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Safety Assessment of PEGylated Alkyl Glycerides as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 60 PEGylated alkyl glycerides. PEGylated alkyl glycerides are mono-, di-, and/or triglycerides that have been modified with ethylene glycol repeat units (in the starting material form as epoxide). Most of the PEGylated alkyl glycerides are reported to function as skin-conditioning agents or surfactants. The Panel reviewed the available animal and clinical data as well as data from the 1999 report for the 5 polyethylene glycol (PEG) glyceryl cocoates and the 2012 report of PEGylated oils, to determine the safety of these ingredients. The Panel concluded these ingredients are safe in the current practices of use and concentration when formulated to be nonirritating; this conclusion supersedes the 1999 conclusion issued on 5 PEG glyceryl cocoate ingredients.

Keywords

cosmetics, safety, PEGylated alkyl glycerides

Introduction

This report assesses the safety of the following 60 PEGylated alkyl glycerides as used in cosmetic formulations:

Polyethylene glycol (PEG)-6 Almond Glycerides
PEG-20 Almond Glycerides
PEG-35 Almond Glycerides
PEG-60 Almond Glycerides
PEG-192 Apricot Kernel Glycerides
PEG-11 Avocado Glycerides
PEG-14 Avocado Glycerides
PEG-11 Babassu Glycerides
PEG-42 Babassu Glycerides
PEG-4 Caprylic/Capric Glycerides
PEG-6 Caprylic/Capric Glycerides
PEG-7 Caprylic/Capric Glycerides
PEG-8 Caprylic/Capric Glycerides
PEG-11 Cocoa Butter Glycerides
PEG-75 Cocoa Butter Glycerides
PEG-7 Cocoglycerides
PEG-9 Cocoglycerides
PEG-20 Corn Glycerides
PEG-60 Corn Glycerides
PEG-20 Evening Primrose Glycerides
PEG-60 Evening Primrose Glycerides
PEG-3 Glyceryl Cocoate
PEG-7 Glyceryl Cocoate*
PEG-30 Glyceryl Cocoate*
PEG-40 Glyceryl Cocoate*
PEG-78 Glyceryl Cocoate*
PEG-80 Glyceryl Cocoate*
PEG-5 Hydrogenated Corn Glycerides
PEG-8 Hydrogenated Fish Glycerides
PEG-20 Hydrogenated Palm Glycerides
PEG-6 Hydrogenated Palm/Palm Kernel Glyceride
PEG-16 Macadamia Glycerides
PEG-70 Mango Glycerides
PEG-13 Mink Glycerides
PEG-25 Moringa Glycerides
PEG-42 Mushroom Glycerides
PEG-2 Olive Glycerides
PEG-6 Olive Glycerides
PEG-7 Olive Glycerides
PEG-10 Olive Glycerides
PEG-40 Olive Glycerides

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PEG-18 Palm Glycerides
PEG-12 Palm Kernel Glycerides
PEG-45 Palm Kernel Glycerides
PEG-60 Passiflora Edulis Seed Glycerides
PEG-60 Passiflora Incarnata Seed Glycerides
PEG-45 Safflower Glycerides
PEG-60 Shea Butter Glycerides
PEG-75 Shea Butter Glycerides
PEG-75 Shorea Butter Glycerides
PEG-35 Soy Glycerides
PEG-75 Soy Glycerides
PEG-2 Sunflower Glycerides
PEG-7 Sunflower Glycerides
PEG-10 Sunflower Glycerides
PEG-13 Sunflower Glycerides
PEG-5 Tsubakiate Glycerides
PEG-10 Tsubakiate Glycerides
PEG-20 Tsubakiate Glycerides
PEG-60 Tsubakiate Glycerides
*originally reviewed in 1999

PEGylated alkyl glycerides are mono-, di-, and/or triglycerides that have been modified with ethylene glycol repeat units (in the starting material form as epoxide). The number of units (eg, "40" in PEG-40 Glyceryl Cocoate) is representative of an average number of ethylene glycol repeat units (ie, PEG-40 Glyceryl Cocoate contains some PEG-39 and PEG-41 glyceryl cocoates, in addition to PEG-40). Most of the PEGylated alkyl glycerides are reported to function as skin-conditioning agents or surfactants[1] (Table 1). As above, ingredient names follow the International Nomenclature Committee conventions for cosmetic labeling (ie, capitalization of the first letter of each word, and no italicization); such nomenclature conventions are utilized throughout this report when denoting specific cosmetic ingredients.

Five PEG glyceryl cocoate ingredients, indicated above, have been reviewed previously, and in 1999, the Expert Panel for Cosmetic Ingredient Safety (Panel) concluded those ingredients were safe as used in rinse-off products and safe at up to 10% in leave-on products. According to the Discussion in that report, the basis of the concentration limit for leave-on products was derived from the ocular and dermal sensitization data.[2] At the September 2014 meeting, the Panel determined that it is appropriate to include those ingredients in this report, and where appropriate, information from the 1999 report is included in this safety assessment.

In 2012, the Panel reviewed a very similar family of ingredients, the PEGylated oils, and concluded the PEGylated oils are safe as used in cosmetics when formulated to be nonirritating.[3] PEGylated oils are complex mixtures of the etherification and transesterification products of fatty acid glycerides and fatty acids derived from identified plant sources with the necessary equivalents of ethylene oxide to achieve the desired polyethylene glycol (PEG) length. The only difference between the PEGylated oils and the PEGylated alkyl glycerides is that prior to the PEGylation step in the production of PEGylated alkyl glycerides, a further refinement of the oil has been performed to retain only the glycerides and in some cases refined (or partially de-esterified) to only the mono-, di-, or triglycerides. In other words, PEGylated alkyl glycerides are a subfraction of PEGylated oils. PEGylated oils mostly contain PEGylated triglycerides and some PEGylated fatty acids (ie, not attached to a molecule of glycerin), while PEGylated alkyl glycerides contain only specific PEGylated glycerides and no (or virtually no) PEGylated fatty acids.

As an example, the PEGylated oil, almond oil PEG-6 esters, consists mostly of triglycerides, wherein the 6 stoichiometric equivalents of ethylene oxide have been inserted between the glycerin core and the attached almond fatty acids. Free almond fatty acids that have been PEGylated to some degree may also be present. In contrast, the PEGylated alkyl glyceride, PEG-6 Almond Glycerides, consists mostly of mono- and diglycerides, wherein 6 stoichiometric equivalents of ethylene oxide have (1) been inserted between the glycerin core and the attached almond fatty acids, (2) etherified the free alcohol(s) of the glyceride, or (3) both. No appreciable free almond fatty acids should be present.

The materials that are used in the manufacture of the PEGylated alkyl glycerides, that is, ethylene oxide (and any incidentally generated free PEG chains) and the applicable glycerides (and the oils from which they are derived), may be present as impurities in the final ingredient. The Cosmetic Ingredient Review (CIR) has reviewed the safety of the majority of the component ingredients, and although the information from those safety assessments may not be relevant for read-across, the reports have some relevance because starting materials may be present as residual impurities. Therefore, summary information and the conclusion of each relevant report are provided (Table 2).[4-11] Previous Panel reports are available on all component oils except hydrogenated corn oil (although a report on corn oil was available), hydrogenated fish oil, mushroom oil, and *Passiflora incarnata* oil. Additionally, the conclusion and a data summary from the PEGylated oils[12] report are provided (Table 2).

Chemistry

Definition and Structure

PEGylated alkyl glycerides are mono-, di-, and/or triglycerides that have been modified with ethylene glycol repeat units (in the starting material form as epoxide).

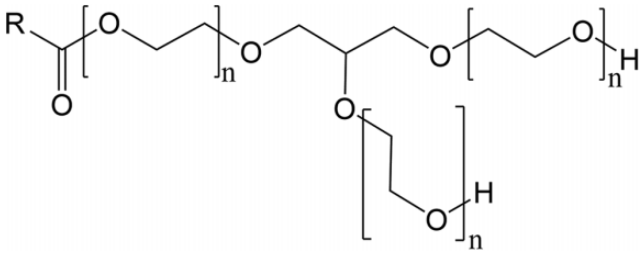
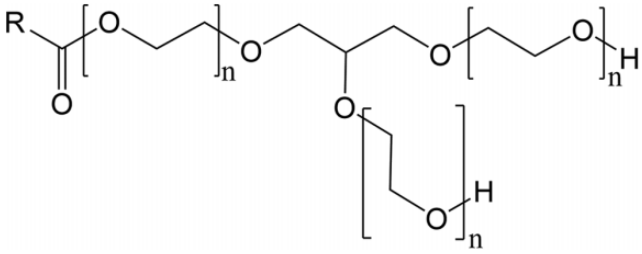
Just as oils and other PEGylated materials are mixtures, the PEGylated alkyl glycerides are mixtures. PEGylation of glycerides occurs not only as an etherification of the free alcohol groups of the glycerides with ethylene oxide groups but also as a transesterification which results in net insertion of PEG groups between the glyceryl and fatty acid components of the glyceride.[13,14] For example, the glycerin core of PEG-6 Caprylic/Capric Glycerides is ethoxylated (Figure 2), wherein the sum of all n is equal to the number of ethylene oxide repeat units and need not be the same at all places of the molecule.

Table 1. Definitions and Functions of the Ingredients in this Safety Assessment.

Ingredients (CAS Nos.)	Definitions[1]; CIR Staff	Functions[1]
PEG-6 Almond Glycerides (124046-50-0; generic)	A polyethylene glycol derivative of the mono- and diglycerides from almond oil with an average of 6 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from almond oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all n is 6.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-20 Almond Glycerides (124046-50-0; generic)	A polyethylene glycol derivative of the mono- and diglycerides from almond oil with an average of 20 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from almond oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all n is 20.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-35 Almond Glycerides (124046-50-0; generic)	A polyethylene glycol derivative of the mono- and diglycerides from almond oil with an average of 35 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from almond oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all n is 35.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-60 Almond Glycerides (124046-50-0; generic)	A polyethylene glycol derivative of the mono- and diglycerides from almond oil with an average of 60 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from almond oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all n is 60.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-192 Apricot Kernel Glycerides	A polyethylene glycol derivative of the mono- and diglycerides from apricot kernel oil with an average of 192 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from apricot kernel oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 192.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-11 Avocado Glycerides (103819-44-9; generic)	A polyethylene glycol derivative of mono- and diglycerides from avocado oil with an average of 11 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from avocado oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 11.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-14 Avocado Glycerides (103819-44-9; generic)	A polyethylene glycol derivative of mono- and diglycerides from avocado oil with an average of 14 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from avocado oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 14.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-11 Babassu Glycerides	A polyethylene glycol derivative of the mono- and diglycerides derived from babassu oil with an average of 11 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from babassu oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 11.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-42 Babassu Glycerides	A polyethylene glycol derivative of the mono- and diglycerides derived from babassu oil with an average of 42 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from babassu oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 42.*	Skin-Conditioning agent—emollient; surfactant—emulsifying agent
PEG-4 Caprylic/Capric Glycerides	A polyethylene glycol derivative of a mixture of mono-, di-, and triglycerides of caprylic and capric acids with an average of 4 moles of ethylene oxide; *wherein the average sum of all cases of n in Figure 2 is 4.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-6 Caprylic/Capric Glycerides (361459-38-3)[80]	A polyethylene glycol derivative of a mixture of mono-, di-, and triglycerides of caprylic and capric acids with an average of 6 moles of ethylene oxide; *wherein the average sum of all cases of n in Figure 2 is 6.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-7 Caprylic/Capric Glycerides	A polyethylene glycol derivative of a mixture of mono-, di-, and triglycerides of caprylic and capric acids with an average of 7 moles of ethylene oxide; *wherein the average sum of all cases of n in Figure 2 is 7.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-8 Caprylic/Capric Glycerides	A polyethylene glycol derivative of a mixture of mono-, di-, and triglycerides of caprylic and capric acids with an average of 8 moles of ethylene oxide; *wherein the average sum of all cases of n in Figure 2 is 8.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-11 Cocoa Butter Glycerides	A polyethylene glycol derivative of the mono- and diglycerides derived from *Theobroma cacao* (cocoa) seed butter with an average of 11 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Theobroma cacao (cocoa) seed butter, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 11.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-75 Cocoa Butter Glycerides	A polyethylene glycol derivative of the glycerides derived from *Theobroma cacao* (cocoa) seed butter with an average of 75 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Theobroma cacao (cocoa) seed butter, where at least 1 R is a fatty acid, and the average sum of all cases of n is 75.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent

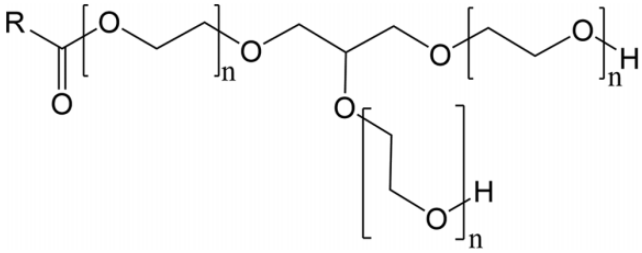
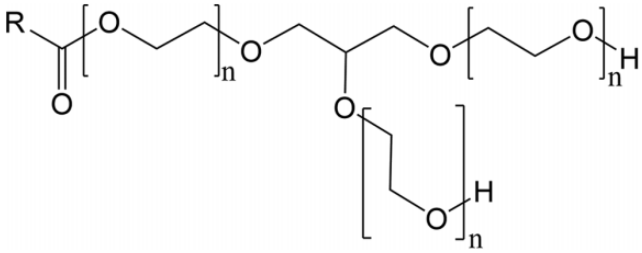
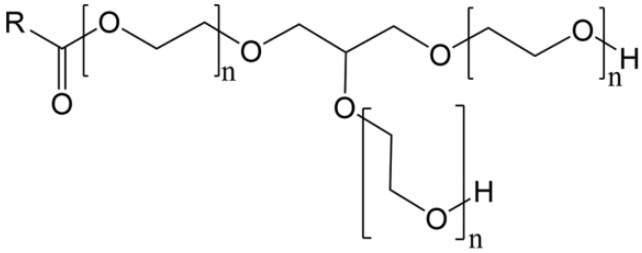
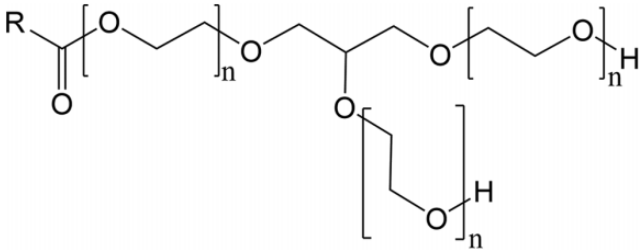
(continued)

Table 1. (continued)

Ingredients (CAS Nos.)	Definitions[1]; CIR Staff	Functions[1]
PEG-7 Cocoglycerides (67762-35-0; generic)	The polyethylene glycol derivative of the mono- and diglycerides of coconut oil with an average ethoxylation value of 7; *wherein R in Figure 1 is hydrogen or the fatty acid residues from coconut oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 7.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-9 Cocoglycerides (67762-35-0; generic)	The polyethylene glycol derivative of the mono- and diglycerides of coconut oil with an average ethoxylation value of 9; *wherein R in Figure 1 is hydrogen or the fatty acid residues from coconut oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 9.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-20 Corn Glycerides	A polyethylene glycol derivative of corn glycerides with an average of 20 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from zea mays (corn) oil, where at least 1 R is a fatty acid, and the average sum of all cases of n is 20.* *Corn Glycerides is a mixture of mono-, di-, and triglycerides derived from Zea mays (corn) oil.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-60 Corn Glycerides	A polyethylene glycol derivative of corn glycerides with an average of 60 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from zea mays (corn) oil, where at least 1 R is a fatty acid, and the average sum of all cases of n is 60; corn glycerides is a mixture of mono-, di-, and tri-glycerides derived from Zea mays (corn) oil.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent; surfactant—solubilizing agent
PEG-20 Evening Primrose Glycerides	A polyethylene glycol derivative of the mono- and diglycerides from evening primrose oil with an average of 20 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from evening primrose oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 20.*	Skin-conditioning agent—emollient
PEG-60 Evening Primrose Glycerides	A polyethylene glycol derivative of the mono- and diglycerides from evening primrose oil with an average of 60 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from evening primrose oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 60.*	Surfactant—emulsifying agent; surfactant—solubilizing agent
PEG-3 Glyceryl Cocoate	The polyethylene glycol ether of glyceryl cocoate that conforms generally to the structure below; *the polyethylene glycol derivative of the monoglyceride of coconut oil with an average ethoxylation value of 3*  *wherein RC(O) represents the fatty acid residues from coconut oil, and the average sum of all cases of n is 3.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-7 Glyceryl Cocoate (66105-29-1; 68201-46-7; generic)	The polyethylene glycol ether of glyceryl cocoate that conforms generally to the structure below; *the polyethylene glycol derivative of the monoglyceride of coconut oil with an average ethoxylation value of 7*  *wherein RC(O) represents the fatty acid residues from coconut oil, and the average sum of all cases of n is 7.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent

(continued)

Table 1. (continued)

Ingredients (CAS Nos.)	Definitions[1]; CIR Staff	Functions[1]
PEG-30 Glyceryl Cocoate (68201-46-7; generic)	The polyethylene glycol ether of glyceryl cocoate that conforms generally to the structure below; *the polyethylene glycol derivative of the monoglyceride of coconut oil with an average ethoxylation value of 30*  *wherein RC(O) represents the fatty acid residues from coconut oil, and the average sum of all cases of n is 30.*	Surfactants—cleansing agent; surfactants—solubilizing agent
PEG-40 Glyceryl Cocoate (68201-46-7; generic)	The polyethylene glycol ether of glyceryl cocoate that conforms generally to the structure below; *the polyethylene glycol derivative of the monoglyceride of coconut oil with an average ethoxylation value of 40*  *wherein RC(O) represents the fatty acid residues from coconut oil, and the average sum of all cases of n is 40.*	Surfactants—cleansing agent; surfactants—solubilizing agent
PEG-78 Glyceryl Cocoate (68201-46-7; generic)	The polyethylene glycol ether of glyceryl cocoate that conforms generally to the structure below; *the polyethylene glycol derivative of the monoglyceride of coconut oil with an average ethoxylation value of 78*  *wherein RC(O) represents the fatty acid residues from coconut oil, and the average sum of all cases of n is 78.*	Surfactants—cleansing agent; surfactants—solubilizing agent
PEG-80 Glyceryl Cocoate (68201-46-7; generic)	The polyethylene glycol ether of glyceryl cocoate that conforms generally to the structure below; *the polyethylene glycol derivative of the monoglyceride of coconut oil with an average ethoxylation value of 80*  *wherein RC(O) represents the fatty acid residues from coconut oil, and the average sum of all cases of n is 80.*	Surfactants—cleansing agent; surfactants—solubilizing agent

(continued)

Table 1. (continued)

Ingredients (CAS Nos.)	Definitions[1]; CIR Staff	Functions[1]
PEG-5 Hydrogenated Corn Glycerides	The polyethylene glycol derivative of mixed glycerides derived from hydrogenated corn oil. It has an average of 5 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from hydrogenated corn oil, where at least 1 R is a fatty acid, and the average sum of all cases of n is 5.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-8 Hydrogenated Fish Glycerides	A polyethylene glycol derivative of hydrogenated fish oil with an average of 8 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from hydrogenated fish oil, where at least 1 R is a fatty acid, and the average sum of all cases of n is 8.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-20 Hydrogenated Palm Glycerides	A polyethylene glycol ether of hydrogenated palm glycerides with an average of 20 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from hydrogenated palm glycerides, where at least 1 R is a fatty acid, and the average sum of all cases of n is 20. (Hydrogenated palm glyceride is the end product of the controlled hydrogenation of palm glyceride.)*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-6 Hydrogenated Palm/ Palm Kernel Glyceride	A polyethylene glycol derivative of a mixture of hydrogenated palm glyceride and hydrogenated palm kernel glyceride containing an average of 6 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from hydrogenated palm glycerides or hydrogenated palm kernel glycerides, where at least 1 R is a fatty acid, and the average sum of all cases of n is 6; palm kernel glycerides is a mixture of mono-, di-, and triglycerides derived from Elaeis guineensis (palm) kernel oil.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-16 Macadamia Glycerides	The polyethylene glycol derivative of the mono- and diglycerides derived from macadamia nut oil with an average of 16 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from macadamia nut oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 16.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-70 Mango Glycerides	A polyethylene glycol derivative of the mono- and diglycerides from mango seed oil containing an average of 70 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from mango seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 70.*	Skin-conditioning agent—emollient; surfactant—cleansing agent; surfactant—solubilizing agent
PEG-13 Mink Glycerides (103819-45-0)	A polyethylene glycol derivative of mono- and diglycerides derived from mink oil with an average of 13 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from mink oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 13.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-25 Moringa Glycerides	A polyethylene glycol derivative of the fatty oil obtained from the seeds of *Moringa pterygosperma* containing an average of 25 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Moringa pterygosperma seed oil, where at least 1 R is a fatty acid, and the average sum of all cases of n is 25.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-42 Mushroom Glycerides	The polyethylene glycol derivative of the mono- and diglycerides of mushroom oil with an average of 42 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from mushroom oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 42.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-2 Olive Glycerides (103819-46-1; generic)	A polyethylene glycol derivative of mono- and diglycerides derived from olive oil with an average of 2 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from olive oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 2.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-6 Olive Glycerides (103819-46-1; generic)	A polyethylene glycol derivative of mono- and diglycerides derived from olive oil with an average of 6 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from olive oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 6.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-7 Olive Glycerides (103819-46-1; generic)	A polyethylene glycol derivative of mono- and diglycerides derived from olive oil with an average of 7 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from olive oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 7.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-10 Olive Glycerides (103819-46-1; generic)	A polyethylene glycol derivative of mono- and diglycerides derived from olive oil with an average of 10 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from olive oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 10.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent

(continued)

Table 1. (continued)

Ingredients (CAS Nos.)	Definitions[1]; CIR Staff	Functions[1]
PEG-40 Olive Glycerides (103819-46-1; generic)	A polyethylene glycol derivative of mono- and diglycerides derived from olive oil with an average of 40 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from olive oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 40.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-18 Palm Glycerides	Is a polyethylene glycol derivative of Palm Glycerides with an average of 18 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Palm Glycerides, where at least 1 R is a fatty acid, and the average sum of all cases of n is 18; palm glycerides is a mixture of mono-, di-, and triglycerides derived from Elaeis guineensis (palm) oil.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-12 Palm Kernel Glycerides (124046-52-2; generic)	A polyethylene glycol derivative of the mono- and diglycerides of palm kernel oil with an average of 12 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from palm kernel oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 12.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-45 Palm Kernel Glycerides (68606-12-2; 124046-52-2; generic)[81]	A polyethylene glycol derivative of the mono and diglycerides of palm kernel oil with an average of 45 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from palm kernel oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 45.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-60 Passiflora Edulis Seed Glycerides	The polyethylene glycol derivative of the mono- and diglycerides derived from the oil of the seeds of *Passiflora edulis* containing an average of 60 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Passiflora edulis seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 60.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-60 Passiflora Incarnata Seed Glycerides	The polyethylene glycol derivative of the mono- and diglycerides derived from the oil of the seeds of *Passiflora incarnata*; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Passiflora incarnata seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 60.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-45 Safflower Glycerides	A polyethylene glycol derivative of the mono- and diglycerides derived from safflower oil with an average of 45 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from safflower oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 45.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-60 Shea Butter Glycerides	A polyethylene glycol derivative of the glycerides derived from *Butyrospermum parkii* (shea) butter with an average ethoxylation value of 60; *wherein R in Figure 1 is hydrogen or the fatty acid residues from oil obtained from Butyrospermum parkii (shea) butter, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 60.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent; surfactant—solubilizing agent
PEG-75 Shea Butter Glycerides	A polyethylene glycol derivative of the glycerides derived from *Butyrospermum parkii* (shea) butter with an average ethoxylation value of 75; *wherein R in Figure 1 is hydrogen or the fatty acid residues from oil obtained from Butyrospermum parkii (shea) butter, where at least 1 R is a fatty acid, and the average sum of all cases of n is 75.*	Skin-conditioning agent—emollient; surfactant—cleansing agent; surfactant—solubilizing agent
PEG-75 Shorea Butter Glycerides	A polyethylene glycol derivative of the glycerides derived from *Shorea stenoptera* seed butter with an average of 75 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from oil obtained from Shorea stenoptera seed butter, where at least 1 R is a fatty acid, and the average sum of all cases of n is 75.*	Skin-conditioning agent—emollient; surfactant—cleansing agent; surfactant—solubilizing agent
PEG-35 Soy Glycerides (61791-23-9)[82]	A polyethylene glycol derivative of the mono- and diglycerides derived from *Glycine soja* (soybean) oil containing an average of 35 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Glycine soja (soybean) oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 35.*	Skin-conditioning agent—miscellaneous; surfactant—emulsifying agent; surfactant—solubilizing agent
PEG-75 Soy Glycerides	A polyethylene glycol derivative of the mono- and diglycerides derived from *Glycine soja* (soybean) oil containing an average of 75 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Glycine soja (soybean) oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 75.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent

(continued)

Table 1. (continued)

Ingredients (CAS Nos.)	Definitions[1]; CIR Staff	Functions[1]
PEG-2 Sunflower Glycerides (180254-52-8; generic 186511-05-7; generic)	A polyethylene glycol derivative of the mono- and diglycerides derived from sunflower seed oil with an average of 2 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from sunflower seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 2.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-7 Sunflower Glycerides (180254-52-8; generic 186511-05-7; generic)	A polyethylene glycol derivative of the mono- and diglycerides derived from sunflower seed oil with an average of 7 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from sunflower seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 7.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-10 Sunflower Glycerides (180254-52-8; generic 186511-05-7; generic)	A polyethylene glycol derivative of the mono- and diglycerides derived from sunflower seed oil with an average of 10 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from sunflower seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 10.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-13 Sunflower Glycerides (186511-05-7; generic 70377-91-2; generic)	A polyethylene glycol derivative of the mono- and diglycerides derived from sunflower seed oil with an average of 13 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from sunflower seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 13.*	Skin-conditioning agent—emollient; surfactant—emulsifying agent
PEG-5 Tsubakiate Glycerides	The polyethylene glycol derivative of the mono- and diglycerides derived from *Camellia japonica* seed oil containing an average of 5 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Camellia japonica seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 5.*	Surfactant—emulsifying agent
PEG-10 Tsubakiate Glycerides	The polyethylene glycol derivative of the mono- and diglycerides derived from *Camellia japonica* seed oil containing an average of 10 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Camellia japonica seed oil, where at least one R (and no more than two) is a fatty acid, and the average sum of all cases of n is 10.*	Surfactant—emulsifying agent
PEG-20 Tsubakiate Glycerides	The polyethylene glycol derivative of the mono- and diglycerides derived from *Camellia japonica* seed oil containing an average of 20 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Camellia japonica seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 20.*	Surfactant—emulsifying agent
PEG-60 Tsubakiate Glycerides	The polyethylene glycol derivative of the mono- and diglycerides derived from *Camellia japonica* seed oil containing an average of 60 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from Camellia japonica seed oil, where at least 1 R (and no more than 2) is a fatty acid, and the average sum of all cases of n is 60.*	Surfactant—cleansing agent

It should be stated that n is not equal to X. In other words, wherein the value of X in PEG-X is equal to 6 (eg, PEG-6 Caprylic/Capric Glycerides), n is not equal to 6. Instead, X represents the number of stoichiometric equivalents of ethylene oxide that were added to one stoichiometric equivalent of caprylic/capric glycerides. Therefore, the sum of all of the different n values in the mixture may be no more than X. Indeed, when one mole of ethylene oxide is reacted with one mole of fatty alcohol, adducts having *no* added ethylene oxide are the predominate material in the mixture.[13] Furthermore, wherein ethylene oxide reacts with mono- or diglyceride, it is approximately twice as likely that it will react at an ester site versus an alcohol site. Moreover, a percentage (13% in one specific case) of the ethylene oxide simply reacts with other molecules of ethylene oxide, resulting in some polyethylene glycols, unattached to glycerides.

Most of the ingredients in this report share in common a specific nomenclature, generically PEG-X "source"/alkyl-chain-common-name glycerides (eg, PEG-6 Caprylic/Capric Glycerides). The PEG glyceryl cocoates have a slightly different order of nomenclature, but they are not structurally distinct from the other ingredients in this report.

Chemical Properties

Much like the oils these ingredients are derived from, the PEGylated alkyl glycerides range from oily liquids to waxy solids, depending on alkyl chain length and degree of PEGylation (Table 3). Owing to the combination of polar and nonpolar functional groups, most of these ingredients are soluble in some organic solvents and are at least dispersible in water, if not

Table 2. Summaries of Previous CIR Safety Assessments.

Ingredient(s)	Conclusion	Summary	Reference
Triethylene Glycol and Polyethylene Glycols (PEGs) $>$ 4	Safe for use in cosmetics in the present practices of use and concentration	In general, PEGs are not oral toxicants, with acute oral LD_{50} values in rodents ranging from 15-22 g/kg. The LC_{50} of aerosolized triethylene glycol in rats was greater than 3.9 mg/L. Minimal dermal irritation and sensitization with undiluted PEGs has been observed. 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. PEGs are not genotoxic (up to $\sim$5,700 mg/kg/d in a rat dominant lethal assay) or carcinogenic (up to 0.25 mL/wk in a rat subcutaneous injection study). PEGs are not reproductive or developmental toxicants at doses up to 6.78 g/kg in mice. Use of antimicrobial creams with a PEG vehicle was associated with renal toxicity when applied to burned skin, but studies of extensively tape stripped skin demonstrated that the levels of PEGs that could penetrate in a worst case analysis are $>$100 times less than the renal toxicity no observable effect level of 1.1 g/kg/d, providing a margin of safety.	[4]
Plant-Derived Fatty Acid Oils includes: almond oil; apricot kernel oil; avocado oil; babassu oil; *Theobroma cacao* (cocoa) seed butter; coconut oil; evening primrose oil; moringa oleifera seed oil; moringa pterygosperma seed oil; olive oil; palm oil; palm kernel oil; safflower oil; *Butyrospermum parkii* (shea) butter; soybean oil; *Carthamus tinctorius* (safflower) seed oil; sunflower seed oil; *Camellia japonica* seed oil	Safe for use in cosmetics in the present practices of use and concentration	Oils are used in a wide variety of cosmetic products for their skin conditioning, occlusive, emollient, and moisturizing properties. Undiluted, technical grade, Arachis Hypogaea (peanut) Oil was moderately irritating to rabbits and guinea pig skin, and 5% aq. solutions of a bar soap containing 13% sodium cocoate had irritation scores of 1.6-4.0/8 in animal studies. However, the remaining animal and clinical irritation and/or sensitization studies conducted on a large number of the oils included in the safety assessment report, primarily in formulation, did not report any significant irritation or sensitization reactions, indicating that refined oils derived from plants are not ocular or dermal irritants or sensitizers.	[5]
Caprylic/Capric Triglyceride	Safe as used (maximum concentration of use, $>$50% in eye products, perfumes, and other dermal products)	Caprylic/capric triglyceride is an oily mixed ester predominantly composed of caprylic and capric fatty acids derived from coconut oil. When absorbed from the digestive tract, it is hydrolyzed, and the fatty acids are catabolized to C2 fragments which may be further metabolized either to CO_2 or to form long-chain fatty acids. It has a very low toxicity to man and animals as shown by tests involving oral ingestion, intraperitoneal and intramuscular injection, skin and eye irritation tests, skin sensitization, percutaneous toxicity and finally, by 2 generation feeding studies. Application of	[6]

(continued)

Table 2. (continued)

Ingredient(s)	Conclusion	Summary	Reference
		undiluted test material to rabbits produced no to mild irritation. A 4% solution in ethanol was not a sensitizer in guinea pigs.	
Coconut Oil includes Cocoglycerides	See Plant-Derived Fatty Acid Oils: safe as used (maximum concentration of use, 80% coconut oil in eye lotion; 14% Cocoglycerides in lipstick)	The genotoxic potential of saponified coconut oil was evaluated in several prokaryote systems; the cytotoxic, antioxidant, and mutagenic effects of saponified coconut oil can be influenced by the aggregational state. Coconut oil, 100%, was not an allergen in a double-blind randomized study in 12 subjects.	7
Corn Oil includes Corn Glycerides	Safe as used (maximum use, 14% corn oil in dermal products; Corn Glycerides had no reported uses)	Corn oil is commonly used as a vehicle in studies of lipid-soluble substances carried out in numerous animal species; corn oil was not found to have effect when evaluated as a vehicle/control.	8
Palm Oil includes palm kernel oil	See Plant-Derived Fatty Acid Oils	Undiluted palm oil has an oral LD_{50} in rats of $>$ 5g/kg. Short-term and subchronic feeding studies showed no evidence of toxicity. Chronic feeding studies produced results suggestive of metabolic hyperactivity. Minimal ocular irritation and no skin irritation (tested undiluted), sensitization (tested at 5%), or photosensitization (1.5% in formulation) were reported in animals studies. Anomalies in 30% of the live fetuses delivered by female albino rats fed commercial grade palm oil were reported; other studies including multigenerational tests of crude palm oil and heated palm oil (as would occur in cooking) reported no reproductive toxicity, developmental toxicity, or differences in endocrine function. Although some data show that palm oil can be mutagenic in certain Ames test *Salmonella* strains, it was negative in other strains and negative in an assay of chromosomal aberrations in bone marrow samples taken from mice dosed orally. Several studies suggesting an inhibitory effect of palm oil on 7,12-dimethylbenz[a]anthracene tumorigenesis have attributed the effect to the high vitamin E content of the oil. There was no evidence of irritation or sensitization in clinical tests; use testing of products containing palm oil produced no ocular or skin irritation.	9
Mink Oil	Safe for use in cosmetics in the present practices of use and concentration	Mink oil does not absorb significant UVA or UVB radiation. It is not an acute oral toxicant ($LD_{50} > 64$ cc/kg) in rats. Nonhuman test data indicate that mink oil is not a dermal or ocular irritant or a dermal sensitizer up to 50%. No irritation was observed in clinical studies of mink oil up to 2.8%, although some transient irritation was noted in exaggerated-use studies. Because mink oil is a mixture of glycerides, namely triglycerides, it may enhance the penetration of other chemicals.	10

(continued)

Table 2. (continued)

Ingredient(s)	Conclusion	Summary	Reference
Safflower Oil	See Plant-Derived Fatty Acid Oils	The pure oil produced slight to moderate comedogenicity. However, products containing up to 5% Safflower Oil were not comedogenic in rabbits. Results of animal tests indicated that undiluted safflower oil was not an eye or skin irritant or contact sensitizer. The oil increased the incidence of mammary tumors induced by 7,12-dimethylbenz[a]anthracene and large bowel tumors induced by dimethylhydrazine in rats.	11
PEGylated Oils	PEGylated oils are safe in the present practices of use and concentration in cosmetics when formulated to be nonirritating. (This conclusion supersedes the earlier conclusion for PEG castor oils issued by the Expert Panel in 1997.)	PEGylated oils are mixtures that are the condensation products of ethylene oxide and water, with the chain length controlled by number of moles of ethylene oxide that are polymerized. PEGs may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation. PEG-40 hydrogenated castor oil had a maximum use concentration 22% in leave-on non-coloring hair products. PEG-30 castor oil and PEG-40 hydrogenated castor oil may be used as nonionic surfactants in oral, topical, and parenteral drug delivery systems. PEG-30 and -40 hydrogenated castor oil are approved as direct and indirect food additives. Various types of PEGs are hydrophilic penetration enhancers and are used in topical dermatological preparations. Unspecified PEG castor oil did not elicit irritation at the site of injection in rabbits when evaluated as a vehicle in an intravenous drug. PEG-60 hydrogenated castor oil produced toxicity, including decreased blood pressure, flush, swelling, itching, and increase histamine levels, in dogs injected intravenously with a single 1.25, 2.5, or 10 mg/kg dose of the test material. No signs of toxicity were observed with PEG-60 hydrogenated castor oil in monkeys, rabbits, guinea pigs, or rats. Several rat studies investigated the effects of the use of PEG-35 castor oil as a vehicle in intravenous drugs; 100 μg/L had effects on cardiac and skeletal muscle function. PEG-60 hydrogenated castor oil was not genotoxic in a reverse mutation test, in a chromosome aberration study, and in a mouse micronucleus test. A microemulsion containing 20% wt/wt PEG-35 castor oil was not an irritation in guinea pigs. A formulation containing 20% PEG-40 hydrogenated castor oil tested in mouse skin would probably not irritate human skin. A formulation containing 20.66% PEG-40 hydrogenated castor oil was not a skin irritant. Nanoemulsions containing up to 13.5% PEG-35 castor oil were nonirritating in rabbit eyes.	12

soluble. The fatty acid compositions of the oils that comprise the alkylated glycerides are provided in Table 4.

Methods of Manufacture

PEG-11 Avocado Glycerides,[15] PEG-9 Cocoglycerides,[16] and PEG-10 Olive Glycerides[17] are produced by the reaction of their respective oil with ethylene oxide. The PEG-6 Caprylic/Capric Glycerides is derived completely from a vegetable/synthetic source, and palm kernel oil and/or rapeseed oil are the starting materials.[18]

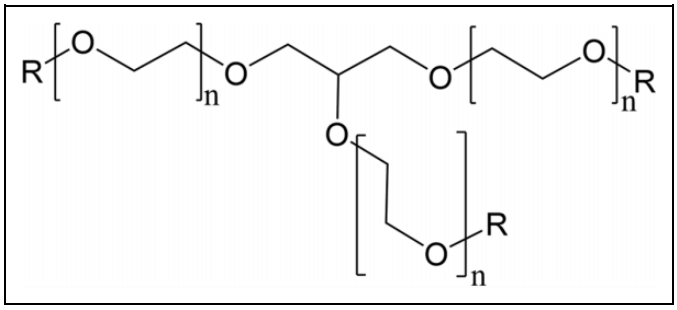


Figure 1. Generic PEGylated alkyl glyceride structure, wherein R is hydrogen or the fatty acids declared in the name or found in the source material, and the sum of all cases of n is "X" in PEG-"X."

One source states that PEG-6 Caprylic/Capric Glycerides is manufactured in a 2-step procedure starting with the preparation of a mono/diglyceride of a C8/C10 fatty acid blend; the C8:C10 ratio is approximately 60:40.[19] The raw materials are charged with an excess of glycerin, the blend is purged with nitrogen and heated under pressure, and the mixture is then cooled, treated with Fuller earth, and filtered. Following filtration, step 2 is initiated and includes the addition of an alkaline catalyst in a solvent, heating, and the removal of the solvent under pressure. The pressure in the reactor is then normalized with nitrogen, and ethylene oxide is added until the desired saponification value is reached; the mixture is then stirred until the ethylene oxide value is $\leq$ 1 ppm. After cooling, the product is neutralized with lactic or acetic acid. Finally, the raw ethoxylate is treated with steam to remove the volatile impurities, and if necessary, the product may be bleached with Fuller earth.

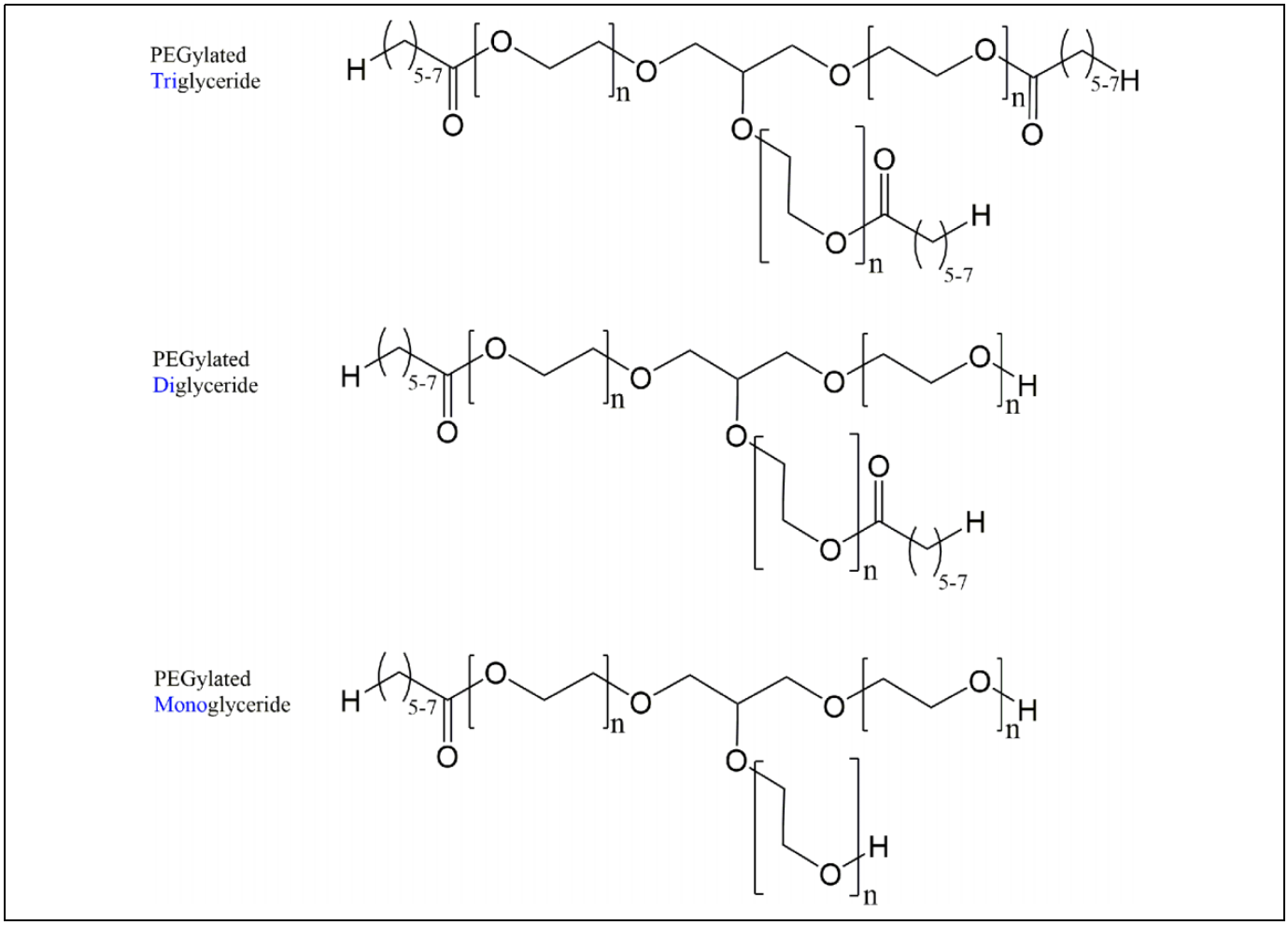


Figure 2. PEG-6 Caprylic/Capric Glycerides, wherein the sum of all instances of "n" is representative of an average number of ethylene glycol repeat units (ie, "PEG-6").

Table 3. Chemical Properties.

Property	Description	Reference
PEG-11 Avocado Glycerides		
Appearance	Brown liquid	83
	Yellow, liquid to pasty	84
	Yellowish to brown liquid with characteristic odor	85
Solubility	Soluble in water	84
pH (10% in water; 25 °C)	5.0-7.0	85
Saponification value (mg KOH/g)	60-80	85
Iodine value (g iodine/100 g)	25-37	85
Surfactant type	Nonionic	84
PEG-20 Almond Glycerides		
Appearance	Yellow liquid with a characteristic odor	86
PEG-42 Babassu Glycerides		
Appearance	Clear to slightly hazy yellow liquid	87
PEG-6 Caprylic/Capric Glycerides		
Appearance	Clear yellow liquid	80,88
Solubility (25 °C; 10% concentration)	Soluble in water, cosmetic alcohol, 1,2-propylene glycol; soluble in sunflower seed oil (slight turbidity); insoluble in paraffin oil and isopropyl myristate; dispersible in glycerol	89
Hydroxyl value (mg KOH/g)	200-220	25
Iodine value (g I/100 g)	$\leq$1	25
Saponification value (mg KOH/g)	85-105	25
Acid value	$<$2	80,88
PEG-8 Caprylic/Capric Glycerides		
Appearance	Pale yellow oily liquid with a faint odor	21,27
Mean molecular wt (Da)	200-400	20,21
Solubility	Very soluble in ethanol (96°), chloroform, methylene chloride; soluble in water; insoluble in mineral oils	27
	Freely soluble in methylene chloride; dispersible in hot water	21
Specific gravity (20 °C; D20/4)	1.060-1.070	27
Refractive index (20 °C)	1.450-1.470	27
Saponification value (mg KOH/g)	85-105	27
Acid value	$\leq$2.0	28,29
Fatty acid composition	Caproic acid (C6): $\leq$2.0% Caprylic acid (C8): 50-80% Capric acid (C10): 20-50% Lauric acid (C12): $\leq$3.0% Myristic acid (C14): $\leq$1.0%	27,28
Free glycerol content	$\leq$5%	27
Hydrophilic-lipophilic balance (HLB)	14	43
PEG-9 Cocoglycerides		
Appearance	Yellow, liquid to pasty	90
Solubility	Soluble in water	90
HLB	13	90
Surfactant-type	Nonionic	90
PEG-60 Corn Glycerides		
Physical appearance	Liquid	91
Surfactant-type	Nonionic	91
PEG-60 Evening Primrose Glycerides		
Appearance	Soft, pale paste	92
PEG-7 Glyceryl Cocoate		
Appearance	Clear, pale yellow oil with a mild fatty odor	2
Solubility	Soluble in water and ethanol; insoluble in mineral oil	2
	25 °C; 10% concentration: soluble in water (slight turbidity) and cosmetic alcohol; insoluble in paraffin oil, isopropyl myristate, and glycerol; dispersible in sunflower seed oil and 1,2-propylene glycol	89
Hydrophile–lipophile balance	15	2
Hydroxyl value	172-187	2
Saponification value	90-100	2

(continued)

Table 3. (continued)

Property	Description	Reference
Acid value (max)	5.0	2
Iodine value (max)	5.0	2
PEG-16 Macadamia Glycerides		
Appearance	Liquid	93
Affinity	Hydrophilic	94
HLB	12-14	94
Hydroxyl value (mg KOH/g)	90-130	93
Saponification value (mg KOH/g)	45-60	93
PEG-70 Mango Glycerides		
Appearance	Solid	95
Solubility	Water-dispersible	96
Surfactant-type	Nonionic	96
HLB	16-18	95,96
Acid value	1.5	96
Saponification value (mg KOH/g)	14-20	96
PEG-10 Olive Glycerides		
Appearance	Yellow, liquid to pasty	97
	Yellowish-brown paste with characteristic odor	98
Solubility	Soluble in water	97
	Solubility, 2.5% in water—almost clear to turbid	98
	Solubility, 10% in isopropyl alcohol - clear	
pH value (10% in water; 25 °C)	5.0-7.0	98
Acid value (max; mg KOH/g)	4.0	98
Saponification value (mg KOH/g)	52-72	98
Iodine value (g iodine/100 g)	26-36	98
Affinity	Hydrophilic	99
surfactant-type	Ionic	97
HLB	13	97
PEG-45 Palm Kernel Glycerides		
Appearance	Clear liquid	81
Surfactant-type	Nonionic	100
PEG-75 Shea Butter Glycerides		
Appearance	Waxy solid	101
Solubility	Water-dispersible	95
pH (10% in water; 25 °C)	5.5-8.5	101
Surfactant-type	Nonionic	95
HLB	16-18	101
PEG-35 Soy Glycerides		
Appearance	Solid or paste	82
Solubility	Soluble in water	82
Surfactant-type	Nonionic	82
PEG-10 Sunflower Glycerides		
Appearance	Liquid	102
Solubility	Soluble in water; dispersible in oil	103
Refractive index	1.460	104
pH (10% in water; 25 °C)	6.9	104
Surfactant-type	Hydrophilic	103
HLB	8-10	104
Hydroxyl value (mg KOH/g)	135-160	102
Acid value (mg KOH/g)	0-1.5	102
Saponification value (mg KOH/g)	60-80	102

PEG-8 Caprylic/Capric Glycerides can be obtained by partial transesterification of medium-chain triglycerides using PEG, by esterification of glycerol and PEG with caprylic acid and capric acid, or as a mixture of glycerol esters and condensates of ethylene oxide with caprylic acid and capric acid.[20,21] Methods of manufacture of the other PEGylated alkyl glycerides were not found in the published literature, nor were unpublished data provided.

Composition and Impurities

Residual PEG may be present in the PEGylated alkyl glycerides. The PEGs are the condensation products of ethylene oxide

Table 4. Total Fatty Acid Composition of Plant-Derived Fatty Acid Oils and of Butters (%).

Fatty acids	Prunus amygdalus (sweet almond) oil[5]	Prunus armeniaca (apricot) kernel oil[5]	Persea gratissima (avocado) oil[5]	Orbignya oleifera seed oil (Babassu)[5]	Theobroma cacao (Cocoa) Seed Butter[5]	Cocos nucifera (coconut) oil[5]	Zea mays (corn) oil[5]
Caproic (C6)						0-1	
Caprylic (C8)				4-8		5-9	
Capric (C10)				4-8		6-10	
Lauric (C12)*				44-47		44-52	
Myristic (C14)	1			15-20		13-19	0.1-1.7
Myristoleic (C14:1)							
Palmitic (C16)	4-9	4.6-6	13-17	6 to 9	24-29	8-11	8-16.5
Palmitoleic (C16:1)	0.8	1-2	3-5.1			0-1	0.2-1.6
Heptadecanoic (C17:0)	0.2						
Stearic (C18)	2-3	0.5-1.2		3-5	34-36	1-3	0-4.5
Oleic (C18:1)	62-86	58-65.7 (total 18:1)	67-72	10-12	30-40	5-8	19-49
Linoleic (C18:2)	20-30	29-33 28.5 (undef. 18:2)	10-12	1-3	2.4	Trace-2.5	34-66
Linolenic (C18:3)	0.4	05-1.0 (undef. 18:3)					0-2
Arachidic (C20)	0.2	0.2					1
Eicosenoic (C20:1)	0.3						1
Behenic (C22)	0.2						
Erucic (C22:1)	0.1						
Lignoceric (C24)							
Others	<C16:0 = 0.1	Oleic/Linoleic = 90-93%					

	Oenothera biennis (evening primrose) oil[5]	Fish oil	Macadamia integrifolia seed oil[5]	Mangifera indica (mango) Seed Oil[5]	Mink oil[10]		Moringa oleifera seed oil	Mushroom oil
					Mink wax oil	Mink crude oil		
Caproic (C6)								
Caprylic (C8)								
Capric (C10)								
Lauric (C12)*			0.1-1.4		0.1	0.1		
Myristic (C14)			0.7-1.5		4.0	3.5	Trace	
Myristoleic (C14:1)					0.7	0.9		
Pentadecanoic (15/0)					0.2	0.1		
Palmitic (C16)	4-10		6-12	5-8	28.0	17.2	5-9.3	
Palmitoleic (C16:1)			12-25		13.3	17.0	1.5-3	
Heptadecanoic (C17:0)					0.5	0.4		
Heptadecanoic (C17:1)					0.6	0.5		
Stearic (C18)	2-4		0.5-8	33-48	4.7	2.5	3-8	
Oleic (C18:1)	5-12		50-67	35-50	35.3	40.9	65-80	
Linoleic (C18:2)	60-85		1.5-5	4.0-8	10.6	15.0	1.5-5	
Linolenic (C18:3)			0.5 -1.9		0.4	0.6	1 -1.5	
Arachidic (C20)			1.5-5	1-7	0.1		2-5	
Eicosenoic (C20:1)			1.5-3.1		0.7	0.6	2.5-4	
Behenic (C22)			0.3-1				8-8.6	
Erucic (C22:1)			1				3	
Lignoceric (C24)							trace	
Others	α-Linolenic (C18:3) = 1% γ-Linolenic = 7-12%							

(continued)

Table 4. (*Continued*)

Fatty acids	Olea europaea (Olive) oil[5]	Elaeis guineensis (palm) Oil[5]	Elaeis guineensis (palm) kernel oil[5]	Passiflora edulis seed oil[5]	Passiflora incarnata seed oil[5]	Carthamus tinctorius (safflower) seed oil[5]	Butyrospermum parkii (Shea) butter[5]
Caproic (C6)			0.3				
Caprylic (C8)			4.4				
Capric (C10)			3.7				
Lauric (C12)*		0.2	48.3				
Myristic (C14)	Trace	1.1	15.6	0.03			0.5
Myristoleic (C14:1)							
Palmitic (C16)	7.5-20	44	7.8	8.57	8	2	3-9
Palmitoleic (C16:1)	0.3-3.5	0.1		0.23			
Heptadecanoic (C17:0)							
Stearic (C18)	0.5-3.5	4.5	2	1.66	2		30-50
Oleic (C18:1)	53-86	39.2	15.1	16.25	12	26	38-50
Linoleic (C18:2)	3.5-20	10.1	2.7	72.69	77	68	3-8
Linolenic (C18:3)	0-1.5	0.4		0.26	1	Trace	0.5 max
Arachidic (C20)	Trace	0.4				Trace	2.5-3
Eicosenoic (C20:1)							
Behenic (C22)	Trace						
Erucic (C22:1)							
Lignoceric (C24)	Trace						
Others			0.2	Unspecified other fatty acids = 0.31			

	Shorea stenoptera seed butter[5]	Glycine soja (soybean) oil[5]	Helianthus annuus (sunflower) seed oil[5]	Camellia japonica seed oil[5]
Caproic (C6)				
Caprylic (C8)				
Capric (C10)				
Lauric (C12)*				
Myristic (C14)				
Myristoleic (C14:1)				
Palmitic (C16)	19.5		5.0-7.2	7.9
Palmitoleic (C16:1)				0.16
Heptadecanoic (C17:0)				
Stearic (C18)	42.4		2.0-6.5	2.46
Oleic (C18:1)	36.9	11.5-60.0	14.7-37.2	84.99
Linoleic (C18:2)	0.2		51.5-73.5	3.76
Linolenic (C18:3)		2.9-12.1	Trace-0.3	
Arachidic (C20)	1.0		0.3-1	0.49
Eicosenoic (C20:1)				
Behenic (C22)				
Erucic (C22:1)				
Lignoceric (C24)				
Others				

and water, with the chain length controlled by number of moles of ethylene oxide that are polymerized. The PEGs may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation; 1,4 dioxane is a known animal carcinogen.[22] The US Food and Drug Administration (FDA) has been periodically monitoring the levels of 1,4-dioxane in cosmetic products, and the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEG-containing ingredients and, thus, uses additional purification steps to limit it in the ingredient before blending into cosmetic formulations.[23,24]

Raw material information sheets for PEG-11 Avocado Glycerides,[15] PEG-9 Cocoglycerides,[16] and PEG-10 Olive Glycerides[17] state that these compounds contain < 5 ppm 1,4-dioxane, < 1 ppm ethylene oxide, and < 1 ppm residual monomers. Solvents are not added to these materials. The PEG-6 Caprylic/Capric Glycerides contains ≤ 5 ppm dioxane and ≤ 1 ppm ethylene oxide, and it meets the valid regulatory requirements for limits on agricultural pesticides.[18,25] Residual solvents, monomers, free amines, and nitrosamines are not by-products of the production process.

Nuclear magnetic resonance spectroscopy indicated PEG-8 Caprylic/Capric Glycerides consists of 30% mono-, di-, and triglycerides of C_8 and C_{10} fatty acids, 50% of mono- and diesters of PEG-8 (ie, esters of capric or caprylic acid with PEG 8; not glycerides), and 20% free PEG-8.[26] It is reported to contain ≤ 10 ppm 1,4-dioxane, < 1 ppm ethylene oxide, and < 10 ppm heavy metals (lead).[27,28]

Use

Cosmetic

Most of the PEGylated alkyl glycerides are reported to function as a skin conditioning agent—emollient and as a surfactant—emulsifying agent (Table 1).[1] Emollients function by their ability to remain on the skin surface or in the stratum corneum to act as lubricants, to reduce flaking, and to improve the skin's appearance. For the surfactant—emulsifying agent function, the efficacy of an emulsifying agent depends on its ability to reduce surface tension, to form complex films on the surface of emulsified droplets, and to create a repulsive barrier on emulsified droplets to prevent their coalescence. A few of the PEGylated alkyl glycerides also are reported to act as surfactant—solubilizing agents or surfactant—cleansing agents.

The FDA collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). In 2014, VCRP data obtained from the FDA[29] and data received in response to surveys of the maximum reported use concentration by category that were conducted by the Personal Care Products Council (Council)[30-32] indicate that 21 of the 60 ingredients included in this safety assessment are used in cosmetic formulations (Table 5). (The ingredients not currently reported to be used are listed in Table 6.)

According to 2014 VCRP data, PEG-7 Glyceryl Cocoate has the most reported uses, that is, 858; the majority of these uses (713) are in rinse-off formulations.[29] PEG-6 Caprylic/Capric Glycerides is reported to be used in 548 formulations, the majority of which are rinse-off formulations, and PEG-60 Almond Glycerides is reported to be used in 163 cosmetic formulations. All other in-use PEGylated alkyl glycerides are reported to be used in less than 45 formulations. The PEG Glyceryl Cocoates have increased in use. In 1996, PEG-7 Glyceryl Cocoate was reported to be used in 173 formulations, and it is now reported to be used in 858 formulations; however, both then and now, PEG-7 Glyceryl Cocoate is used mostly in rinse-off formulations.[2,29] The frequency of use also has increased for PEG-30 Glyceryl Cocoate (from 10 to 44 uses), PEG 40 Glyceryl Cocoate (from 5 to 23 uses), and PEG-80 Glyceryl Cocoate (from 2 to 11 uses).

The results of the concentration of use survey conducted by the Council indicate the highest leave-on concentrations reported are 11.3% and 6% for PEG-7 Glyceryl Cocoate in tonics, dressings, and other hair grooming aids and "other" fragrance preparations.[30] PEG-7 Glyceryl Cocoate also has the highest rinse-off concentration of use reported, that is, 10% in skin cleansing products.

At the time of the original safety assessment, concentration of use data were not available from the FDA. However, based on ocular and sensitization data, a concentration limit of 10% was placed on leave-on products containing PEG glyceryl cocoates. The current reported concentration of use in leave-on products is slightly higher, that is, 11.3% in tonics, dressings, and other hair grooming aids.

One ingredient is used in products that could be incidentally ingested (ie, PEG-75 Cocoa Butter Glycerides is reported to be used in 2 lipstick formulations) and a few of the ingredients are used near the eye (eg, PEG-20 Hydrogenated Palm Glycerides is used at 1.2% in an eyebrow pencil) or mucous membranes (PEG-7 Glyceryl Cocoate is used at up to 6.9% in other personal cleanliness products). Five PEGylated alkyl glycerides were reported to the VCRP as used in baby products, but concentration of use data were not submitted by industry for these uses. Additionally, according to the VCRP, several ingredients are used in products that can be incidentally inhaled, and results of the Council survey reported concentrations of up to 6% PEG-7 Glyceryl Cocoate in "other" fragrance preparations, 2% PEG-7 Glyceryl Cocoate in a pump spray deodorant, and up to 1.9% PEG-45 Palm Kernel Glycerides in a pump spray suntan product. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters $> 10\,\mu m$.[33,34] 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.[35,36] The PEGylated alkyl glycerides named in this safety assessment are listed in the European Union inventory of cosmetic ingredients.[37]

Non-Cosmetic

PEG-8 Caprylic/Capric Glycerides has use as a pharmaceutical excipient.[38] It has a maximum potency of 70 mg in oral soft

Table 5. Frequency and Concentration of Use According to Duration and Type of Exposure.

	# of use[29]	Max. conc. of use (%)[30-32]	# of uses[29]	Max. conc. of use (%)[30-32]	# of use[29]	Max. conc. of Use (%)[30-32]
	PEG-20 Almond glycerides		PEG-60 Almond glycerides		PEG-192 Apricot kernel glycerides	
Totals*	11	0.01	163	0.0001-6.5	24	0.1
Duration of use						
Leave on	*3*	*0.01*	*75*	*0.0001-3.2*	*24*	*0.1*
Rinse off	*8*	*NR*	*87*	*0.001-6.5*	*NR*	*NR*
Diluted for (bath) use	*NR*	*NR*	*1*	*NR*	*NR*	*NR*
Exposure type						
Eye area	NR	NR	6	0.01-0.2	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	2[a]	0.01[a]	2; 30[a]; 24[b]	aerosol: 0.5; pump: 0.2; 0.001-1[a]	4	NR
Incidental inhalation-powder	NR	NR	24[b]	0.005-3.2[c]	NR	NR
Dermal contact	4	NR	91	0.0001-6.5	NR	0.1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair non-coloring	7	0.01	65	0.05-1	24	NR
Hair coloring	NR	NR	6	0.25	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	2	NR	21	0.05-1	NR	NR
Baby products	NR	NR	2	NR	NR	NR
	PEG-6 Caprylic/Capric Glycerides		PEG-7 Caprylic/Capric Glycerides		PEG-8 Caprylic/Capric Glycerides	
Totals*	548	0.000002-5	2	2	22	NR
Duration of Use						
Leave on	*96*	*0.1-3.5*	*NR*	*2*	*16*	*NR*
Rinse off	*434*	*0.000002-5*	*2*	*NR*	*4*	*NR*
Diluted for (bath) use	*18*	*0.38-5*	*NR*	*NR*	*2*	*NR*
Exposure type						
Eye area	17	0.35	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	3; 17[a]; 10[b]	0.1-3.5[a]	NR	NR	3[a]; 11[b]	NR
Incidental inhalation-powder	10[b]	0.13-0.75[c]	NR	2[c]	11[b]	NR
Dermal contact	476	0.0002-5	2	2	21	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair non-coloring	71	0.000002-3.5	NR	NR	1	NR
Hair coloring	NR	1.9	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	340	0.0002-5	NR	NR	4	NR
Baby products	2	NR	NR	NR	NR	NR
	PEG-75 Cocoa Butter Glycerides as (PEG-75 Cocoa Butter in VCRP)		PEG-3 Glyceryl Cocoate		PEG-7 Glyceryl Cocoate	
Totals*	20	NR	2	NR	858	0.01-11.3
Duration of use						
Leave on	*15*	*NR*	*2*	*NR*	*124*	*0.02-11.3*
Rinse off	*5*	*NR*	*NR*	*NR*	*713*	*0.01-10*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*21*	*NR*
Exposure type						
Eye area	NR	NR	NR	NR	12	0.02
Incidental ingestion	2	NR	NR	NR	NR	NR
Incidental inhalation-spray	1; 10[a]	NR	2[b]	NR	1; 25[a]; 50[b]	6; 0.18-11.3[a]
Incidental inhalation-powder	NR	NR	2[b]	NR	50[b]; 1[c]	0.35-3.5[c]
Dermal contact	13	NR	2	NR	700	0.01-10
Deodorant (underarm)	NR	NR	NR	NR	14[a]	not spray: 3; pump spray: 2
Hair non-coloring	5	NR	NR	NR	146	0.18-11.3
Hair coloring	NR	NR	NR	NR	11	1.8-4.6

(continued)

Table 5. (continued)

	# of use[29]	Max. conc. of use (%)[30-32]	# of uses[29]	Max. conc. of use (%)[30-32]	# of use[29]	Max. conc. of Use (%)[30-32]
Nail	NR	NR	NR	NR	1	0.5
Mucous membrane	3	NR	NR	NR	453	0.5-6.9
Baby products	NR	NR	NR	NR	10	NR
	PEG-30 Glyceryl Cocoate		PEG-40 Glyceryl Cocoate		PEG-80 Glyceryl Cocoate	
Totals*	44	0.09-3	23	0.88-4.8	11	0.1-1
Duration of use						
Leave on	*2*	*0.1-2.4*	*1*	*NR*	*0*	*NR*
Rinse off	*42*	*0.09-2.4*	*21*	*0.88-4.8*	*11*	*0.1-1*
Diluted for (bath) use	*NR*	*NR*	*1*	*NR*	*0*	*NR*
Exposure type						
Eye area	NR	NR	2	0.88	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	NR	0.1[a]	1	NR	NR	NR
Incidental inhalation-powder	NR	0.5-2.4[c]	NR	NR	NR	NR
Dermal contact	22	0.09-3	20	0.88-4.8	10	0.1-1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair non-coloring	22	0.1-1	3	NR	1	NR
Hair coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	11	3	7	NR	2	0.1
Baby products	1	NR	NR	NR	NR	NR
	PEG-20 Hydrogenated Palm Glycerides		PEG-16 Macadamia Glycerides		PEG-70 Mango Glycerides	
Totals*	NR	0.23 -1.2	8	0.05-1	31	0.01-0.1
Duration of use						
Leave on	*NR*	*0.23 -1.2*	*3*	*NR*	*30*	*0.05*
Rinse off	*NR*	*NR*	*5*	*0.05-1*	*1*	*0.01-0.1*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure type						
Eye area	NR	0.26 -1.2	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	NR	NR	1[a]	NR	4; 4[a]	0.05[a]
Incidental inhalation-powder	NR	NR	NR	NR	NR	NR
Dermal contact	NR	0.23 -1.2	8	0.05-1	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair non-coloring	NR	NR	NR	NR	30	0.01-0.1
Hair coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	4	0.05	1	NR
Baby products	NR	NR	NR	NR	NR	NR
	PEG-10 Olive Glycerides		PEG-45 Palm Kernel Glycerides		PEG-75 Shea Butter Glycerides (includes PEG-75 Shea Butter in VCRP)	
Totals*	1	0.02-0.5	43	0.5-5	29	0.005-1
Duration of use						
Leave on	*1*	*NR*	*15*	*0.9-5*	*9*	*0.005-1*
Rinse off	*NR*	*NR*	*19*	*0.5*	*19*	*0.1-1*
Diluted for (bath) use	*NR*	*NR*	*9*	*NR*	*1*	*NR*
Exposure type						
Eye area	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR

(continued)

Table 5. (continued)

	# of use[29]	Max. conc. of use (%)[30-32]	# of uses[29]	Max. conc. of use (%)[30-32]	# of use[29]	Max. conc. of Use (%)[30-32]
Incidental inhalation-spray	1[a]	0.02[a]	4; 7[b]	pump:1.9	1; 2[a]; 2[b]	0.005; pump: 0.15; 0.1[b]
Incidental inhalation-powder	NR	NR	7[b]	0.92[c]	2[b]	0.1[b]; 1[c]
Dermal contact	NR	0.02	36	0.5 -1.9	23	0.005-1
Deodorant (underarm)	NR	0.02	NR	NR	NR	NR
Hair non-coloring	1	0.2-0.5	7	5	5	0.1-0.4
Hair coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	1	NR
Mucous membrane	NR	NR	25	NR	16	0.1-0.4
Baby products	NR	NR	NR	NR	1	NR
	PEG-35 Soy Glycerides		PEG-10 Sunflower Glycerides		PEG-13 Sunflower Glycerides	
Totals*	1	NR	11	0.8-5	1	NR
Duration of use						
Leave on	*NR*	*NR*	*2*	*5*	*1*	*NR*
Rinse off	*1*	*NR*	*8*	*0.8-2.5*	*NR*	*NR*
Diluted for (bath) use	*NR*	*NR*	*1*	*NR*	*NR*	*NR*
Exposure type						
Eye area	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	NR	NR	2[a]	5[a]	1[a]	NR
Incidental inhalation-powder	NR	NR	NR	NR	NR	NR
Dermal contact	1	NR	4	2.5	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair non-coloring	NR	NR	7	0.8-5	1	NR
Hair coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	2	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR

Abbreviation: NR, none reported.

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

[a]Includes products that can be sprays, but it is not known whether the reported uses are sprays.

[b]Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation.

[c]Includes products that can be powders, but it is not known whether the reported uses are powders.

gelatin capsules and 6.12% in oral solutions.[39] A mixture of mono-, di-, and triglycerides and PEG mono- and diesters of fatty acids (polyglycides) of hydrogenated vegetable oils may be safely used as an excipient in dietary supplement tablets, capsules, and liquid formulations that are intended for ingestion in daily quantities measured in drops or similar small units of measure when the total ester content is $> 90\%$, the acid value is < 2, the hydroxyl value is < 56, the lead content is < 0.1 mg/kg, and < 10 mg/kg 1,4-dioxane and < 1 mg/kg ethylene oxide is present (21CFR172.736).

Fats, oils, fatty acids, and fatty alcohols derived from coconut, palm, and soybean oils and reacted with 400-3,000 Da PEG are approved for use as indirect food additives in polymers for use as components of articles intended for repeated use in textiles and textile fibers (21CFR177.2800). Also, the fatty acids and alcohols derived from coconut, corn, palm, and soybean oils reacted with 200-4,600 Da PEG, with or without dehydration, to form an ester are approved for use as an indirect food additive in defoaming agents used in the manufacture of paper and paperboard components (21CFR176.210).

Toxicokinetics

Penetration Enhancement

Surfactants can enhance penetration of some compounds through the skin. The ability of PEG-8 Caprylic/Capric Glycerides to be a dermal penetration enhancer has been investigated in a number of studies; a few examples of those studies are provided. In one study in which transdermal delivery of lidocaine (lipophilic) and prilocaine hydrochloride (hydrophilic) was measured in vitro in Franz-type diffusion cells, several microemulsion systems that contained 11.5% to 53% PEG-8 Caprylic/Capric Glycerides, 3% to 70% isostearyl isostearate, 8% to 35% polyglyceryl-6 isostearate, and 7% to 65% water increased delivery of lidocaine up to 4 times compared to an oil/water emulsion vehicle, and increased the delivery of

Table 6. Ingredients Not Reported to be Used.

PEG	6 Almond Glycerides
PEG	35 Almond Glycerides
PEG	11 Avocado Glycerides
PEG	14 Avocado Glycerides
PEG	11 Babassu Glycerides
PEG	42 Babassu Glycerides
PEG	4 Caprylic/Capric Glycerides
PEG	11 Cocoa Butter Glycerides
PEG	7 Cocoglycerides
PEG	9 Cocoglycerides
PEG	20 Corn Glycerides
PEG	60 Corn Glycerides
PEG	20 Evening Primrose Glycerides
PEG	60 Evening Primrose Glycerides
PEG	78 Glyceryl Cocoate
PEG	5 Hydrogenated Corn Glycerides
PEG	8 Hydrogenated Fish Glycerides
PEG	6 Hydrogenated Palm/Palm Kernel Glyceride
PEG	13 Mink Glycerides
PEG	25 Moringa Glycerides
PEG	42 Mushroom Glycerides
PEG	2 Olive Glycerides
PEG	6 Olive Glycerides
PEG	7 Olive Glycerides
PEG	40 Olive Glycerides
PEG	18 Palm Glycerides
PEG	12 Palm Kernel Glycerides
PEG	60 Passiflora Edulis Seed Glycerides
PEG	60 Passiflora Incarnata Seed Glycerides
PEG	45 Safflower Glycerides
PEG	60 Shea Butter Glycerides
PEG	75 Shorea Butter Glycerides
PEG	75 Soy Glycerides
PEG	2 Sunflower Glycerides
PEG	7 Sunflower Glycerides
PEG	5 Tsubakiate Glycerides
PEG	10 Tsubakiate Glycerides
PEG	20 Tsubakiate Glycerides
PEG	60 Tsubakiate Glycerides

prilocaine hydrochloride almost 10 times compared to a hydrogel.[26] The increase in delivery was attributed to increased solubility of the drug and appeared to be dependent on drug mobility in the vehicle.

Another example is the effect of PEG-8 Caprylic/Capric Glycerides on the transdermal flux of carvedilol, a nonselective β adrenergic antagonist, through porcine skin. The flux of carvedilol from a PEG-8 Caprylic/Capric Glycerides vehicle (ie, 14.28 μg/cm2/h) was 8.6 times greater than that obtained with the control vehicle (ie, 1.66 μg/cm2/h) composed of phosphate buffered saline containing 40% vol/vol PEG 400.[40] However, when placed in the donor compartment, flux was only 4.7 times greater with 5% PEG-8 Caprylic/Capric Glycerides compared to controls. In another study, when used as a vehicle, PEG-8 Caprylic/Capric Glycerides was only a weak penetration enhancer of cyclosporin A, a nonpolar cyclic oligopeptide, through excised rat skin.[41]

A formulation containing 40% PEG-8 Caprylic/Capric Glycerides, 39.75% ethoxydiglycol, 10% ethanol, 5% ethyl oleate, and 5% sorbitan oleate improved the skin delivery of kahalalide F, a lipophilic cyclic molecule with a high molecular weight; however, the amount of kahalalide F that penetrated and permeated through the skin was much greater with dimethyl sulfoxide.[41] Additionally, a formulation containing 39.75% PEG-8 Caprylic/Capric Glycerides, 35% propylene glycol, 10% ethanol, 10% n-methyl-2-pyrrolidone, and 5% isopropyl myristate did not improve skin delivery of kahalalide F.

Toxicological Studies

Single Dose (Acute) Toxicity

Oral. PEG-6 Caprylic/Capric Glycerides has an oral LD_{50} of $>$ 5 g/kg in rats; 5 males and 5 females were given a single dose of 5.5 g/kg, and none of the animals died.[42] PEG-8 Caprylic/Capric Glycerides has an oral LD_{50} of 22 g/kg in rats.[43] The oral LD_{50} of PEG-7 Glyceryl Cocoate in rats was $>$ 19.9 mg/g, the highest dose administered.[2]

Repeated Dose Toxicity

Oral

PEG-8 Caprylic/Capric Glycerides. The oral toxicity of a blend of 3 solvents was evaluated in Wistar rats; the blend consisted of 40% PEG-8 Caprylic/Capric Glycerides, 40% apricot kernel oil PEG-6 esters, and 20% ethoxydiglycol.[44] (In the published paper, the blend was described using trade names; trade name and other information suggests that the second portion of the blend is apricot kernel oil PEG-6 esters.) Groups of 10 male and 10 female rats were given by gavage a volume of 5, 10, or 20 mL/kg/d test article for 4 weeks. A negative control group of 10 rats/sex received 20 mL/kg/d 1% (wt/vol) hydroxyethyl cellulose in purified water. The animals were examined daily for signs of toxicity, and hematology, clinical chemistry, and urinalysis parameters were measured at study termination; at necropsy, organs were examined grossly and microscopically, and hepatic cytochrome P450 (CYP450) content and related activities were evaluated.

The test article was relatively well tolerated at 5 mL/kg/d, and this volume was considered the no-observed adverse effect level (NOAEL). Adverse effects were observed with the greater doses, and the main effects were observed in the liver, kidneys, and adrenal glands. One female of the 20 mL/kg/d group died on day 28; the death was considered test article–related because the animal had worsening clinical condition prior to death and necropsy results included enlarged and pale kidneys, a dilated stomach with multiple dark red areas on the glandular mucosa, a dilated caecum, and several whitish areas on the liver. In the surviving 20 mL/kg/d animals, there was an increase in clinical signs of toxicity, including ptyaliasm, partial blepharoptosis, and piloerection, and a statistically significant decrease in feed consumption and water intake in males and females and in body weights in males, when compared to

control animals. At study termination, most of the high-dose animals had dilated caecums containing soft brownish content, and 12 of the animals had pale adrenal glands; 5 of the 10 males and 3 of the 9 surviving females had enlarged kidneys. Absolute and relative organ-to-body weights were also statistically significantly affected; increases were reported in absolute and relative kidney weights in males and females, relative liver weights in males, and absolute and relative liver weights in females, and decreases were reported in absolute and relative spleen weights in males and females, absolute thymus weights in males, and absolute and relative thymus weights in females. Microscopic findings at this dose included mild centrilobular hepatocellular hypertrophy, mostly mild bilateral diffuse tubular dilation and bilateral multifocal tubular epithelium degeneration and necrosis in the kidney, and vacuolation of adrenal gland cortex. Changes in some hematological parameters were also reported. A volume-related statistically significant increase in induction of hepatic CYP450 was reported. Some similar effects were reported in animals given 10 mL/kg/d but not at the same rate of incidence. No adverse effects were observed in dogs that were dosed orally for 13 weeks with 1.0 g/kg/d PEG-8 Caprylic/Capric Glycerides.[43] Further details were not provided.

PEG-7 Glyceryl Cocoate. Groups of 10 male rats were fed a diet containing 0%, 2.5%, 5.0%, or 7.5% of a formulation containing 0.8% PEG-7 Glyceryl Cocoate for 28 days.[45] All animals survived until study termination. For all groups, select tissues were weighed at necropsy. Select tissues of animals in the control and high-dose group were examined microscopically. Spleen weights were significantly decreased in high-dose animals; although there were no associated microscopic changes, the researchers stated the change could be associated with dosing. Soft feces, a distended cecum, and enlarged mesenteric lymph nodes were observed at necropsy in the mid- and high-dose animals. The no-observable effect level (NOEL) was 2.5% of the formulation containing 0.8% PEG-7 Glyceryl Cocoate.

Reproductive and Developmental Toxicity

A segment II developmental toxicity test was performed in rats with PEG-8 Caprylic/Capric Glycerides.[46] The animals were dosed with 0, 1,000, 2,000, or 3,000 mg/kg/d by gavage on days 6 through 17 of gestation. The maternal NOAEL was 2,000 mg/kg/d; effects on body weigh were reported at 3,000 mg/kg/d. The embryo/fetal NOAEL was 3,000 mg/kg/d. No signs of embryotoxicity, fetotoxicity, or teratogenicity were noted at any dose level. No other details were provided.

Genotoxicity

PEG-6 Caprylic/Capric Glycerides, PEG-7 Glyceryl Cocoate, and PEG-10 Olive Glycerides were not mutagenic, with or without metabolic activation. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were exposed to concentrations of 50-5,000 μg/plate PEG-6 Caprylic/Capric Glycerides in one study,[42] and *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to 0.04% PEG-6 Caprylic/Capric Glycerides in 0.9% saline in another.[47] *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 also were exposed to 0.625% PEG-7 Glyceryl Cocoate in 0.9% saline.[48] Details of testing with PEG-10 Olive Glycerides, including strains used and concentrations tested, were not provided.[17] Genotoxicity studies of other PEGylated alkyl glycerides were not found in the published literature nor were additional unpublished data provided.

Carcinogenicity

Carcinogenicity data on PEGylated alkyl glycerides were not found in the published literature nor were unpublished data provided.

Irritation and Sensitization

Dermal

The irritation and sensitization potentials of several PEGylated alkyl glycerides were evaluated in alternative,[26,49-55] nonhuman,[2,17,42,56-62] and human studies,[2,17,42,63-72] and these ingredients generally were not irritants or sensitizers in the alternative and human studies (Table 7). Mixed results were observed in the nonhuman studies; specifically, undiluted PEG-20 Almond Glycerides,[61] PEG-60 Almond Glycerides,[60] PEG-12 Palm Kernel Glycerides,[59] and PEG-45 Palm Kernel Glycerides[58] were irritating to rabbit skin in primary skin irritation studies, and PEG-7 Glyceryl Cocoate (concentration not specified) was mildly irritating to rabbit skin.[2] The only reaction reported in clinical testing was PEG-10 Olive Glycerides (2% active matter) was nonirritating to mildly irritating.[17] In other clinical studies, up to 20% PEG-60 Almond Glycerides,[64,69] undiluted PEG-6 Caprylic/Capric Glycerides,[42,63,66] undiluted PEG-7 Glyceryl Cocoate,[2,65,70-72] and a formulation containing 1% PEG-75 Shea Butter Glycerides[67,68] were not irritants or sensitizers.

Phototoxicity

PEG-7 Glyceryl Cocoate was not phototoxic in mice at a concentration of 50%.[2] Formulations containing 0.3% PEG-7 Glyceryl Cocoate were not photosensitizers in clinical testing.

Ocular

In a hen's egg test utilizing the chorioallantoic membrane (HET-CAM), a formulation containing 11% PEG-7 Glyceryl Cocoate had practically no irritation potential,[73] and concentrations of 10, 50, and 100% PEG-7 Glyceryl Cocoate were slightly irritating;[74] in a neutral red uptake (NRU) assay, the ocular irritation potential of PEG-7 Glyceryl Cocoate was not classified[75] (Table 8). The PEG-10 sunflower glyceride was a nonirritant in a chorioallantoic membrane vascular assay

Table 7. Dermal Irritation and Sensitization.

Test article	Concentration/dose	Test population	Procedure	Results	Reference
Alternative studies					
PEG-60 Almond Glycerides	100%; 100 μL	NHEK	EpiDerm in vitro toxicity test; MTT was used to measure cell viability	$ET_{50} > 24$ hours; expected in vivo dermal irritancy is nonirritating	52
PEG-60 Almond Glycerides	100%; 100 μL	NHEK	EpiDerm in vitro toxicity test	$ET_{50} = 5.3$ hours; expected in vivo dermal irritancy is moderate to mild	51
PEG-6 Caprylic/Capric Glycerides	1% and 10%; 50 μL	Skin[2] (a 3D human skin tissue)	Model ZK1300 in vitro toxicity test; MTT was used to measure cell viability	Mild to moderate dermal irritation potential	49
PEG-8 Caprylic/Capric Glycerides	35% in an ME also containing 10% isostearylic isostearate and 35% polyglyceryl-6 isostearate	Male Wistar rat skin	1 mL of the ME or water was applied to the skin sample for 20 hours in a Franz-type diffusion cell	Low potential for skin irritancy The ME did not perturb the skin barrier	26
PEG-7 Glyceryl Cocoate	100%; 100 μL	NHEK	EpiDerm in vitro toxicity test	$ET_{50} > 24$ hours; expected in vivo dermal irritancy is nonirritating	53
PEG-7 Glyceryl Cocoate	1% and 10%; 50 μL	Skin[2]	Model ZK1300 in vitro toxicity test	Mild dermal irritation potential	50
PEG-13 Sunflower Glycerides	100%; 100 μL	NHEK	EpiDerm in vitro toxicity test	$ET_{50} > 24$ hours; expected in vivo dermal irritancy is nonirritating	54
PEG-13 Sunflower Glycerides	100%	Skin[2]	Model ZK1350 MTT assay for corrosivity	Expected to be noncorrosive	55
Nonhuman					
PEG-20 Almond Glycerides	Neat; 0.5 mL	6 female NZW rabbits	24-hour semiocclusive patches (2.5 cm2) applied to an approximately 6 sq. in. area of intact and abraded skin that was clipped free of hair Test sites were scored 1 and 48 hours after patch removal	PII = 4.5/8; marked irritant effect, but not a primary irritant (which is PII≥5) 24 hours: moderate erythema at both sites of 3 rabbits, and well-defined erythema at both sites of the other 3 rabbits; slight edema at 1 abraded and 2 intact sites, moderate edema at 3 abraded and 4 intact sites, and severe edema at 2 abraded sites 72 hours: some decline in edema but not in erythema	61
PEG-60 Almond Glycerides	Neat; 0.5 mL	6 female NZW rabbits	24-hour semiocclusive patches (2.5 cm2) applied to an approximately 6 sq. in. area of intact and abraded skin that was clipped free of hair Test sites were scored 1 and 48 hours after patch removal	PII = 2.6/8; some irritant effect, that was reversible 24 h: defined erythema at all treated sites, except 1 intact site had moderate erythema; moderate edema at both sites of 2 rabbits, and slight edema in the other animals 72 hours: reactions declined; very slight erythema at both sites of 4 rabbits; very slight edema at the abraded site of 1 rabbit; desquamation or scaling at the abraded sites of 2 rabbits and the intact site of 1 rabbit	60
PEG-6 Caprylic/Capric Glycerides	4% in formulation, 0.5 mL	3 NZW rabbits/sex	4-hour occlusive patch applied to shaved intact skin	Not corrosive; mildly irritating	56
PEG-6 Caprylic/Capric Glycerides	Undiluted, 0.5 g	3 rabbits	Draize test; 4-hour semiocclusive patches were applied to intact and abraded skin The test sites were scored at 24 and 72 h	Not an irritant	42
PEG-6 Caprylic/Capric Glycerides	Undiluted at induction 50% aq. at challenge	Not specified	Bühler test, according to OECD Guideline 406	Not an irritant or a sensitizer	42
PEG-8 Caprylic/Capric Glycerides	ME containing 1.3% diclofenac epolamine wt/wt in 30% propylene glycol monocaprylate, 50% PEG-8 Caprylic/Capric Glycerides/ethoxydiglycol (1:2 wt/wt), and 20% water	3 albino Wistar rats	100 μL was applied for 24 hours to the left ear of each rat	Not an irritant No erythema	62

(continued)

Table 7. (continued)

Test article	Concentration/dose	Test population	Procedure	Results	Reference
PEG-7 Glyceryl Cocoate	5%, 10%, 20%, and 50% in sterile water, and undiluted, 0.2 mL	5 female Dunkin-Hartley guinea pigs	Topical application tolerance test using 24-hour occlusive patches; each animal was patched with 2 concentrations	No irritation at any concentration	57
PEG-7 Glyceryl Cocoate	50% in Vaseline	4 male and female mutant hairless mice	Fixed patches applied with porous leucoplastic to shaved skin for 24 hours	No reaction	2
PEG-7 Glyceryl Cocoate	50% in Vaseline	4 male NZW rabbits	24-hour patch test	Slight reaction; reaction score of 3/4	2
PEG-7 Glyceryl Cocoate	50% in Vaseline	4 male Pirbright white guinea pigs	Fixed patches applied with porous leucoplastic to shaved skin for 24 hours	No reaction	2
PEG-7 Glyceryl Cocoate	Not specified	3 albino rabbits	Draize primary irritation test; patches were applied to intact and abraded skin	Mild dermal irritant; PII = 1.66 Moderate erythema and mild edema were reported	2
PEG-7 Glyceryl Cocoate	Not specified	2 albino rabbits	Draize primary irritation test sites were rinsed after 1 hour and scored at 24 and 48 hours	Skin had reddening directly after rinsing; no irritation observed after 24 hours	2
PEG-7 Glyceryl Cocoate	1% in sterile water at intradermal induction, 0.1 mL 0 and 100% for both topical induction (0.4 mL) and challenge (0.2 mL)	10 female Dunkin-Hartley guinea pigs/group	Magnusson-Kligman maximization study, with FCA at intradermal induction Topical induction was performed 1 week later; 48-hour occlusive patches were applied over the intradermal injection sites; the test site was pretreated with 10% SLS in petrolatum the day before patching 2 weeks after topical induction, the challenge was performed with 24-hour occlusive patches applied to a previously untreated site of test animals and to control animals	Not a sensitizer	57
PEG-7 Glyceryl Cocoate	10% solution	5 male Pirbright white W58 guinea pigs	Ten 0.1-mL intracutaneous injections at 2-day intervals; the challenge was performed 14 days after the last induction injection	Not a sensitizer Sharply demarcated necrotic changes of the skin (about the size of a pea), but no general signs, that subsided during the 14-day interval	2
PEG-10 Olive Glycerides	3% active matter	Rabbits, number not provided	No details provided	Not an irritant	17
PEG-10 Olive Glycerides	50% active matter	Guinea pigs, number not provided	Sensitization study; no details provided	Not an irritant or sensitizer	17
PEG-12 Palm Kernel Glycerides	Neat; 0.5 mL	6 female NZW rabbits	24-hour occlusive patches (2.5 cm2) applied to intact and abraded skin that was clipped free of hair test sites were scored 1 and 48 hours after patch removal	PII = 4.5/8; definite irritant effect 24 hours: well-defined erythema at all test sites; moderate edema at both test sites of 3 rabbits and slight edema at the remaining test sites 48 hours: some increase in erythema and some decrease in edema; erythema increased to moderate to severe at both test sites of one animal and the abraded site of another; edema was moderate at both sites of 2 animals, slight at both sites of 3 animals, and very slight at both sites of 1 animal	59
PEG-45 Palm Kernel Glycerides	neat; 0.5 ml	6 female NZW rabbits	24-h occlusive patches (2.5 cm^2) applied to intact and abraded skin that was clipped free of hair test sites were scored 1 and 48 h after patch removal	PII = 2.6/8; definite irritant effect 24 h: well-defined erythema at all test sites; slight edema at both test sites of 3 rabbits, and very slight edema at the remaining test sites 72 h: reactions declined; well-define erythema in one animal, very slight erythema at both sites of 3	58

(continued)

Table 7. (continued)

Test article	Concentration/dose	Test population	Procedure	Results	Reference
				animals, very slight erythema with desquamation at the abraded site and no erythema at the intact site of 1 animal, and no erythema at either site of 1 animal; slight edema at both test sites of 1 animal (this was an increase), very slight edema at both test sites of 1 animal, very slight edema at the abraded sites and no edema at the intact sites of 3 animals, and no edema at either site of 1 animal	
HUMAN					
PEG-20 almond glyceride	5.0% aq; 0.4 mL	93 subjects	Occlusive HRIPT; nine 24-hour patches were applied to a site on the upper arm 3×/wk for 3 weeks; the 24-hour challenge patch was applied after a 17 day nontreatment period	Not a sensitizer	69
PEG-60 Almond Glycerides	20% aq; 0.2 mL	51 subjects	Occlusive HRIPT; 24-hour semiocclusive patches (1 sq. in.) were applied to a site on the upper back 3×/wk for a total of 10 applications Challenge patches were applied to the original and untreated sites after a 14-day nontreatment period, and the sites were scored 24 and 48 hours after application	Not an irritant or a sensitizer	64
PEG-6 Caprylic/Capric Glycerides	2% aq	50 subjects	48-hour patch was applied to the back of each subject; it was not specified whether the patch was occlusive The test site was observed at 48 and 72 hours	Not an irritant	42
PEG-6 Caprylic/Capric Glycerides	Concentration not specified; assumed undiluted	112 subject; 48 had sensitive skin	Single 48-hour patch; the type of patch was not specified	Not irritating	42
PEG-6 Caprylic/Capric Glycerides	4% in formulation	81 subjects	HRIPT; 24-hour patch were applied to a site on the arm 3×/wk for 3 weeks; the challenge patch was applied after a 10-day nontreatment period	Not a sensitizer	63
PEG-6 Caprylic/Capric Glycerides	10% aq; 0.2 mL	57 subjects	Occlusive HRIPT; 24-hour semiocclusive patches (1 in. × 0.75 in.) were applied to a site on the upper back 3×/wk for a total of 10 applications Challenge patches were applied to the original and untreated sites after a 14-day nontreatment period, and the sites were scored 24 and 48 hours after application	Not an irritant or a sensitizer	66
PEG-6 Caprylic/Capric Glycerides	Concentration not specified; assumed undiluted	10 subjects	Five 48-h patches were applied at 48-hour intervals; a 48-hour challenge patch was applied after a 10-day nontreatment period	No reactions were observed	42
PEG-7 Glyceryl Cocoate	50%	4 subjects	24-hour patches (not specified if occlusive or not)	No reactions	2
PEG-7 Glyceryl Cocoate	Undiluted	40 subjects	Primary irritation patch test (details not provided)	No signs of irritation	2
PEG-7 Glyceryl Cocoate	Not specified	5 subjects	Test plaster applied to forearm for 1 h	No signs of irritation	2
PEG-7 Glyceryl Cocoate	8% in formulation applied neat; 0.1 g	103 subjects	Semiocclusive HRIPT; nine 24-h patches were applied to a site on the back 3×/wk for 3 weeks; the 24-hour challenge patch was applied after a 10-15 day nontreatment period	Not a sensitizer	70
PEG-7 Glyceryl Cocoate	8% in formulation applied neat; 0.1 g	103 subjects (same subjects as above)	Semiocclusive HRIPT, followed the same protocol as above	Not a sensitizer	71

(continued)

Table 7. (continued)

Test article	Concentration/dose	Test population	Procedure	Results	Reference
PEG-7 Glyceryl Cocoate	11% in formulation; 0.2 g	205 subjects	Semiocclusive HRIPT; nine 24-hour patches were applied to a site on the back 3×/wk for 3 weeks; the 24-hour challenge patch was applied after a 10- to 15-day nontreatment period	Not a sensitizer One subject had definite erythema and edema (++) at the second induction reading and was removed from the study	72
PEG-7 Glyceryl Cocoate	Neat; 0.2 mL	57 subjects	Occlusive HRIPT; 24-hour semiocclusive patches (1 in. × 0.75 in.) were applied to a site on the upper back 3×/wk for a total of 10 applications Challenge patches were applied to the original and untreated sites after a 14-day nontreatment period, and the sites were scored 24 and 48 hours after application	Not an irritant or a sensitizer	65
PEG-10 Olive Glycerides	2% active matter	Not stated	Duhring-chamber test; no details provided	Not irritating to mildly irritating	17
PEG-75 Shea Butter Glycerides	1% in formulation	10 subjects	Cutaneous tolerance test; product was applied to the whole face, including the eyes, 2×/d for 5 days	Cutaneous irritant potential is "practically nil"	68
PEG-75 Shea Butter Glycerides	1% in formulation; tested neat; 0.2 g	219 subjects	Semiocclusive HRIPT; nine 24-hour patches were applied to a site on the back 3×/wk for 3 weeks; the 24-hour challenge patch was applied after a 2-week nontreatment period	Not a sensitizer 2 subjects had ± reactions during induction (one on D1; one on D7) 5 subjects had ±/1 reactions at challenge	67

Abbreviations: ET_{50}, time at which percent viability would be 50%; FCA, Freund complete adjuvant; HRIPT, human repeated insult patch test; ME, microemulsion; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide; NHEK, normal, human-derived epidermal keratinocytes; NZW, New Zealand White; PII, primary irritation index; SLS, sodium lauryl sulfate.

Table 8. Ocular Irritation Studies.

Test article	Concentration/dose	Test system	Procedure	Results	Reference
Alternative studies					
PEG-7 Glyceryl Cocoate	11% in formulation; tested at 50%; 0.3 mL	White Leghorn chicken eggs	HET-CAM	Practically no irritation potential Mean score 1.25/32	73
PEG-7 Glyceryl Cocoate	10 and 50% in water and undiluted, 0.3 mL	Chicken eggs	HET-CAM	Slight irritant	74
PEG-7 Glyceryl Cocoate	100-1,468 μg/mL	Human keratinocytes (HaCaT)	NRU	Cytotoxic to the HaCaT cells, resulting in a median MRU-50 value of 427 μg/mL; considered not classified (≥750 is classified as nonirritant, and <110 is classified as a severe irritant)	75
PEG-10 sunflower glyceride	Neat; 40 μL	DeKalb chicken eggs	CAMVA	Nonirritant RC_{50} was 80% (>5.0% is a nonirritant)	76
Nonhuman studies					
PEG-6 Caprylic/Capric Glycerides	4% in formulation—tested neat (2 groups) and at 10% aq.; 0.1 mL	3 NZW rabbits/group	Undiluted test article was instilled into the conjunctival sac of the eye, and the eye was rinsed in one group and not rinsed in the other; the eyes of the animals dosed with 10% were not rinsed	Not an ocular irritant	78
PEG-6 Caprylic/Capric Glycerides	1 and 5% aq.; 0.1 ml	4 rabbits/group	Test substance was applied, and the eyes were evaluated for up to 72 hours	No irritant effects 1%: no redness, swelling, secretion, or corneal changes 5%: slight conjunctival redness, slight swelling, and secretion in 1 animal; these signs were reversed by 48 hours	42
PEG-6 Caprylic/Capric Glycerides	Undiluted; 0.1 mL	2 rabbit	Draize test; the eyes were observed for up to 8 days	Strong irritation, including redness, swelling, and secretion, was observed No corneal changes were reported Swelling decreased over the 8-day period, but redness was not completely reversible	42
PEG-8 Caprylic/Capric Glycerides	0.5%-5.0% in phosphate buffer (pH 7.4); 0.1 mL/dose	6 NZW rabbits	Instilled into the conjunctival sac of the left eye 4×/d for 7 days	0.5-3% was not irritating 5% was a slight irritant	77
PEG-7 Glyceryl Cocoate	10% aq.	2 rabbits	Instilled into the conjunctival sac	Not irritating	2
Human studies					
PEG-75 Shea Butter Glycerides	1% in formulation	10 subjects	Ocular tolerance test; product was applied to the whole face, including the eyes, 2×/d for 5 days	No ocular irritation; ocular irritation rate of 0.15%	68

Abbreviations: CAMVA, chorioallantoic membrane vascular assay; HET-CAM, hen's egg test utilizing the chorioallantoic membrane; NRU, neutral red uptake; NZW, New Zealand White; OECD, Organisation for Economic Co-operation and Development; RC_{50}, theoretical concentration producing a positive reaction in 50% of treated eggs.

(CAMVA).[76] In rabbits, 10% aq. The PEG-7 Glyceryl Cocoate[2] and up to 3% PEG-8 Caprylic/Capric Glycerides were not ocular irritants,[77] and 5% PEG-8 Caprylic/Capric Glycerides was a slight irritant to rabbit eyes.[77] Undiluted PEG-6 Caprylic/Capric Glycerides was a strong ocular irritant; however, aq. solutions of up to 5%[42] and formulations containing 4% PEG-6 Caprylic/Capric Glycerides[78] were not ocular irritants in rabbits. In clinical testing, a formulation containing 1% PEG-75 Shea Butter Glycerides did not induce ocular irritation in a tolerance test.[68]

Mucous Membrane

PEG-10 Olive Glycerides, 3% active matter, did not irritate the mucous membrane.[17] (No details were provided.) A female hygiene product containing 0.1% PEG-75 Shea Butter Glycerides did not induce any evidence of vaginovulvar irritation in a use study.[79] Twenty-one female subjects bathed in a bubble bath using a "quarter-size amount" of the test material for 10 to 20 minute daily for 1 week.

Summary

This report addresses the safety of 60 PEGylated alkyl glycerides as used in cosmetics. PEGylated alkyl glycerides are mono-, di-, and/or triglycerides that have been modified with ethylene glycol repeat units (in the starting material form as epoxide). Most of the PEGylated alkyl glycerides are reported to function as skin conditioning agents or surfactants.

VCRP data obtained from the FDA, and data received in response to surveys of the maximum reported use concentration by category that were conducted by the Council, indicate that 21 of the 60 ingredients included in this safety assessment are used in cosmetic formulations. The PEG-7 Glyceryl Cocoate has the most reported uses, that is, 858, followed by PEG-6 Caprylic/Capric Glycerides with 548 reported uses; the majority of uses for both of these ingredients are in rinse-off formulations. The highest concentrations of use reported for products resulting in leave-on dermal exposure are 11.3% and 6% PEG-7 Glyceryl Cocoate in tonics, dressings, and other hair grooming aids and other fragrance preparations. The PEG-7 Glyceryl Cocoate also has the highest rinse-off concentration of use reported, tha is, 10% in skin cleansing products.

Since the original safety assessment was published, the frequency of use of PEG-7 Glyceryl Cocoate increased from 173 reported uses in 1996 to 858 reported uses in 2014. At the time of the original safety assessment, concentration of use data were not available from the FDA. However, based on ocular and sensitization data, a concentration limit of 10% was placed on leave-on products containing PEG Glyceryl Cocoates. The current reported concentration of use in leave-on products is slightly higher, that is, 11.3% PEG-7 Glyceryl Cocoate in tonics, dressings, and other hair grooming aids.

PEG-8 Caprylic/Capric Glycerides can be a dermal penetration enhancer. In rats, PEG-6 Caprylic/Capric Glycerides had an oral LD_{50} of $>$ 5 g/kg, PEG-8 Caprylic/Capric Glycerides had an oral LD_{50} of 22 g/kg, and PEG-7 Glyceryl Cocoate has an oral LD_{50} of $>$ 19.9 mg/g. In a 4-week study in rats, the NOAEL for a blend of 40% PEG-8 Caprylic/Capric Glycerides, 40% apricot kernel oil PEG-6 esters, and 20% ethoxydiglycol was 5 mL/kg/d. Test-article related effects were reported in the kidneys, livers, and gastrointestinal systems of animals dosed with 20 mL/g/d; effects were also observed in animals given 10 mL/kg/d, but they did not occur at the same rate of incidence. In a 4-week dietary study in rats, the NOEL of a formulation containing 0.8% PEG-7 Glyceryl Cocoate was 2.5%; at higher concentrations, soft feces, a distended cecum, and enlarged mesenteric lymph nodes were observed, and a decrease in spleen weights was reported. No adverse effects were observed in dogs that were dosed orally for 13 weeks with 1.0 g/kg/d PEG-8 Caprylic/Capric Glycerides.

PEG-8 Caprylic/Capric Glycerides, up to 3,000 mg/kg in purified water, did not produce embryotoxicity, fetotoxicity, or teratogenicity. The maternal embryo/fetal NOAELs were 2,000 and 3,000 mg/kg/d, respectively. The PEG-6 Caprylic/Capric Glycerides, PEG-7 Glyceryl Cocoate, and PEG-10 Olive Glycerides were not mutagenic in the Ames test.

The irritation and sensitization potentials of several PEGylated alkyl glycerides were evaluated in alternative, nonhuman, and human studies, and these ingredients generally were not irritants or sensitizers in the alternative and human studies. Mixed results were observed in the nonhuman studies; specifically, undiluted PEG-20 Almond Glycerides, PEG-60 Almond Glycerides, PEG-12 Palm Kernel Glycerides, and PEG-45 Palm Kernel Glycerides were irritating to rabbit skin in primary skin irritation studies, and PEG-7 Glyceryl Cocoate was mildly irritating to rabbit skin in one study. The only reactions reported in clinical testing was PEG-10 Olive Glycerides (2% active matter) was nonirritating to mildly irritating. In other clinical studies, up to 20% PEG-60 Almond Glycerides, undiluted PEG-6 Caprylic/Capric Glycerides, undiluted PEG-7 Glyceryl Cocoate, and a formulation containing 1% PEG-75 Shea Butter Glycerides were not irritants or sensitizers.

In a HET-CAM, a formulation containing 11% PEG-7 Glyceryl Cocoate had practically no ocular irritation potential, and concentrations of 10%, 50%, and 100% PEG-7 Glyceryl Cocoate were slightly irritating. The PEG-10 Sunflower Glycerides was classified as a nonirritant in a CAMVA. In rabbits, formulations containing 4% PEG-6 Caprylic/Capric Glycerides and up to 3% PEG-8 Caprylic/Capric Glycerides were not ocular irritants and 5% PEG-8 Caprylic/Capric Glycerides was a slight irritant. Undiluted PEG-6 Caprylic/Capric Glycerides was a strong ocular irritant; however, aq. solutions of up to 5%, and formulations containing 4% PEG-6 Caprylic/Capric Glycerides were not ocular irritants in rabbits. In clinical testing, a formulation containing 1% PEG-75 Shea Butter Glycerides did not induce ocular irritation in a tolerance test.

PEG-10 Olive Glycerides, 3% active matter, did not irritate the mucous membrane. In a use study, a female hygiene product containing 0.1% PEG-75 Shea Butter Glycerides did not induce any evidence of vaginovulvar irritation.

Data on the carcinogenicity of PEGylated alkyl glycerides were not found in the published literature nor were unpublished data provided.

Discussion

Five of the ingredients included in this review, that is, PEG-7 Glyceryl Cocoate, PEG-30 Glyceryl Cocoate, PEG-40 Glyceryl Cocoate, PEG-78 Glyceryl Cocoate, and PEG-80 Glyceryl Cocoate were reviewed previously; in 1999, the Panel concluded these 5 ingredients are safe as used in rinse-off products and safe at up to 10% in leave-on products. The safety assessment of these ingredients was scheduled for rereview in 2014; however, the Panel found it appropriate to include the PEG Glyceryl Cocoates in this report, rather than conduct a separate rereview.

The Panel used the 1999 PEG Glyceryl Cocoates repor as well as the 2012 safety assessment of the PEGylated oils and the findings on skin irritation and sensitization included in this current report to inform the safety of these PEGylated alkyl glycerides. There are no data on skin penetration by the PEGylated alkyl glycerides, but many of the PEGylated alkyl glycerides are approved for use in dietary supplements and as indirect food additives, and PEG-8 Caprylic/Capric Glycerides is reported to be used as a pharmaceutical excipient. Data on carcinogenicity were not found, and these ingredients were not mutagenic and lack structural features of concern. Thus, the Panel focused its review on the safety of topical application.

Some ingredients demonstrated irritation, but at concentrations above those used in cosmetic formulations; however, because the potential exists for dermal irritation with the use of products containing PEGylated alky glycerides, the Panel specified that products containing these ingredients must be formulated to be nonirritating. It should be noted that although the conclusion of the 1999 report of PEG glyceryl cocoates limited their use to 10% in leave-on products, negative HRIPT data at and above the reported concentration of use, and the inclusion of the specification that these ingredients be used in products when formulated to be nonirritating, alleviated the need for that concentration limit in the current report.

The Panel recognized that these ingredients can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data or when dermal absorption was a concern.

The Panel noted that some of the PEGylated alkyl glycerides are used in products that could be incidentally inhaled. Although reported concentrations of use included 6% PEG-7 Glyceryl Cocoate in "other" fragrance preparations and 2% PEG 7 Glyceryl Cocoate in a pump spray deodorant, and there were no inhalation data available, the Panel was not concerned with the use of these ingredients in such formulations. The Panel noted that in aerosol products, 95% to 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. 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.

Finally, because these ingredients are obtained from plant sources, the Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. The Panel stressed that the cosmetics industry should continue to use current good manufacturing practices to limit these impurities in the ingredient before blending into cosmetic formulation.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 60 PEGylated alkyl glycerides are safe in cosmetics in the present practices of use and concentration when formulated to be nonirritating:

PEG-6 Almond Glycerides*
PEG-20 Almond Glycerides
PEG-35 Almond Glycerides*
PEG-60 Almond Glycerides
PEG-192 Apricot Kernel Glycerides
PEG-11 Avocado Glycerides*
PEG-14 Avocado Glycerides*
PEG-11 Babassu Glycerides*
PEG-42 Babassu Glycerides*
PEG-4 Caprylic/Capric Glycerides*
PEG-6 Caprylic/Capric Glycerides
PEG-7 Caprylic/Capric Glycerides
PEG-8 Caprylic/Capric Glycerides
PEG-11 Cocoa Butter Glycerides*
PEG-75 Cocoa Butter Glycerides
PEG-7 Cocoglycerides*
PEG-9 Cocoglycerides*
PEG-20 Corn Glycerides*
PEG-60 Corn Glycerides*
PEG-20 Evening Primrose Glycerides*
PEG-60 Evening Primrose Glycerides*
PEG-3 Glyceryl Cocoate
PEG-7 Glyceryl Cocoate
PEG-30 Glyceryl Cocoate
PEG-40 Glyceryl Cocoate
PEG-78 Glyceryl Cocoate*
PEG-80 Glyceryl Cocoate
PEG-5 Hydrogenated Corn Glycerides*
PEG-8 Hydrogenated Fish Glycerides*
PEG-20 Hydrogenated Palm Glycerides

PEG-6 Hydrogenated Palm/Palm Kernel Glyceride*
PEG-16 Macadamia Glycerides
PEG-70 Mango Glycerides
PEG-13 Mink Glycerides*
PEG-25 Moringa Glycerides*
PEG-42 Mushroom Glycerides*
PEG-2 Olive Glycerides*
PEG-6 Olive Glycerides*
PEG-7 Olive Glycerides*
PEG-10 Olive Glycerides
PEG-40 Olive Glycerides*
PEG-18 Palm Glycerides*
PEG-12 Palm Kernel Glycerides*
PEG-45 Palm Kernel Glycerides
PEG-60 Passiflora Edulis Seed Glycerides*
PEG-60 Passiflora Incarnata Seed Glycerides*
PEG-45 Safflower Glycerides*
PEG-60 Shea Butter Glycerides
PEG-75 Shea Butter Glycerides
PEG-75 Shorea Butter Glycerides*
PEG-35 Soy Glycerides
PEG-75 Soy Glycerides*
PEG-2 Sunflower Glycerides*
PEG-7 Sunflower Glycerides*
PEG-10 Sunflower Glycerides
PEG-13 Sunflower Glycerides
PEG-5 Tsubakiate Glycerides*
PEG-10 Tsubakiate Glycerides*
PEG-20 Tsubakiate Glycerides*
PEG-60 Tsubakiate Glycerides*

*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 those would be used in product categories and at concentrations comparable to others in this group.

Author Contributions

Fiume, M. contributed to conception and design; acquisition, analysis, and interpretation; drafted manuscript; and critically revised manuscript. Bergfeld, W., Belsito, D., Hill, R., Klaassen, C., Liebler, D., Marks, J., Shank, R., Slaga, T., Snyder, P., and Gill, L. contributed to conception and design, analysis and interpretation, and critically revised manuscript. Heldreth, B. contributed to analysis and interpretation and critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Authors' Note

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