Amended Safety Assessment of PEG Propylene Glycol Derivatives as Used in Cosmetics

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The 2016 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.

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1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢ cirinfo@cir-safety.org

ABSTRACT

This is an amended safety assessment of PEG propylene glycol derivatives as used in cosmetics. These seven ingredients mostly function as surfactants and skin-conditioning agents. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed relevant data related to these ingredients. Because there were little data on these ingredients, the Panel relied on other CIR reports on related ingredients, the moieties, and component parts of these ingredients for read across and informational purposes. The Panel agreed that the caveat from the previous safety assessment, i.e., that ingredients containing PEGs should not be used on damaged skin, should be removed. The Panel concluded that these PEG propylene glycol derivatives are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

In 2001, a safety assessment of six PEG propylene glycol derivatives was published by the CIR Expert Panel with a conclusion of safe as used with the caveat that ingredients containing PEGs should not be used on damaged skin.[1] CIR evaluates the conclusions of previously-issued reports every 15 years to determine whether the conclusion should be reaffirmed or the safety assessment re-opened based on new data since the original safety assessment. In accordance with its Procedures, the Panel examined the data presented in this assessment to determine if the original conclusion could be reaffirmed. There was a significant increase in the number of uses of PEG-55 Propylene Glycol Oleate. Since the original safety assessment was published, PEGs were re-reviewed and the caveat that PEGs should not be used on damaged skin was removed by the Panel (in 2010).[2] Also, the Panel added PEG-6 Propylene Glycol Caprylate/Caprate to the group based on chemical and use similarities to the other ingredients in the original report. Thus, the Panel concluded that it was appropriate to re-open this safety assessment. Therefore, this report is a re-review of the PEG propylene glycol derivatives with the addition of PEG-6 Propylene Glycol Caprylate/Caprate, a PEG propylene glycol ester that has not yet been reviewed.

The seven ingredients in this safety assessment are:

PEG-25 Propylene Glycol Stearate
PEG-75 Propylene Glycol Stearate
PEG-120 Propylene Glycol Stearate
PEG-10 Propylene Glycol
PEG-8 Propylene Glycol Cocoate
PEG-55 Propylene Glycol Oleate
PEG-6 Propylene Glycol Caprylate/Caprate

According to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), these ingredients mostly function as surfactants and skin-conditioning agents (Table 1).[3]

There were little data available on the individual ingredients in the original safety assessment, and an extensive literature search revealed no new data on the PEG propylene glycol derivatives. In the original assessment, the Panel applied a read-across approach using data available for similar ingredients (analogs), and considered the data available for moieties and components of the ingredients;[1] the Panel used this same approach for this safety assessment.

Since the publication of the original report, CIR has conducted safety assessments or re-reviews of the component acids, related moieties, and other components of the PEG propylene glycol derivatives (Table 2). In re-reviews, PEG stearates (PEG monoesters), Oleic Acid and Stearic Acid were reaffirmed to be safe as used.[4-7] PEG diesters (including PEG distearates) were found to be safe when formulated to be non-irritating.[8] In 2010, the Panel removed the caveat that PEGs are not to be used on damaged skin; therefore, PEGs are safe for use in cosmetics in the present practices of use and concentration.[2] Summaries of the safety assessments conducted since the original review are presented in Table 3. Full reports can be viewed at the CIR website (http://www.cir-safety.org/ingredients).

Summaries of data on PEG propylene glycol derivatives from the original report are included in the appropriate sections in *italics*. Detailed data on these ingredients are available in the original report.[1]

CHEMISTRY

Definition and Structure

PEG propylene glycol derivatives are polyethylene glycol derivatives of propylene glycol, and in most cases, are the result of the esterification of a fatty acid (Figure 1). Definitions and structures of the ingredients included in this report are provided in Table 1.

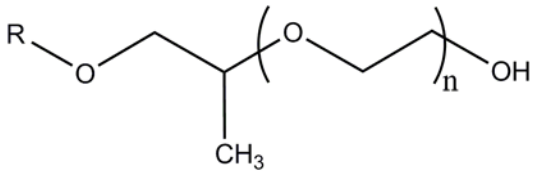


Figure 1. PEG propylene glycol derivatives, wherein "n" is equal to the number of the ethylene glycol repeat units and R is hydrogen or a fatty acid residue (e.g., in PEG-8 Propylene Glycol Cocoate, "n" is 8 and R represents the fatty acid residues derived from coconut.

Method of Manufacture

PEG-8 Propylene Glycol Cocoate

PEG-8 Propylene Glycol Cocoate is a specialty chemical that is prepared by esterification of polyoxyalkyl alcohols with lauric acid.

PEG-55 Propylene Glycol Oleate

The method for the production of PEG-55 Propylene Glycol Oleate is described as a two-step process. In the first step, propylene glycol is ethoxylated with 55 moles of ethylene oxide, yielding a polyether. In the second step, the polyether is esterified with oleic acid. No solvents are involved in this process.

Information on the methods of production of the following ingredients was not found in the published literature: PEG-25 Propylene Glycol Stearate, PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, and PEG-10 Propylene Glycol.

Impurities

Impurities data (provided only on PEG-55 Propylene Glycol Oleate) are summarized as follows: oleic acid (maximum 5% w/w), ethylene oxide (maximum 1 ppm), dioxane (maximum 5 ppm), polycyclic aromatic compounds (maximum 1 ppm), and heavy metals-lead, iron, cobalt, nickel, cadmium, and arsenic included (maximum 10 ppm combined).

USE

Cosmetic

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

According to VCRP survey data received in 2016, PEG-55 Propylene Glycol Oleate was reported to be used in 149 formulations, which included 1 leave-on product and 148 rinse-off products; the VCRP reported no uses for this ingredient in the 2001 safety assessment (Table 4).[9] In 2016, PEG-25 Propylene Glycol Stearate and PEG-8 Propylene Glycol Cocoate were reported to be used in 3 (reduced from 10) and 2 (increased from 1) formulations, respectively.

The results of the concentration of use survey submitted by the Council in 2016 indicate that PEG-55 Propylene Glycol Oleate has the highest reported maximum concentration of use, at up to 2% in bath soaps and detergents; this is a decrease from the maximum concentrations of use of up to 10% in fragrances reported in 1998.[10] The highest reported maximum concentration of use for a leave-on product was 1.2% PEG-8 Propylene Glycol Cocoate in tonics, dressings and other hair grooming aids; there is no reported concentration of use for leave-on products applied to the skin.

With the exception of PEG-55 Propylene Glycol Oleate and PEG-8 Propylene Glycol Cocoate, the reported frequency of use of these ingredients has decreased or remained at zero. PEG-25 Propylene Glycol Stearate, which was reported to be used at up to 5% in 1984, had no reported concentrations of use in 2016. PEG-8 Propylene Glycol Cocoate, which was reported to be used at up to 1.2% in 2016, was reported to be used up to 0.6% in 1998. PEG-25 Propylene Glycol Stearate is reported to be used in deodorants (no concentration of use was reported). Propylene Glycol Cocoate is no longer reported to be used in eye products or face powders.

The ingredients not in use based on both the 2016 VCRP data and Industry surveys are:

- PEG-75 Propylene Glycol Stearate
- PEG-120 Propylene Glycol Stearate

- PEG-10 Propylene Glycol
- PEG-6 Propylene Glycol Caprylate/Caprate

In some cases, reports of use were received from the VCRP, but concentration of use data were not provided. For example, PEG-25 Propylene Glycol Stearate is reported to be used in 3 cosmetic formulations, but no use concentration data were reported.

None of the PEG propylene glycol derivatives named in this report are restricted for use in any way under the rules governing cosmetic products in the European Union.[11]

TOXICOKINETIC STUDIES

No toxicokinetics studies on the PEG propylene glycol derivatives were found in the published literature, and unpublished data were not provided.

TOXICOLOGICAL STUDIES

In an acute oral toxicity study, PEG-25 Propylene Glycol Stearate was classified as relatively harmless in rats (LD_{50} >25.1 g/kg).

No new toxicological studies on the PEG propylene glycol derivatives were found in the published literature, and unpublished data were not provided.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

No DART studies on the PEG propylene glycol derivatives were found in the published literature, and unpublished data were not provided.

GENOTOXICITY STUDIES

No genotoxicity studies on the PEG propylene glycol derivatives were found in the published literature, and unpublished data were not provided.

CARCINOGENICITY STUDIES

No carcinogenicity studies on the PEG propylene glycol derivatives were found in the published literature, and unpublished data were not provided.

DERMAL IRRITATION AND SENSITIZATION STUDIES

No new dermal irritation or sensitization studies on the PEG propylene glycol derivatives were found in the published literature, and unpublished data were not provided.

Irritation

Animal

An antiperspirant product containing 2.0% PEG-25 Propylene Glycol Stearate was classified as practically nonirritating to the skin of rabbits in single insult occlusive patch tests.

Human

Clinical test data on 10% aqueous PEG-25 Propylene Glycol Stearate and 10% aqueous PEG-55 Propylene Glycol Oleate were negative in at least one patient suspected of having an allergy to cosmetic products. In another study, no significant differences in irritancy were observed between 20 normal subjects patch-tested with an antiperspirant containing 2.0% PEG-25 Propylene Glycol Stearate and 20 control subjects patch-tested with a different antiperspirant.

Sensitization

Animal

In a guinea pig sensitization test, PEG-25 Propylene Glycol Stearate was classified as nonallergenic at challenge concentrations of 25% and 50% in petrolatum.

Human

Negative results were reported in a sensitization study in which 50 volunteers were patch-tested with PEG-25 Propylene Glycol Stearate.

OCULAR IRRITATION STUDIES

An antiperspirant product containing 2.0% PEG-25 Propylene Glycol Stearate was classified as nonirritating to mildly irritating to the eyes of rabbits.

No new ocular irritation studies on the PEG propylene glycol derivatives were found in the published literature, and unpublished data were not provided.

SUMMARY

A safety assessment of six PEG propylene glycol derivatives was published in 2001 by the CIR Panel with a conclusion of safe as used. In accordance with its procedures, CIR evaluates the conclusions of previously issued reports every 15 years to determine whether the conclusion should be reaffirmed or the safety assessment re-opened. There was a significant increase in the number of uses of PEG-55 Propylene Glycol Oleate. Since the original safety assessment was published, PEGs were re-reviewed and the caveat that PEGs should not be used on damaged skin was removed by the Panel. Also, the Panel added PEG-6 Propylene Glycol Caprylate/Caprate to the group based on chemical and use similarities to the other ingredients in the original report. Thus, the Panel concluded that it was appropriate to re-open this safety assessment. Therefore, this report is a re-review of the PEG propylene glycol derivatives with the addition of PEG-6 Propylene Glycol Caprylate/Caprate, a PEG propylene glycol ester that has not yet been reviewed.

According to the *Dictionary*, these ingredients mostly function as surfactants and skin-conditioning agents.

Because there were limited data available on the individual ingredients in the original safety assessment, the Panel applied a read-across approach using data on analogues, and on moieties and components of the individual ingredients. An extensive literature search revealed no new data on the PEG propylene glycol derivatives.

The VCRP survey data received in 2016 shows that PEG-55 Propylene Glycol Oleate was reported to be used in 149 formulations, which included 1 leave-on product and 148 rinse-off products; there were no reported uses for this ingredient in the 2001 safety assessment. PEG-25 Propylene Glycol Stearate and PEG-8 Propylene Glycol Cocoate were reported to be used in 3 and 2 formulations, respectively.

Based on the results of the concentration of use survey submitted by the Council in 2016, PEG-55 Propylene Glycol Oleate has the highest reported maximum concentration of use at up to 2% in bath soaps and detergents; this is a decrease from up to 10% used in fragrances in 1998. In 2016, the highest reported maximum concentration of use for leave-on products was for 1.2% PEG-8 Propylene Glycol Oleate in tonics, dressings and other hair grooming aids; there is no reported concentration of use for leave-on products with dermal exposure.

With the exception of PEG-55 Propylene Glycol Oleate and PEG-8 Propylene Glycol Cocoate, the frequency of use of these ingredients has decreased or remained at zero. PEG-8 Propylene Glycol Cocoate is no longer reported to be used in eye products or face powders.

DISCUSSION

The Panel reopened the safety assessment of the PEG propylene glycol derivatives to address the increase in the frequency of use of PEG-55 Propylene Glycol Oleate and to remove the caveat that PEGs are not to be used on damaged skin. The Panel also found it appropriate to add PEG-6 Propylene Glycol Caprylate/Caprate to this safety assessment because of its chemical and use similarities to the ingredients in the original report.

The Panel noted the lack of new safety data on the PEG propylene glycol derivatives in this safety assessment. In the original safety assessment, there were limited available safety data on some of the ingredients. These limited data are supported by the data from other CIR safety assessments on related ingredients (analogs), the moieties, and components of these ingredients. The Panel determined that the close structural similarity and similar use data permitted inference about the safety of other members of the group.

The Panel also expressed concern about pesticide residues and heavy metals that may be present in these ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

In the original safety assessment of PEGs, the Panel concluded that PEG-based ingredients should not be used on damaged skin because of concern about sensitization and nephrotoxicity in burn patients treated with a PEG-based antimicrobial. However, PEGs were re-reviewed in 2010 and the data showed that there was no safety concern with using

PEGs on damaged skin. The Panel removed the caveat regarding the use of PEGs on damaged skin. This conclusion reflects the Panel's recommendation to apply this change to all reports that included PEG-containing ingredients.

CONCLUSION

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

PEG-25 Propylene Glycol Stearate
PEG-75 Propylene Glycol Stearate*
PEG-120 Propylene Glycol Stearate*
PEG-10 Propylene Glycol*
PEG-8 Propylene Glycol Cocoate
PEG-55 Propylene Glycol Oleate
PEG-6 Propylene Glycol Caprylate/Caprate*

This conclusion supersedes the earlier conclusion issued by the Expert Panel in 2001.

* Not reported to be in current use. 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

Table 1. Definitions and functions of the PEG propylene glycol derivatives in this safety assessment.[3,CIR staff]

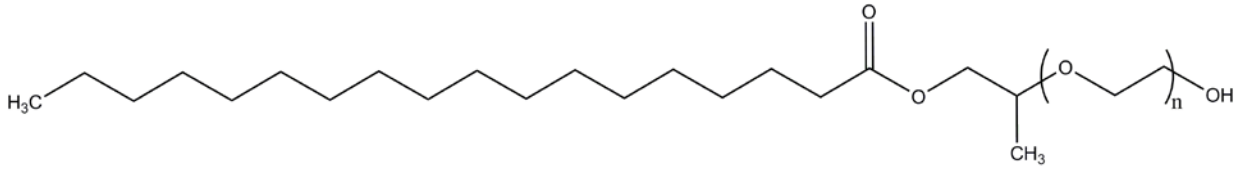
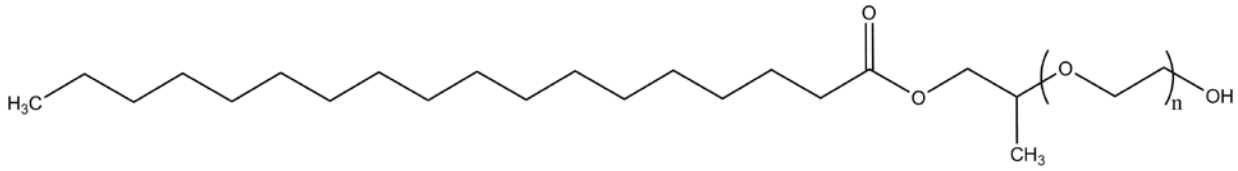
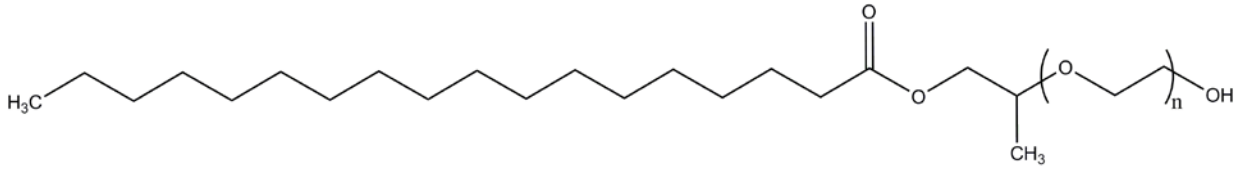
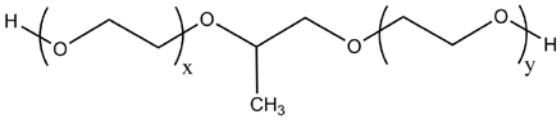
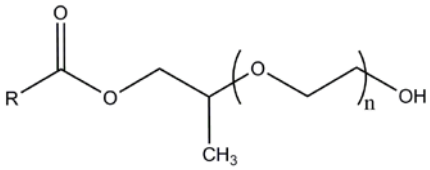
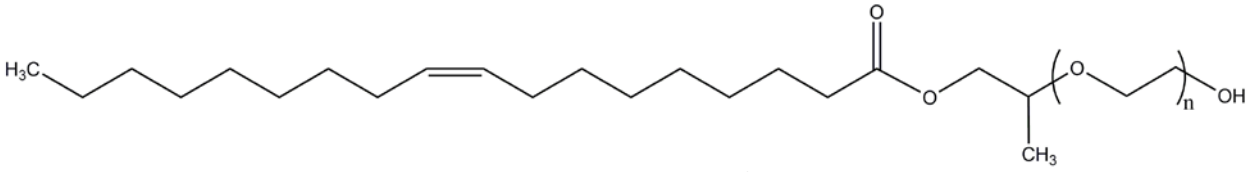
Ingredient	Definition	Function(s)
PEG-25 Propylene Glycol Stearate	PEG-25 Propylene Glycol Stearate is the polyethylene glycol ether of Propylene Glycol Stearate that conforms generally to the formula:  where n has an average value of 25	Surfactant – Cleansing agent; surfactant – solubilizing agent
PEG-75 Propylene Glycol Stearate	PEG-75 Propylene Glycol Stearate is the polyethylene glycol ester of Propylene Glycol Stearate that conforms to the formula:  where n has an average value of 75	Surfactant – Cleansing agent; surfactant – solubilizing agent
PEG-120 Propylene Glycol Stearate	PEG-120 Propylene Glycol Stearate is the polyethylene glycol ether of Propylene Glycol Stearate that conforms generally to the formula:  where n has an average value of 120	Surfactant – Cleansing agent; surfactant – solubilizing agent
PEG-10 Propylene Glycol	PEG-10 Propylene Glycol is the polyethylene glycol ether of propylene glycol that conforms generally to the formula:  where x + y has an average value of 10	Skin-conditioning agent – humectant; solvent
PEG-8 Propylene Glycol Cocoate 126645-98-5	PEG-8 Propylene Glycol Cocoate is the polyethylene glycol ether of propylene glycol cocoate that conforms generally to the formula:  where RCO- represents the coconut fatty radical and n has an average value of 8	Skin-conditioning agent – emollient; surfactant – emulsifying agent
PEG-55 Propylene Glycol Oleate	PEG-55 Propylene Glycol Oleate is the polyethylene glycol ether of propylene glycol oleate. It conforms generally to the formula:  where n has an average value of 55	Surfactant – cleansing agent; surfactant – solubilizing agent

Table 1. Definitions and functions of the PEG propylene glycol derivatives in this safety assessment.[3,CIR staff]

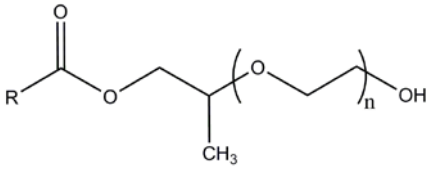
Ingredient	Definition	Function(s)
PEG-6 Propylene Glycol Caprylate/Caprate	PEG-6 Propylene Glycol Caprylate/Caprate is the organic compound that conforms generally to the formula:  where RCO- represents the capryloyl/caproyl moiety and n has an average value of 6	Skin-conditioning agent – emollient; surfactant – emulsifying agent

Table 2. Previously reviewed related ingredients and components

Component	Conclusion (year; maximum concentrations of use)	Reference
PEG Diesters (including PEG Distearates)	Safe in cosmetics when formulated to be non-irritating (2015; 12% in leave-ons and 33.2% in rinse-offs)	8
PEG Stearates	Safe as cosmetic ingredients in the present practices of concentration and use (2005 re-review, not reopened; 9% in leave-ons and 7% in rinse-offs)	4
PEGs	Safe in the present practices of use and concentration[a] (2010; 66% in leave-ons and 17% in rinse-offs, 85% in hair products, 67% in bath products)	2
Oleic Acid and Stearic Acid	Safe in the present practices of use and concentration (2006; 9% in leave-ons and 4% in rinse-offs, 20% in hair products, 15% in bath products)	5,12

[a] The CIR Expert Panel removed the caveat that PEGs should not be used on damaged skin.

Table 3. Summaries of most recent reports on the moieties and components of PEG propylene glycol derivatives.

Ingredient Group	Summary	Reference
PEG Diesters (including PEG Distearates)	Dermal Penetration Enhancement - Neither PEG-8 dioleate nor PEG-8 dilaurate at 5% enhanced the dermal penetration of ketoprofen through mouse skin when added to a drug delivery plaster preparation. PEG-12 dioleate at 5% enhanced the dermal penetration of ketoprofen with an ER of 1.54±0.22. Acute Oral Toxicity - The oral LD_{50}s reported for PEG-4 diheptanoate in rats ranged from >2 to >25 g/kg. Inhalation - Vaporized PEG-4 diheptanoate was lethal within 4 h to rats at 14.2 mg/L but not at 13.7 mg/L. Clinical signs included salivation, red nasal discharge, and irregular respiration during the exposure period. The rats recovered quickly during the recovery period. Oral Toxicity - There were no adverse effects observed when 1 g/kg PEG-4 diheptanoate was administered by gavage to rats for 28 consecutive days. Inhalation Toxicity - In the repeated inhalation exposure study of vaporized PEG-4 diheptanoate at 1.0 mg/L for 6 h/day, 5 days/week for 4 weeks, clinical signs for rats were mild salivation, reduced response to auditory stimulation, and shallow, rapid respiration sporadically during the exposure periods. Mutagenicity - PEG-4 diheptanoate was not mutagenic in a reverse mutation assay up to 10 000 µg/plate using *S. typhimurium* or in a mammalian cell gene mutation assay using Chinese hamster ovary cells up to 23.9 mM. Dermal Irritation - At 100%, PEG-4 diheptanoate caused slight to moderate erythema and edema when administered to rabbit skin for 24 h. There was no skin irritation observed in guinea pigs treated with PEG-4 diheptanoate at 5% or 25% but mild irritation was observed in 1 of 3 guinea pigs at 50% and in 3 of 3 at 100%. Ocular Irritation - There were no lasting reactions observed when PEG-4 diheptanoate at 100% was instilled in the conjunctival sac of rabbits. Sensitization - In a dermal sensitization study using guinea pigs, PEG-4 diheptanoate at 5% or 25% was not sensitizing when challenged at 5% or 50%.	[8]
PEG Stearates	Re-Review Summary - A safety assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates was published in 1983 with the conclusion "safe as cosmetic ingredients in the present practices of concentration and use" (Elder 1983). Studies available since that safety assessment was completed, along with updated information regarding use concentrations, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment. In 1979, PEG Stearates were used in 374 cosmetic products, typically at concentrations ranging from >0.1% to 10%. In 2002, there were uses reported in 1459 products, typically at concentrations <4%.	[4]
PEGs	Metabolism (Absorption and Excretion) - In metabolism studies with rats, rabbits, dogs, and humans, the lower molecular weight PEGs were absorbed by the digestive tract and excreted in the urine and feces. The greater molecular weight PEGs were absorbed more slowly or not at all. For example, PEG-8 is rapidly absorbed by the GI tracts of several mammalian species and excreted primarily in the urine with less excretion in the feces and PEG-150 in water was not absorbed from the gastrointestinal tract of humans. Acute Toxicity - In general, PEGs had low acute oral toxicity. The higher-molecular-weight PEGs appeared to be less toxic than the lower PEGs in oral studies. Oral LD_{50} values in rodents ranged from 15 to 22 g/kg, and the intravenous LD_{50} in rodents ranged from 7.3 to 9.5 g/kg. The LC_{50} of aerosolized Triethylene Glycol in rats was greater than 3.9 mg/L. Repeated Dose Toxicity - PEG-8 administered for 13 weeks of gavage treatment in Fischer 344 rats at doses of 1.1, 2.8 and 5.6 g/kg/day for resulted in no mortality or changes in hematology or clinical chemistry measurements attributed to PEG-8. Inhalation of aerosolized PEG-75 at concentrations up to 1008 mg/m^3 five times/week for 2 weeks caused little or no toxicity in rats. Dermal Irritation and Sensitization - Dermal exposure to PEGs was not irritating in rabbits in several studies. Overall, PEGs were not irritating to the skin of rabbits and guinea pigs. PEG-75 was not a sensitizer in guinea pigs. Ocular Irritation - Ocular exposure to Triethylene Glycol in rabbits produced no corneal injury, however all rabbits displayed acute iritis and minor transient conjunctival irritation. Overall, PEGs cause mild, transient ocular irritation in rabbits. Reproductive/Developmental Toxicity - In reproductive and developmental toxicity studies in rats and mice, PEGs did not produce biologically significant maternal toxicity or embryotoxicity or teratogenicity. Mutagenicity - PEGs were not mutagenic or genotoxic in the Ames assay, a Chinese Hamster ovary cell mutation assay, an *in vivo* bone marrow assay, a dominant lethal assay, the mouse TK+/-+TK-/- forward mutation assay, or a sister chromosome exchange assay. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to various test animals. Dermal Irritation - In clinical studies, PEG-6 and PEG-8 caused mild cases of immediate hypersensitivity. Extensive clinical studies of patients with normal skin demonstrate that PEG-8 was not a sensitizer and one large study in patients with eczematous skin, only 0.3% positive reactions were seen to PEG-8. Cases of delayed allergic contact dermatitis have been reported in burn patients treated with antimicrobial creams with a PEG vehicle. Use of antimicrobial creams with a PEG vehicle have been associated with renal toxicity when applied	[2]

Table 3. Summaries of most recent reports on the moieties and components of PEG propylene glycol derivatives.

Ingredient Group	Summary	Reference
	to burned skin. Measured values for dermal penetration of PEG-4 as a function of number of tape strippings demonstrated that tape stripping can increase dermal penetration. Exposure estimates that combined type and use quantity of cosmetic product, concentration of PEGs, and dermal penetration were used to determine exposures to skin in which tape stripping had removed the stratum corneum. These exposures were used with the renal toxicity NOEL to develop a margin of safety calculation, with values ranging from 113 to over 2,600.	
Oleic Acid and Stearic Acid	Metabolism - Fatty acids are absorbed, digested, and transported in animals and humans. Radioactivity from labeled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph. β-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl-CoA. Although placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied, no studies on the teratogenicity of Oleic, Laurie, Palmitic, Myristic, or Stearic Acids were found. High intake of dietary saturated fatty acids has been associated with the incidence of atherosclerosis and thrombosis. Acute Toxicity - Little acute toxicity was observed when Oleic, Laurie, Palmitic, Myristic, or Stearic Acid, or cosmetic formulations containing these fatty acids at concentrations of 2.2% to 13% were given to rats orally at doses of 15 to 19 g/kg. Repeated Dose toxicity - In subchronic oral toxicity studies, Oleic, Palmitic, and Stearic Acids were fed to rats in diets at doses ranging from 5% to 50%. Thrombosis, aortic atherosclerosis, anorexia, and mortality were observed. In a subchronic study, no signs of toxicity were observed in chicks fed 5% dietary Stearic and Oleic Acids. Feeding of 15% dietary Oleic Acid to rats in a chronic study resulted in normal growth and general health, but reproductive capacity of female rats was impaired. Results from topical application of Oleic Acid (at concentrations from 50% Oleic Acid to commercial grade Oleic Acid) to the skin of mice, rabbits, and guinea pigs ranged from no toxicity to signs of erythema, hyperkeratosis, and hyperplasia. lntradermal administration to guinea pigs of 25% Oleic Acid to commercial grade Oleic Acid resulted in local inflammation and necrosis. A formulation containing 2.2% Palmitic Acid was considered nontoxic to rabbits. A topically applied dose of 5 g/kg commercial grade Stearic Acid was not toxic to rabbits. lntradermal administration of I0 to 100 mM Stearic Acid to guinea pigs and rabbits resulted in mild erythema and slight induration. Dermal Irritation - Eighteen mmol% concentrations of the fatty acids topically applied to the of the external ear canals of albino rabbits for 6 weeks produced a range of responses, varying from no irritation with Stearic Acid to slight irritation with Myristic and Palmitic Acids to defined erythema, desquamation, and persistent follicular keratosis with Oleic and Laurie Acids. Slight local edema and no deaths were observed among NZW rabbits after 4 weeks of topical administration of product formulations containing 2.0% Stearic Acid. In 13-week dermal toxicity studies, 2 cosmetic product formulations containing, at most, 5% Stearic Acid produced moderate skin irritation in rats receiving 4.0 ml/kg and 227 mg/kg doses. All other physiological parameters were normal. In single insult occlusive patch tests for primary irritation, commercial grades of all 5 fatty acids, at doses of 35% to 65% in vehicles (Stearic Acid only) and at 1% to 13% in cosmetic product formulations (other fatty acids), produced no to moderate erythema and slight, if any, edema in the skin of rabbits. Slight increases in irritation were observed in the short-term repeated patch tests (daily for 3 to 14 days) of Oleic and Myristic Acids. Sensitization - In maximization studies with 2 cosmetic product formulations containing 5.08% Oleic Acid and 1.0% Stearic Acid, slight reactions were observed to challenge patches. These formulations were considered weak, grade I sensitizers In another maximization study, after intradermal induction and booster injections of a formulation containing 3.5% Stearic Acid, reactions to topical challenge applications of the formulation were few and minimal in intensity. Photosensitization - Skin lotion formulations containing 2.8% Stearic Acid were not photosensitizing to the skin of Hartley guinea pigs. Comedogenicity - Oleic Acid and its UVA-induced peroxides were associated with increased comedo formation on the treated ears of two species of rabbits. Ocular Irritation - In ocular irritation studies, the fatty acids alone and at concentrations ranging from 1% to 19.4% in cosmetic product formulations produced no to minimal irritation after single and multiple (daily, 14-day) instillations into the eyes of albino rabbits. Irritation was primarily in the form of very slight conjunctival erythema. A single instillation of Laurie Acid also produced cornea1 opacity and iritis. Mutagenicity - Although Oleic and Laurie Acids induced mitotic aneuploidy in *in vitro* mutagenicity tests, both have been indicated as inhibitors of mutagenicity produced by positive controls, such as N-nitrosopyrrolidine and sodium azide, in other tests. Stearic Acid was inactive in aneuploidy induction tests and in the Ames test, and it did not inhibit mutagenicity, as did Oleic and Laurie Acids. No increase of mitotic crossing-over events was induced by Oleic, Laurie, or Stearic Acids. Oleic Acid did not increase the number of sister chromatid exchanges over background. Carcinogenicity - In carcinogenicity studies, no malignant tumors were induced by repeated	5

Table 3. Summaries of most recent reports on the moieties and components of PEG propylene glycol derivatives.

Ingredient Group	Summary	Reference
	subcutaneous injections of 1-16.5 mg Oleic Acid in two species of mice. Intestinal and gastric tumors were found in mice receiving dietary Oleic Acid at daily concentrations up to 200 mg/mouse. Treatment of mice with repeated subcutaneous injections of 25 and 50 mg Laurie Acid was not carcinogenic. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of 25 and 50 mg Palmitic and up to 82 mg Stearic Acid. Feeding of up to 50 g/kg/day dietary Stearic Acid to mice was not carcinogenic. Irritation - In clinical primary and cumulative irritation studies, Oleic, Myristic, and Stearic Acids at concentrations of 100% or 40% to 50% in mineral oil were nonirritating. Mild to intense erythema in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies were produced by cosmetic product formulations containing 2% to 93% Oleic, Palmitic, Myristic, or Stearic Acid and were generally not related to the fatty acid concentrations in the formulations. Sensitization - In clinical repeated insult patch tests (open, occlusive, and semiocclusive), maximization tests, and prophetic patch tests with cosmetic product formulations containing Oleic, Laurie, Palmitic, and Stearic Acids at concentrations ranging from < 1% to 13%, no primary or cumulative irritation or sensitization was reported. A few subjects (< 5% of the approximate 4000 subjects tested) reacted to a few, isolated induction patches. Slight, if any, reactions were observed after challenge patching at original or adjacent sites on the upper backs or forearms of some subjects (-< 2%). Intensity of observed reactions to the formulations was not directly related to the concentrations of the fatty acid ingredients. Cosmetic product formulations containing 1% to 13% Oleic, Palmitic, or Stearic Acid produced no photosensitization in human subjects. There were slight reactions to a few induction patches. Use Studies - There was no treatment-related ocular irritation in female subjects, some of whom were contact lens wearers, involved in two 3-week exaggerated-use studies of mascara formulations containing 2 and 3% Oleic Acid. These formulations were used in combination with other eye area cosmetics. Re-Review Summary - A safety assessment of the Oleic Acid group was published in 1987 with a conclusion that these ingredients are safe in present practices of use and concentration in cosmetics New studies regarding these fatty acids available since then, along with updated information regarding uses and use concentrations, were considered by the 2002 CIR Expert Panel The Panel determined to not reopen this safety assessment. Oleic Acid usage increased from 424 in 1981 to 1131 in 2002, based on industry voluntary reports provided to FDA. An industry survey in 2004 indicated that use concentrations range from 0.00004% to 20%, within the range reported in 1981. Lauric Acid usage increased from 22 in 1981 to 121 in 2002, based on industry voluntary reports provided to FDA. An industry survey in 2004 indicated that use concentrations range from 0.00003% to 11%, within the range reported in 1981. Palmitic Acid usage increased from 29 in 1981 to 132 in 2002, based on industry voluntary reports provided to FDA. An industry survey in 2004 indicated that use concentrations range from 0.00006% to 20%, within the range reported in 1981. Myristic Acid usage increased from 36 in 1981 to 73 in 2002, based on industry voluntary reports provided to FDA. An industry survey in 2004 indicated that use concentrations range from 0.00001% to 38%, within the range reported in 1981. Stearic Acid usage decreased from 2465 in 1981 to 2133 in 2002, based on industry voluntary reports provided to FDA. An industry survey in 2004 indicated that use concentrations range from 0.000002% to 43%, within the range reported in 1981. The most recent information now constitutes the present practices of use and concentration The newly available studies reported findings consistent with the data in the original safety assessment. One area not covered in the original report was reproductive and developmental toxicity. One new study was available that demonstrated little or no toxicity to sperm cells by Oleic Acid, Palmitic Acid, and Stearic Acid. These fatty acids may be plant derived In such cases, established limits for pesticide and heavy metal residues should not be exceeded (lead ≤10 ppm, arsenic ≤3 ppm, mercury ≤1 ppm, total PCB/pesticide ≤40 ppm, with ≤10 ppm for any specific pesticide residue). These fatty acids may also be derived from animal sources, including beef. The Panel agrees with the Food and Drug Administration's position that tallow derivatives, including these fatty acids, would not present any risk of transmissible encephalopathies.	

ER=enhancement ratio

Table 4. Current and historical frequency and concentration of use of PEG propylene glycol derivatives according to duration and exposure.[9,10]

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2016	1998	2016	1984**	2016	1998	2016	1998
	PEG-25 Propylene Glycol Stearate				PEG-8 Propylene Glycol Cocoate			
Totals*	**3**	**10**	**NR**	**1-5[c]**	**2**	**1**	**1.2**	**0.3-0.6**
Duration of Us								
Leave-On	*3*	*3*	*NR*	*NR*	*2*	*1*	*1.2*	*0.3-0.6*
Rinse-Off	*NR*	*7*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	0.6
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	1[a];1[b]	NR	NR	1[a]	1[a]	NR	NR
Incidental Inhalation-Powder	NR	1[b]	NR	NR	NR	NR	NR	0.3
Dermal Contact	3	9	NR	NR	1	NR	NR	0.3-0.6
Deodorant (underarm)	3[a]	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	1	NR	NR	1	1	1.2	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	6	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	2016	1998	2016	1998
	PEG-55 Propylene Glycol Oleate			
Totals*	**149**	**NR**	**0.1-2**	**1-10**
Duration of Use				
Leave-On	*1*	*NR*	*NR*	*1-10*
Rinse-Off	*148*	*NR*	*0.1-2*	*1-5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	1-10
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	71	NR	1.8-2	1-10
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	78	NR	0.1-0.4	1-5
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	67	NR	2	1-5
Baby Products	NR	NR	NR	NR

NR – no reported use

*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.

**at the time of the 2001 safety assessment, concentration of use data were not reported by the FDA; 1984 data were presented when data from Industry were not provided.

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

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] The total range of the concentration of use was provided but a list of product categories was not provided.

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