 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 <sup>14</sup>C-labeled PGS show that it is readily metabolized following ingestion. In rats, the acute oral LD<sub>50</sub> 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<sub>50</sub> 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)**

Please note that the report on myristic acid and its salts and esters includes no specific data about propylene glycol myristate.<sup>6</sup> The safe conclusion is based on data on butyl myristate and related salts and esters, coupled with the data on the related chemicals (ie, myristic acid, myristyl myristate, and isopropyl myristate).

### **Propylene Glycol Diisoononanoate (2011)**

It should be noted that information not relevant to propylene glycol diisononanoate has been removed from the following summary.

*Straight-chain pelargonic acid esters are likely hydrolyzed to component alcohols and pelargonic acid, which is further metabolized by β-oxidation.<sup>5</sup> Iso-fatty acids and straight-chain fatty acids both are metabolized at the β-carbon to yield 2-carbon fractions [sic] 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.*

*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 oleate, and propylene glycol laurate are liquids at room temperature that are either clear or yellowish.<sup>2</sup> Structures are provided in Table 1.

## **Impurities**

Impurity data were provided in the previous reports, and no new data were provided or discovered in the literature.

## **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 of industry was conducted of industry by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group (Tables 4-6).<sup>7,8</sup> Both historical and current use data are provided in Table 4.

In 2014, propylene glycol dicaprylate/dicaprate had the greatest number of uses reported to the VCRP in this ingredient group, 525, which is greater than 202 reported in 1995 (Table 4).<sup>2,7</sup> This ingredient had reported uses in all use categories. The reported frequency of use of propylene glycol dicaprate increased from 1 in 1995 to 102 in 2014; during the same interval, the use frequency of propylene glycol dicaprylate increased from 1 to 49. Reported uses for propylene glycol stearate increased from 60 in 2002 to 168 in 2014. The use frequencies of most of the other previously reviewed ingredients that had reported uses (ie, propylene glycol dipelargonate, propylene glycol isostearate, propylene glycol laurate, propylene glycol myristate, propylene glycol oleate, and propylene glycol stearate SE) decreased; these ingredients are reported to be used in products applied to the skin, around the eyes, and in lipsticks. Of the ingredients being reviewed for the first time in this safety assessment, only propylene glycol diethylhexanoate had uses reported (28) to the VCRP (Table 5).<sup>2,6,7,9</sup>

Propylene glycol dipelargonate was reported to be used at the highest concentration, 60% in perfumes, which is greater than the highest concentration of use reported in 1995 (33.796%) in hair preparations. The use concentration of propylene glycol dicaprylate/dicaprate also increased, from a reported highest concentration of 45% (1995) to 51.8% (2014) in a blusher. For the remaining ingredients, the 2014 survey indicated maximum concentrations of use of 15.8% or less.<sup>2,6,8,9</sup> PG esters with no reported uses by either the VCRP or the Council survey are listed in Table 6.

In some cases, reports of uses were not received by the VCRP, but concentrations of use data were available. For example, propylene glycol dicaprylate/dicaprate was reported to be used in baby lotions, oils and creams 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.<sup>7,8</sup>

PG esters were reported to be used in hair sprays (propylene glycol dicaprylate/dicaprate up to 0.13%), in spray face and neck skin care products (propylene glycol diethylhexanoate up to 2%), and perfumes (propylene glycol dipelargonate up to 60%) and could possibly be inhaled. 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.<sup>10-13</sup> 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.<sup>10,13</sup>

### **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 use in adhesives and as components of coatings for packaging that comes in contact with food. [21CFR175.105, 21CFR175.300, 21CFR176.170, 21CFR176.210, 21CFR177.2800]

## **TOXICOKINETICS**

### **Penetration Enhancement**

In multiple in vitro experiments, several PG esters enhanced the penetration of drugs through human and animal skin (Table 8). Propylene glycol caprylate increased the dermal penetration of diclofenac through rat abdominal skin.<sup>14</sup> 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 Franz cells, by ratios of 1.91, 2.11, 1.68, 1.44, 1.70, and 1.37, respectively, compared to controls.<sup>15</sup> Propylene glycol dipelargonate increased the dermal penetration of [<sup>3</sup>H(G)] heparin sodium salt, thiocolchicoside, and caffeine but not testosterone.<sup>16-18</sup> A saturated solution of propylene glycol dipelargonate increased the dermal penetration of methyl nicotinate.<sup>19</sup> A mixture of propylene glycol dilaurate/propylene glycol laurate in combination with ethoxydiglycol (50:50) enhanced the dermal penetration of carbenoxolone.<sup>20</sup> Propylene glycol dicaprylate did not increase the penetration of water-soluble drugs.<sup>21</sup> Propylene glycol caprylate and propylene glycol laurate did not enhance the dermal penetration of loxoprofen.<sup>22</sup>

Propylene glycol dipelargonate (estimated by CIR staff to be 0.8%), with 20 g of ethanol in an aqueous foam formulation, enhanced the dermal penetration of thiocolchicoside through fresh, clipped rat skin, using Franz cells.<sup>23</sup>

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.<sup>24</sup> Adding propylene glycol caprylate (5%) to the hydroscopic 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. In this test, 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 submitted.

### **Repeated Dose Toxicity**

#### **PROPYLENE GLYCOL DICAPRYLATE/DICAPRATE**

The oral administration of propylene glycol dicaprylate/dicaprate, up to 1000 mg/kg/d for 90 days, showed no adverse effects in male and female Wistar rats.<sup>25</sup> The no observed adverse effects level (NOAEL) was concluded to be 1000 mg/kg/d. No evidence of adverse effects were found in clinical signs, mortality, body weight, feed consumption, ophthalmoscopic examination, hematology, clinical chemistry, gross pathology, organ weights, and histopathology. In this study, the rats (n=10, 15/sex) were exposed to 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/dicaprante (0, 100, 300 or 1000 mg/kg/d in arachis oil) on days 6-15 of gestation, was not embryotoxic and yielded no effects in the Sprague-Dawley CD rat dams.<sup>25</sup> The NOAEL was concluded to be to >1000 mg/kg/d. There were no differences in number of 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 - Non-human***

##### **PROPYLENE GLYCOL STEARATE, PROPYLENE GLYCOL OLEATE, PROPYLENE GLYCOL LINOLEATE**

In a primary skin irritation test using male albino rabbits (n=3), dermal application of propylene glycol stearate (1% in tetraglycol:distilled water 1:1, with and without 1% lidocaine) did not cause signs of irritation; however, 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) yielded mild erythema.<sup>15</sup> No edema was observed during the 7-day observation period after treatment with any of the 3 PG esters. In this study, the test substances were applied to the clipped backs of the rabbits in adhesive plasters, and the diameter of the exposure area was 1.5 cm<sup>2</sup>. The test sites were kept under occlusion, except when the dressing was removed on days 1, 3, 5, and 7, and only long enough for examination. The used pads were replaced with sterile pads and the rabbits' backs were re-occluded after each examination was completed.

#### ***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/dicaprante dermally applied to human subjects.<sup>26</sup> The concentration was not specified, but propylene glycol dicaprylate/dicaprante was part of a blend (dimethylacrylamide/ethyltrimonium chloride methacrylate copolymer, propylene glycol dicaprylate/dicaprante, PPG-1 trideceth-6, and C10-11 isoparaffin) that was present in the product at 3%. The test substance (0.1 g) was applied once to the volar forearms over a 50 cm<sup>2</sup> area to yield a dose of 2 mg/cm<sup>2</sup>. The test sites were examined at 24, 48, and 120 h.

### **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, based on the relevant scientific literature and available unpublished data. 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 in 1999 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 the PG ester ingredient group. Since this is a re-review of this group, only new data are summarized here.

In 2014, propylene glycol dicaprylate/dicaprate was reported to have the greatest number of uses in this group reported to the VCRP (525), which is greater than the 202 uses reported in 1995. Propylene glycol dicaprate increased from 1 in 1995 to 102 in 2014; during the same interval, the use frequency of propylene glycol dicaprylate increased from 1 to 49. Reported uses for propylene glycol stearate increased from 60 in 2002 to 168 in 2014. The use frequencies of most of the other previously reviewed ingredients that had reported uses have decreased in the number of reported uses. The PG esters are mostly reported to be used in dermal products, around the eye, 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.

Propylene glycol dipelargonate was reported to be used at the highest maximum concentration of 60% in perfumes; this is an increase from a highest maximum concentration of use of 33.796% in hair preparations in 1995. This was followed by a maximum use concentration of propylene glycol dicaprylate/dicaprate at 51.8% in blushers, an increase from 45%. The rest of the ingredients with current reported concentrations of use were 15.8% or less.

In multiple in vitro experiments, several PG esters enhanced the penetration 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 [<sup>3</sup>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 diethylene glycol monoethyl ether 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**

This safety assessment is a re-review of several PG esters from previous reports. In 1999, the Panel determined that 13 PG esters were safe as used in cosmetic ingredients. An additional 3 PG esters also have been found safe as used in cosmetics. The Panel supported combining the 16 previously reviewed ingredients with an additional 16 PG ester ingredients reviewed for the first time in this report, thereby creating 1 report of 32 PG esters. Although there are data gaps, the similar chemical structures, physicochemical properties, functions, and use concentrations in cosmetics allow grouping these ingredients and using the available toxicological data to support the safety of the ingredients in this group.

The Panel acknowledged that the 1999 safety assessment relied upon data based on the safety of chemical structure moieties of these ingredients (eg, propylene glycol and the acids of the esters). The Panel agreed that this approach is acceptable for the PG esters in this safety assessment when coupled with the original data on propylene glycol stearate. In addition, the available new repeated dose and reproductive toxicity data and irritation data for propylene glycol dicaprylate/dicaprate did not raise concern.

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

Because some of the components of the PG esters are obtained from plant sources (eg, propylene glycol soyate and avocado oil propylene glycol esters), the Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities in the ingredient before blending into cosmetic formulations.

The Panel discussed the issue of incidental inhalation exposure from the use of these ingredients in hair sprays, perfumes, and spray face and neck skin care products. Propylene glycol esters are also reported to be used in face powders. There were no chronic inhalation toxicity data available. However, the Panel believes that the sizes of a substantial majority

of the particles from these formulations are larger than the respirable range. These ingredients are reportedly used at concentrations up to 60% in cosmetic products that may be aerosolized and up to 38% in loose powder products that may become airborne. The Panel noted that 95%–99% of droplets/particles from sprays would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the use concentrations of the ingredients, 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, and the absence of genotoxicity in Ames tests. 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 when formulated to be nonirritating:

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

\*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

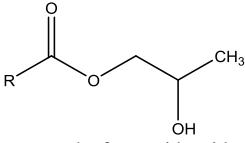
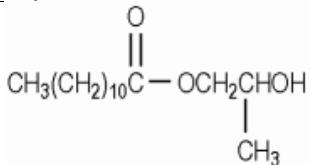
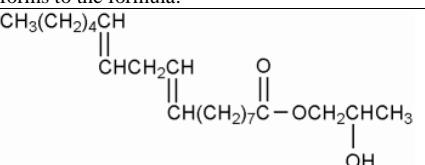
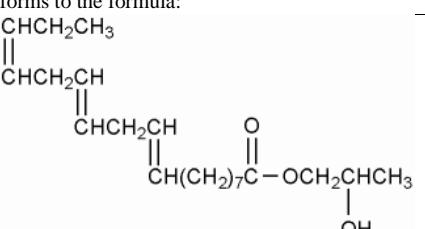
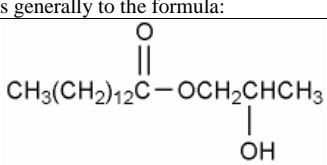
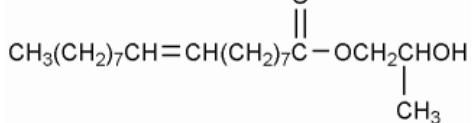
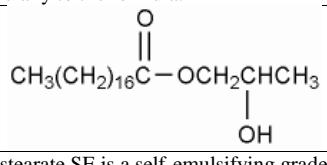
**Table 1.** Ingredient names, CAS nos., definitions, and functions of PG esters used in cosmetics.<sup>1</sup>

Ingredient CAS No.	Definition	Function
Propylene glycol behenate 100214-87-7 27923-61-1	Propylene glycol behenate is the ester of propylene glycol and behenic acid.  $\begin{array}{c} \text{O} \\    \\ \text{CH}_3(\text{CH}_2)_{20}\text{C}-\text{OCH}_2\text{CHCH}_3 \\   \\ \text{OH} \end{array}$	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:  $\begin{array}{c} \text{O} \\    \\ \text{CH}_3(\text{CH}_2)_6\text{C}-\text{OCH}_2\text{CHCH}_3 \\   \\ \text{OH} \end{array}$	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.  $\begin{array}{c} \text{O} \\    \\ \text{R}-\text{C(O)}-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_3 \\   \\ \text{OH} \end{array}$ <p>Wherein RC(O) represents the fatty acid residues of coconut acid</p>	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.  $\begin{array}{c} \text{O} \quad \text{O} \\    \quad    \\ \text{CH}_3(\text{CH}_2)_8\text{C}-\text{OCH}_2\text{CHO}-\text{C}(\text{CH}_2)_8\text{CH}_3 \\   \\ \text{CH}_3 \end{array}$	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.  $\begin{array}{c} \text{O} \quad \text{O} \\    \quad    \\ \text{CH}_3(\text{CH}_2)_4\text{C}-\text{OCH}_2\text{CHO}-\text{C}(\text{CH}_2)_4\text{CH}_3 \\   \\ \text{CH}_3 \end{array}$	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:  $\begin{array}{c} \text{O} \quad \text{O} \\    \quad    \\ \text{CH}_3(\text{CH}_2)_6\text{C}-\text{OCH}_2\text{CHO}-\text{C}(\text{CH}_2)_6\text{CH}_3 \\   \\ \text{CH}_3 \end{array}$	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.  $\begin{array}{c} \text{O} \\    \\ \text{R}-\text{C(O)}-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_3 \\   \\ \text{OH} \end{array}$ <p>Wherein RC(O) represents the residues of caprylic and capric acids.</p>	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.  $\begin{array}{c} \text{O} \quad \text{O} \\    \quad    \\ \text{RC}-\text{OCH}_2\text{CHO}-\text{CR} \\   \\ \text{CH}_3 \end{array}$	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous

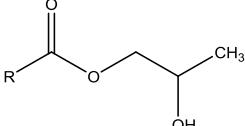
**Table 1.** Ingredient names, CAS nos., definitions, and functions of PG esters used in cosmetics.<sup>1</sup>

Ingredient CAS No.	Definition	Function
Propylene glycol diethylhexanoate 93981-97-6	Propylene glycol diethylhexanoate is the diester of propylene glycol and 2-ethylhexanoic acid.  $\begin{array}{c} \text{O} & \text{O} \\    &    \\ \text{CH}_3(\text{CH}_2)_3\text{CHC}-\text{OCH}_2\text{CHO}-\text{CCH}(\text{CH}_2)_3\text{CH}_3 \\   &   \\ \text{CH}_3\text{CH}_2 & \text{CH}_3 \\ &   \\ & \text{CH}_2\text{CH}_3 \end{array}$	Skin-conditioning agent – occlusive
Propylene glycol diisononanoate 125804-17-3	Propylene glycol diisononanoate is the diester of propylene glycol and branched chain nonanoic acids.  $\begin{array}{c} \text{O} & \text{O} \\    &    \\ \text{C}_8\text{H}_{17}\text{C}-\text{OCH}_2\text{CHO}-\text{CC}_8\text{H}_{17} \\   \\ \text{CH}_3 \end{array}$	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.  $\begin{array}{c} \text{O} & \text{O} \\    &    \\ \text{C}_{17}\text{H}_{35}\text{C}-\text{OCH}_2\text{CHO}-\text{CC}_{17}\text{H}_{35} \\   \\ \text{CH}_3 \end{array}$	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:  $\begin{array}{c} \text{O} \\    \\ \text{CH}_3(\text{CH}_2)_{10}\text{C}-\text{OCH}_2\text{CHCH}_3 \\   \\ \text{O}-\text{C}(\text{CH}_2)_{10}\text{CH}_3 \\    \\ \text{O} \end{array}$	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.  $\begin{array}{c} \text{O} & \text{CH}_3 & \text{O} \\    &   &    \\ \text{CH}(\text{CH}_2)_7\text{C}-\text{OCH}_2\text{CHO}-\text{C}(\text{CH}_2)_7\text{CH} \\    & &    \\ \text{CH}(\text{CH}_2)_7\text{CH}_3 & & \text{CH}_3(\text{CH}_2)_7\text{CH} \end{array}$	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:  $\begin{array}{c} \text{O} & \text{O} \\    &    \\ \text{CH}_3(\text{CH}_2)_7\text{C}-\text{OCH}_2\text{CHO}-\text{C}(\text{CH}_2)_7\text{CH}_3 \\   \\ \text{CH}_3 \end{array}$	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.  $\begin{array}{c} \text{O} & \text{O} \\    &    \\ \text{CH}_3(\text{CH}_2)_{16}\text{C}-\text{OCH}_2\text{CHO}-\text{C}(\text{CH}_2)_{16}\text{CH}_3 \\   \\ \text{CH}_3 \end{array}$	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.  $\begin{array}{c} \text{O} & \text{O} \\    &    \\ \text{CH}_3(\text{CH}_2)_9\text{C}-\text{OCH}_2\text{CHO}-\text{C}(\text{CH}_2)_9\text{CH}_3 \\   \\ \text{CH}_3 \end{array}$	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:  $\begin{array}{c} \text{O} \\    \\ \text{CH}_3(\text{CH}_2)_5\text{C}-\text{OCH}_2\text{CHCH}_3 \\   \\ \text{OH} \end{array}$	Skin-conditioning agent – emollient; surfactant – emulsifying agent

**Table 1.** Ingredient names, CAS nos., definitions, and functions of PG esters used in cosmetics.<sup>1</sup>

Ingredient CAS No.	Definition	Function
Propylene glycol isostearate 63799-53-1 68171-38-0	Propylene glycol isostearate is the ester of propylene glycol and isostearic acid.   <p>Wherein <math>\text{RC(O)}</math> represents the fatty acid residues of isostearic acid.</p>	Skin-conditioning agent-emollient; surfactant – 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 soyate 67784-79-6	Propylene glycol soyate is the ester of propylene glycol and soy acid.	Skin-conditioning agent-emollient; 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

**Table 1.** Ingredient names, CAS nos., definitions, and functions of PG esters used in cosmetics.<sup>1</sup>

Ingredient CAS No.	Definition	Function
Avocado oil propylene glycol esters No CAS no.	The product obtained from the transesterification of <i>persea gratissima</i> (avocado) oil and propylene glycol.	Skin-conditioning agent-emollient; surfactant-emulsifying agent
Olive oil propylene glycol esters	The product obtained by the transesterification of <i>olea europaea</i> (olive) fruit oil	Skin-conditioning agent-emollient
Soybean oil propylene glycol esters No CAS no.	Soybean oil propylene glycol esters is the product obtained by the transesterification of <i>glycine soja</i> (soybean) oil with propylene glycol.	Skin-conditioning agent-emollient
 <p>Wherein RC(O) represents the fatty acid residues of <i>glycine soja</i> (soybean) oil.</p>		

**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 moieties of ingredients in this report.

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

**Table 3.** Toxicity data for heptanoic acid and undecanoic acid, moieties of propylene glycol heptanoate and propylene glycol diundecanoate.

Ingredient	Study/assay	Results	Reference
<b>Dermal effects</b>			
Undecanoic acid (0.16 M)	Penetration enhancement on human subjects (n=35).	Did not increase the dermal penetration of hexyl nicotinate measured by change in transdermal water loss (TEWL) and laser Doppler velocimetry (LDV). Hill-Top chambers in place for 3 h then measured 3 h later by both techniques.	40
Heptanoic acid (0.16 M in propylene glycol)	Penetration enhancement	Enhancement ratio of <i>p</i> -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
<b>Acute toxicity</b>			
Heptanoic acid	IV in mice	LD <sub>50</sub> = 1200 ± 56 mg/kg	42
Undecanoic acid	IV in mice	LD <sub>50</sub> = 140 ± 4.2 mg/kg	42
<b>Dermal irritation – in vitro</b>			
Heptanoic 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-1 $\alpha$ release, more than the lactic acid. The lowest concentration of heptanoic acid, 0.1% induced a release of 76.3 pg/mL IL-1 $\alpha$ , compared to 17.0 pg/mL for the PBS negative control. 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 <sub>50</sub> 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 approximately 2 (MTT reduction assay, <50% viability); but not for IL-1 $\alpha$ release, score approximately 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 approximately 5 (MTT reduction assay, criteria for irritation: <50% viability); IL-1 $\alpha$ release score approximately 110 (criteria for irritation: >105 pg/mL); histological observation score approximately 0 (criteria for irritation: score < 75).	44
Undecanoic acid (80 µL/0.78 cm <sup>2</sup> )	Artificial skin (fibroblast-populated collagen gel)	Not predicted to be irritating. No morphology changes. No effect to IL-1 $\alpha$ and IL-8 levels.	40
<b>Dermal irritation – in vivo</b>			
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 using humans (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, and then a new patch placed.	45
Undecanoic acid (10%, in ethanol; 0.2 mL)	21-day continuous closed patch test using humans (n=8)	Cumulative irritation index=0. Patches were left in place on the forearm for 23.5 h, removed, read at 30 min, and 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, and then a new patch placed.	45
<b>Other assessment</b>			
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.<sup>2,3,5-8</sup>

	# 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
<b>Totals*</b>	<b>102</b>	<b>1</b>	<b>0.025-0.76</b>	<b>NR</b>	<b>49</b>	<b>1</b>	<b>0.0042-1.2</b>	<b>NR</b>
<i>Duration of Use</i>								
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
<i>Exposure Type*</i>								
Eye Area	13	NR	0.3-0.55	NR	7	NR	NR	NR
Incidental Ingestion	3	NR	0.025-0.76	NR	9	NR	NR	NR
Incidental Inhalation-Spray	47 <sup>a</sup> ; 18 <sup>c</sup>	1 <sup>a</sup>	NR	NR	25 <sup>a</sup>	1 <sup>b</sup>	NR	NR
Incidental Inhalation-Powder	46 <sup>b</sup> ; 18 <sup>c</sup>	NR	55 <sup>b</sup>	NR	24 <sup>b</sup>	1 <sup>b</sup>	0.21-2 <sup>b</sup>	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	NR	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
<b>Totals</b>	<b>525</b>	<b>202</b>	<b>0.045-51.8</b>	<b>7-45</b>	<b>1</b>	<b>NR</b>	<b>15.8</b>	<b>NR</b>
<i>Duration of Use</i>								
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
<i>Exposure Type</i>								
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 <sup>a</sup> ; 108 <sup>c</sup>	78 <sup>a</sup> ; 21 <sup>c</sup>	0.13; 0.13-2 <sup>b</sup> ; 1.8-8 <sup>c</sup>	16-24 <sup>a</sup>	NR	NR	NR	NR
Incidental Inhalation-Powder	126 <sup>b</sup> ; 108 <sup>c</sup>	57 <sup>b</sup> ; 21 <sup>c</sup>	0.1-38; 1.8-8 <sup>c</sup>	16 <sup>b</sup>	NR	NR	NR	NR
Dermal Contact	371	174	0.045-51.8	7-45	1	NR	15.8	NR
Deodorant (underarm)	1 <sup>b</sup>	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
<b>Totals</b>	<b>42</b>	<b>82</b>	<b>0.71-60</b>	<b>1-33.796</b>	<b>19</b>	<b>22</b>	<b>0.3-15</b>	<b>1.4</b>
<i>Duration of Use</i>								
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
<i>Exposure Type</i>								
Eye Area	2	2	NR	NR	1	1	NR	NR
Incidental Ingestion	9	8	NR	NR	1	1	NR	NR
Incidental Inhalation-Spray	6 <sup>a</sup> ; 14 <sup>c</sup>	17 <sup>c</sup>	60	1 <sup>a</sup> ; 4 <sup>c</sup>	6 <sup>c</sup>	2	NR	NR
Incidental Inhalation-Powder	6 <sup>b</sup> ; 14 <sup>c</sup>	16 <sup>c</sup>	NR	1 <sup>a</sup> ; 4 <sup>c</sup>	6 <sup>c</sup>	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.<sup>2,3,5-8</sup>

**Table 4.** Current and historical frequency and concentration of use of PG esters according to duration and exposure.<sup>2,3,5-8</sup>

	# of Uses	Max Conc of Use (%)		# of Uses	Max Conc of Use (%)
	Propylene glycol stearate SE				
	2014	2002	2014	2002	
<b>Totals</b>	<b>34</b>	<b>60</b>	<b>1-1.4</b>	<b>NR</b>	
<i>Duration of Use</i>					
Leave-On	33	59	1	NR	
Rinse-Off	1	1	1.4	NR	
Diluted for (Bath) Use	NR	NR	NR	NR	
<i>Exposure Type</i>					
Eye Area	14	5	1	NR	
Incidental Ingestion	NR	1	NR	NR	
Incidental Inhalation-Spray	14 <sup>a</sup>	12 <sup>a</sup> ; 4 <sup>c</sup>	NR	NR	
Incidental Inhalation-Powder	14 <sup>b</sup>	12 <sup>b</sup> ; 4 <sup>c</sup>	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	

NR=Not Reported; 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.

<sup>a</sup> It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.<sup>b</sup> It is possible these products may be powders, but it is not specified whether the reported uses are powders.<sup>c</sup> Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.**Table 5.** Frequency of use and concentration according to duration and exposure of PG esters not previously reviewed by CIR.<sup>7,8</sup>

Use type	Maximum Concentration	
	Uses	(%)
	Propylene glycol diethylhexanoate	
<b>Total/range</b>	<b>28</b>	<b>0.000099-2</b>
<i>Duration of use</i>		
Leave-on	26	0.000099-2
Rinse-off	2	NR
Diluted for (bath) use	NR	NR
<i>Exposure type<sup>a</sup></i>		
Eye area	3	0.0008-0.5
Incidental ingestion	NR	NR
Incidental Inhalation-sprays	9 <sup>a</sup> ; 9 <sup>c</sup>	2; 0.0008 <sup>a</sup>
Incidental inhalation-powders	6 <sup>b</sup> ; 9 <sup>c</sup>	0.000099-2 <sup>b</sup>
Dermal contact	28	0.000099-2
Deodorant (underarm)	1 <sup>a</sup>	NR
Hair-noncoloring	NR	NR
Hair-coloring	NR	NR
Nail	NR	NR
Mucous Membrane	1	NR
Baby	NR	NR

NR=Not Reported; 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.

<sup>a</sup> It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.<sup>b</sup> It is possible these products may be powders, but it is not specified whether the reported uses are powders.<sup>c</sup> 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.<sup>7,8,47</sup>

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

**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	21CFR175.300

**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	<p>prior sanction or approval and employed under the specific conditions, if any, of the prior sanction or approval.</p> <p>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.</p> <p>(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:</p> <p>Propylene glycol</p> <p>(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.</p> <p>(c ) Polyhydric alcohols: Propylene glycol</p> <p>(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</p>	21CFR176.170
Propylene glycol esters	<p>PART 176 -- INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS</p> <p>Subpart B--Substances for Use Only as Components of Paper and Paperboard</p> <p>Sec. 176.170 Components of paper and paperboard in contact with aqueous and fatty foods.</p> <p>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 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.</p> <p>(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: <i>Provided</i>, That the components of the food-contact surface consist entirely of one or more of the substances identified in this paragraph: <i>And provided further</i>, 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.</p> <p>(1) Substances generally recognized as safe in food.</p> <p>(2) Substances generally recognized as safe for their intended use in paper and paperboard products used in food packaging.</p> <p>(3) Substances used in accordance with a prior sanction or approval.</p> <p>(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.</p>	21CFR176.210
Propylene glycol esters	<p>PART 176 -- INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS</p> <p>Subpart B--Substances for Use Only as Components of Paper and Paperboard</p> <p>Sec. 176.210 Defoaming agents used in the manufacture of paper and paperboard.</p> <p>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:</p> <p>(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.</p> <p>(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.</p> <p>(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.</p> <p>(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.</p> <p>(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:</p> <p>Propylene glycol (esters)</p>	21CFR177.2800
Propylene glycol esters	<p>PART 177 -- INDIRECT FOOD ADDITIVES: POLYMERS</p> <p>Subpart C--Substances for Use Only as Components of Articles Intended for Repeated Use</p> <p>Sec. 177.2800 Textiles and textile fibers.</p> <p>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.</p> <p>(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.</p> <p>(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.</p>	21CFR177.2800

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

Ingredient(s)	Rule	Citation	
Propylene glycol caprylate, propylene glycol caprate, and propylene glycol laurate	(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	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, glycerol monicaprate, and glycerol monolaurate) and propylene glycol (propylene glycol monocaprylate, propylene glycol monicaprate, 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.	40CFR180.1250

**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 <sup>2</sup> ). Samples were collected every 2 h for 24 h.	<sup>22</sup>
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 <sup>2</sup> ). 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.	<sup>14</sup>
Propylene glycol dicaprylate (5)	Increased the dermal penetration of diclofenac through rat abdominal skin using Franz cells (effective area 0.785 cm <sup>2</sup> ). Samples were collected for 24 h. The permeability index was calculated to be 0.32±0.06 cm/h.	<sup>14</sup>
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 <sub>0-8</sub> ) and maximum concentration (C <sub>max</sub> ) were 65.0±8.0 µg h/mL and 10.5±1.5 µg/mL at 4.3±1.3 h (t <sub>max</sub> ) 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.	<sup>14</sup>
Propylene glycol dicaprylate (concentration 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 <sup>2</sup> .	<sup>21</sup>
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: propylene glycol oleate, 1.91; propylene glycol dioleate, 2.11; propylene glycol linoleate, 1.68; propylene glycol dilinoleate, 1.44; propylene glycol linolenate, 1.70; and propylene glycol dilinolenate, 1.37. 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).	<sup>15</sup>
Propylene glycol dipelargonate (5)	Increased the dermal penetration of [ <sup>3</sup> H(G)] heparin sodium salt (0.49 mCi/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 <sup>2</sup> . The gel was placed in the donor cell and the receptor cell was sampled periodically over 24 h.	<sup>16</sup>

**Table 8.** Penetration enhancement studies of PG esters.

Ingredient(s); concentration (%)	Experiment/results	Reference
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 [ <sup>3</sup> 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	<sup>16</sup>
Propylene glycol dipelargonate (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 dipelargonate'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 <sup>2</sup> . 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.	<sup>17</sup>
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 µg/cm <sup>2</sup> /h, respectively.	<sup>18</sup>
Propylene glycol dipelargonate	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 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 dipelargonate. There was no difference in dermal penetration between the 2 tests.	<sup>23</sup>
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 diethylene glycol monoethyl ether (50:50) enhanced the dermal penetration of carbenoxolone through human abdominal skin using Franz cells. The k <sub>p</sub> 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 <sub>p</sub> =1.23).	<sup>20</sup>
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 <sup>2</sup> ). Samples were collected every 2 h for 24 h.	<sup>22</sup>
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 diethylene glycol monoethyl ether (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.	<sup>20</sup>
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 <sup>2</sup> ). 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.	<sup>19</sup>

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 Review 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*. 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 thiocolchicicide. *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 Pharmaceutics*. 1993;100:41-47.
19. Lafforgue, C, Eynard, I, Falson, F, Watkinson, AC, and Hadgraft, J. Percutaneous absorption of methyl nicotinate. *International Journal of Pharmaceutics*. 1995;121(1):89-93.
20. Hirata, K, Helal, F, Hadgraft, J, and Lane, ME. Formulation of carbinoxolone 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 permeation 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 chemical 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.
47. Personal Care Products Council. 12-23-2015. Concentration of Use Information for Additional Propylene Glycol Ester Ingredients (results of the October 2014 survey). Unpublished data submitted by Personal Care Products Council. 1 pages.