Safety Assessment of PEGylated Alkyl Glycerides as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	August 18, 2014
Panel Meeting Date:	September 8-9, 2014

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

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Assistant Director/Senior Scientific Analyst
Date: August 18, 2014
Subject: Safety Assessment of PEGylated Alkyl Glycerides as Used in Cosmetics

Enclosed is the Draft Report on the Safety Assessment of PEGylated Alkyl Glycerides as Used in Cosmetics. (It is identified as *PEGgly092014rep_final for posting* in the pdf document.) This is the first time the Panel is seeing this document on this family of 60 ingredients. The Scientific Literature Review was issued on June 5, 2014.

PEGylated alkyl glycerides are mono-, di-, and/or tri-glycerides that have been modified with a specific number of ethylene glycol repeat units. Most of the PEGylated alkyl glycerides are reported to function as skin conditioning agents or surfactants.

All of the PEG glyceryl cocoates except for the PEG-3 glyceryl cocoate were reviewed in 1999, and the Panel concluded these ingredients were safe as used in rinse-off products and safe at up to 10% in leave-on products. The concentration limit for leave-on products was based on the ocular and sensitization data. It has been 15 years since that safety assessment was published, and therefore it is time to consider whether these ingredients should be re-reviewed. Rather than initiate a separate re-review, it is proposed these ingredients be included in this safety assessment of PEGylated alkyl glycerides because of structural similarity. Additionally, it is proposed that PEG-3 glyceryl cocoate also be included in the current safety assessment. The frequency of use of the PEG glyceryl cocoates has increased since the 1999 report; however, a statement cannot be made about the concentration of use because those data were not available from the FDA at that time. The 1999 report is included with this submission (*PEGgly092014prev_1*).

A family of very similar ingredients was recently reviewed by the Panel. In 2012, the Panel concluded that the PEGylated oils are safe as used in cosmetics when formulated to be non-irritating. 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 equivalents of ethylene oxide to reach the desired polyethylene glycol (PEG) length. Therefore, PEGylated alkyl glycerides are a sub-fraction of PEGylated oils, with the only difference being 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. The PEGylated Oils report is included with this submission (*PEGgly092014prev_2*).

The materials that are used in the manufacture of the PEGylated alkyl glycerides may be present as impurities in the final ingredient. The 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 the starting material may be present as residual impurities. Therefore, a data summary and conclusion of each relevant report can be found in Table 2. The safety assessments on the components are not included with this submission; however, if you would like to view these reports, they are accessible on the CIR website (http://www.cir-safety.org/ingredients).

The following data submissions were received from the Council and are included for your review:

1. Specifications of PEG-11 Avocado Glycerides and PEG-10 Olive Glycerides; memo dated June 16, 2014. (*PEGgly092014data_1*)
    a. Anonymous. 2013. Specification/certificate of analysis PEG-11 Avocado Glycerides.
    b. Anonymous. 2013. Specification/certificate of analysis PEG-10 Olive Glycerides.
2. Information on PEG-10 Olive Glycerides, PEG-11 Avocado Glycerides, and PEG-9 Cocoglycerides; memo dated June 24, 2014. (*PEGgly092014data_2*)
    a. Zschimmer & Schwarz GmbH & Co KG. 2013. Raw material information PEG-10 Olive Glycerides.
    b. Zschimmer & Schwarz GmbH & Co KG. 2012. Raw material information PEG-11 Avocado Glycerides.
    c. Zschimmer & Schwarz GmbH & Co KG. 2013. Raw material information PEG-9 Cocoglycerides.
3. Personal Care Products Council. 2014. Concentration of use by FDA product category – PEGylated alkyl glycerides; updated May 12, 2014. (*PEGgly092014data_3*)
4. Personal Care Products Council; memo dated July 15, 2014. Concentration of use by FDA product category: PEG-6 Hydrogenated Palm/Palm Kernel Glyceride. (*PEGgly092014data_4*)
5. Personal Care Products Council. Concentration of use by FDA product category: PEG glyceryl cocoate ingredients. (*PEGgly092014data_5)*
6. Information on Products Containing PEG Alkyl Glycerides; memo dated July 9, 2014. (*PEGgly092014data_6*)
    a. Peritesco. 2004. Ocular and cutaneous tolerance study of self foaming cleansers containing 1% PEG-75 Shea Butter Glycerides.
    b. Consumer Product Testing Co. 2013. The hen's egg test- utilizing the chorioallantoic membrane (HET-CAM) of a hair styling product containing 11% PEG-7 Glyceryl Cocoate.
    c. TKL Research. 2013. Repeated insult patch test of a hair styling product containing 11% PEG-7 Glyceryl Cocoate.
    d. Harrison Research Laboratories, Inc. 2008. Repeated insult patch test of a hair setting lotion containing 1% PEG-75 Shea Butter Glycerides.
    e. Consumer Product Testing Co. 2005. Safety in use of a female hygiene product containing 0.1% PEG-75 Shea Butter Glycerides.
7. Information on PEG Alkyl Glycerides; memo dated July 24, 2014.
    a. Anonymous. 2005. Assessment of the eye irritation potential of PEG-7 Glyceryl Cocoate in the hen's egg test on the chorioallantoic membrane (HET-CAM) (*PEGgly092014data_7*)
    b. Anonymous. 2005. Assessment of the eye irritation potential of PEG-7 Glyceryl Cocoate by cytotoxicity measurement in the neutral red uptake assay (NRU) on human. (*PEGgly092014data_7*)
    c. Hazleton Laboratories America, Inc. 1989. Summary of 28-day subchronic oral toxicity study in rats with a material containing 0.8% PEG-7 Glyceryl Cocoate. (*PEGgly092014data_7*)
    d. Research Toxicology Centre S.p.A. 1995. Delayed dermal sensitization study in the guinea pig (PEG-7 Glyceryl Cocoate). (*PEGgly092014data_7*)
    e. TKL Research, Inc. 2004. Repeated insult patch test of a styling pomade (BCS578-094) containing 8% PEG-7 Glyceryl Cocoate. (*PEGgly092014data_8*)
    f. TKL Research, Inc. 2004. Repeated insult patch test of a styling pomade (BCS578-098) containing 8% PEG-7 Glyceryl Cocoate. (*PEGgly092014data_8)*
    g. Pharmaco UK Ltd. 1994. Human repeat insult patch test of PEG-20 Almond Glycerides, 100% neat tested at 5%. (*PEGgly092014data_9*)
    h. Leberco-Celsis Testing. 1997. Ocular irritation screen of PEG-10 Sunflower Glycerides using the chorioallantoic membrane vascular assay (CAMVA). (*PEGgly092014data_9*)
    i. Raltech Scientific Services. 1981. Skin corrosivity (DOT procedure) of a perfume containing 4% PEG-6 caprylic/capric glycerides. (*PEGgly092014data_10*)
    j. Springborn Institute for Bioresearch, Inc. 1981. Rabbit eye irritation (perfume containing 4% PEG-6 caprylic/capric glycerides). (*PEGgly092014data_10*)
    k. Anonymous. 1981. Human sensitization test of a perfume containing 4% PEG-6 caprylic/capric glycerides. (*PEGgly092014data_10)*

Comments on the SLR also were received from the Council and have been addressed. These are also included in this submission (*PEGgly092014PCPC*).

If the data included in this report adequately address the safety of the PEGylated alkyl glycerides, the Panel should be prepared to formulate a tentative conclusion, provide the rationale to be described in the Discussion, and issue a Tentative Report for public comment. If the data are not sufficient for making a determination of safety, then an Insufficient Data Announcement should be issued that provides a listing of the additional data that are needed.

PEGylated Alkyl Glycerides

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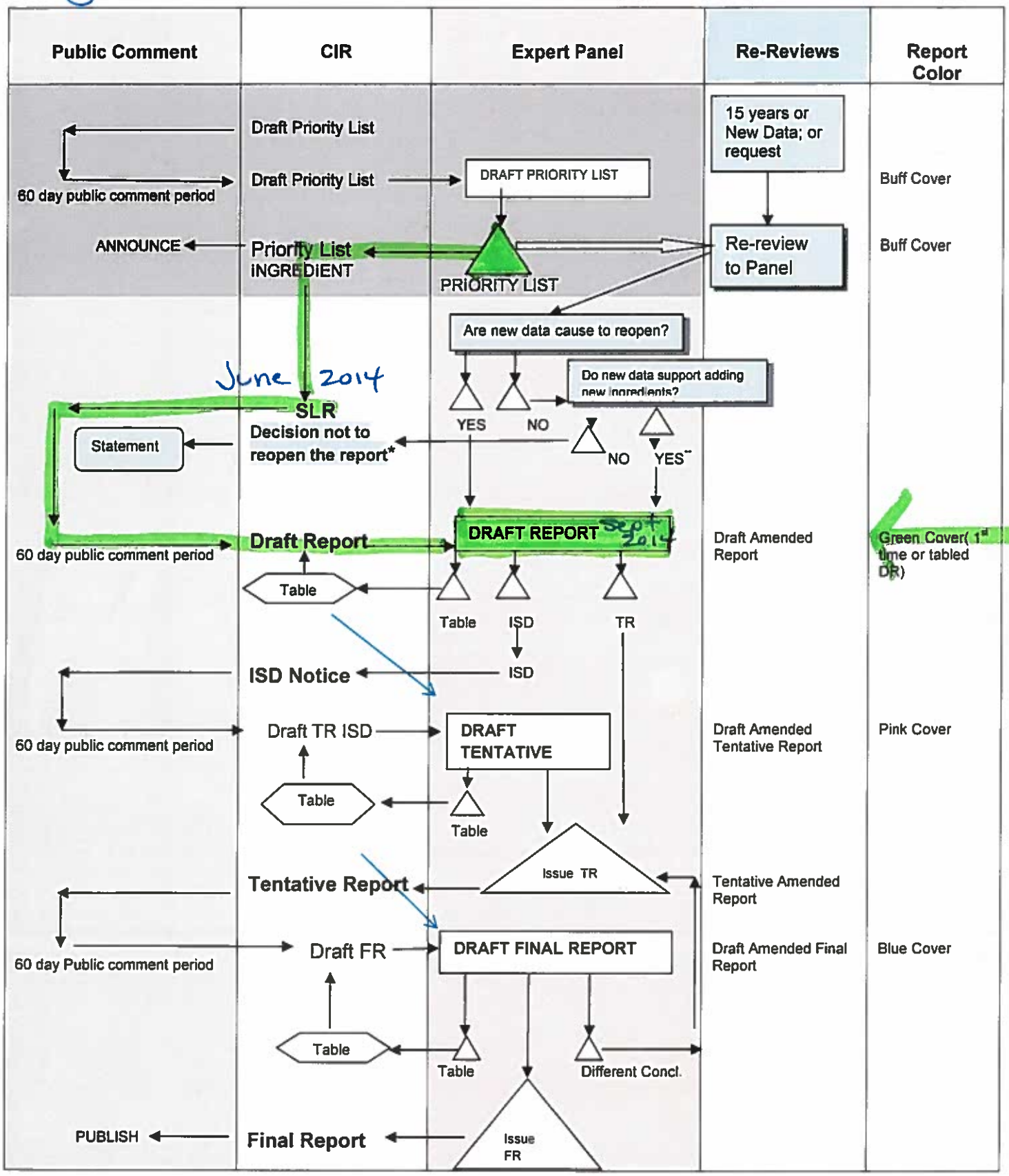
SAFETY ASSESSMENT FLOW CHART

Sept 2014



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

PEGylated Alkyl Glycerides - History

Scientific Literature Review: June 5, 2014
Concentration of use data were received and included in the SLR.

Draft Report: September 8-9, 2014
The following unpublished data submissions were received after the SLR was issued:

1. Specifications of PEG-11 Avocado Glycerides and PEG-10 Olive Glycerides; memo dated June 16, 2014.
    a. Anonymous. 2013. Specification/certificate of analysis PEG-11 Avocado Glycerides.
    b. Anonymous. 2013. Specification/certificate of analysis PEG-10 Olive Glycerides.
2. Information on PEG-10 Olive Glycerides, PEG-11 Avocado Glycerides, and PEG-9 Cocoglycerides; memo dated June 24, 2014.
    a. Zschimmer & Schwarz GmbH & Co KG. 2013. Raw material information PEG-10 Olive Glycerides.
    b. Zschimmer & Schwarz GmbH & Co KG. 2012. Raw material information PEG-11 Avocado Glycerides.
    c. Zschimmer & Schwarz GmbH & Co KG. 2013. Raw material information PEG-9 Cocoglycerides.
3. Information on Products Containing PEG Alkyl Glycerides; memo dated July 9, 2014.
    a. Peritesco. 2004. Ocular and cutaneous tolerance study of self foaming cleansers containing 1% PEG-75 Shea Butter Glycerides.
    b. Consumer Product Testing Co. 2013. The hen's egg test- utilizing the chorioallantoic membrane (HET-CAM) of a hair styling product containing 11% PEG-7 Glyceryl Cocoate.
    c. TKL Research. 2013. Repeated insult patch test of a hair styling product containing 11% PEG-7 Glyceryl Cocoate.
    d. Harrison Research Laboratories, Inc. 2008. Repeated insult patch test of a hair setting lotion containing 1% PEG-75 Shea Butter Glycerides.
    e. Consumer Product Testing Co. 2005. Safety in use of a female hygiene product containing 0.1% PEG-75 Shea Butter Glycerides.
4. Information on PEG Alkyl Glycerides; memo dated July 24, 2014.
    a. Anonymous. 2005. Assessment of the eye irritation potential of PEG-7 Glyceryl Cocoate in the hen's egg test on the chorioallantoic membrane (HET-CAM)
    b. Anonymous. 2005. Assessment of the eye irritation potential of PEG-7 Glyceryl Cocoate by cytotoxicity measurement in the neutral red uptake assay (NRU) on human.
    c. Hazleton Laboratories America, Inc. 1989. Summary of 28-day subchronic oral toxicity study in rats with a material containing 0.8% PEG-7 Glyceryl Cocoate.
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    e. TKL Research, Inc. 2004. Repeated insult patch test of a styling pomade (BCS578-094) containing 8% PEG-7 Glyceryl Cocoate.
    f. TKL Research, Inc. 2004. Repeated insult patch test of a styling pomade (BCS578-098) containing 8% PEG-7 Glyceryl Cocoate.
    g. Pharmaco UK Ltd. 1994. Human repeat insult patch test of PEG-20 Almond Glycerides, 100% neat tested at 5%.
    h. Leberco-Celsis Testing. 1997. Ocular irritation screen of PEG-10 Sunflower Glycerides using the chorioallantoic membrane vascular assay (CAMVA).
    i. Raltech Scientific Services. 1981. Skin corrosivity (DOT procedure) of a perfume containing 4% PEG-6 caprylic/capric glycerides.
    j. Springborn Institute for Bioresearch, Inc. 1981. Rabbit eye irritation (perfume containing 4% PEG-6 caprylic/capric glycerides).
    k. Anonymous. 1981. Human sensitization test of a perfume containing 4% PEG-6 caprylic/capric glycerides.

Comments on the SLR also were received from the Council.

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PEGylated Alkyl Glycerides – Sept 2014 – Monice Fiume

	Reported Use	Method of Mfg	Toxicokinetics	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhal.	Animal Tox – Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhal	Repro/Dev Tox	Genotox	Carciniogenicity	PhotocarC	Dermal Irr/Sens	Phototoxicity	Ocular Irritation	Mucous Membrane Irr
PEG-6 Almond Glycerides																		
PEG-20 Almond Glycerides	X														X			
PEG-35 Almond Glycerides																		
PEG-60 Almond Glycerides	X																	
PEG-192 Apricot Kernel Glycerides	X																	
PEG-11 Avocado Glycerides		X																
PEG-14 Avocado Glycerides																		
PEG-11 Babassu Glycerides																		
PEG-42 Babassu Glycerides																		
PEG-4 Caprylic/Capric Glycerides																		
PEG-6 Caprylic/Capric Glycerides	X														X		X	
PEG-7 Caprylic/Capric Glycerides	X																	
PEG-8 Caprylic/Capric Glycerides	X	X				X			X						X		X	
PEG-11 Cocoa Butter Glycerides																		
PEG-75 Cocoa Butter Glycerides	X																	
PEG-7 Cocoglycerides																		
PEG-9 Cocoglycerides		X																
PEG-20 Corn Glycerides																		
PEG-60 Corn Glycerides																		
PEG-20 Evening Primrose Glycerides																		
PEG-3 Glyceryl Cocoate	X																	
PEG-7 Glyceryl Cocoate	X					X			X						X	X	X	
PEG-30 Glyceryl Cocoate	X																	
PEG-40 Glyceryl Cocoate	X																	

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PEGylated Alkyl Glycerides – Sept 2014 – Monice Fiume																			
	Reported Use	Method of Mfg	Toxicokinetics	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhal.	Animal Tox – Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhal	Repro/Dev Tox	Genotox	Carciniogenicity	PhotocarC	Dermal Irr/Sens	Phototoxicity	Ocular Irritation	Mucous Membrane Irr
PEG-78 Glyceryl Cocoate																		
PEG-80 Glyceryl Cocoate	X																	
PEG-60 Evening Primrose Glycerides																		
PEG-5 Hydrogenated Corn Glycerides																		
PEG-8 Hydrogenated Fish Glycerides																		
PEG-20 Hydrogenated Palm Glycerides	X																	
PEG-6 Hydrogenated Palm/Palm Kernel Glyceride																		
PEG-16 Macadamia Glycerides	X																	
PEG-70 Mango Glycerides	X																	
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	X	X										X			X			X
PEG-40 Olive Glycerides]																		
PEG-18 Palm Glycerides																		
PEG-12 Palm Kernel Glycerides																		
PEG-45 Palm Kernel Glycerides	X																	
PEG-60 Passiflora Edulis Seed Glycerides																		
PEG-60 Passiflora Incarnata Seed Glycerides																		

PEGylated Alkyl Glycerides – Sept 2014 – Monice Fiume																			
	Reported Use	Method of Mfg	Toxicokinetics	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhal.	Animal Tox – Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhal	Repro/Dev Tox	Genotox	Carciniogenicity	PhotocarC	Dermal Irr/Sens	Phototoxicity	Ocular Irritation	Mucous Membrane Irr
PEG-45 Safflower Glycerides																		
PEG-60 Shea Butter Glycerides																		
PEG-75 Shea Butter Glycerides	X														X		X	X
PEG-75 Shorea Butter Glycerides																		
PEG-35 Soy Glycerides	X																	
PEG-75 Soy Glycerides																		
PEG-2 Sunflower Glycerides																		
PEG-7 Sunflower Glycerides																		
PEG-10 Sunflower Glycerides	X																X	
PEG-13 Sunflower Glycerides	X																	
PEG-5 Tsubakiate Glycerides																		
PEG-10 Tsubakiate Glycerides																		
PEG-20 Tsubakiate Glycerides																		
PEG-60 Tsubakiate Glycerides																		

*"X" indicates that data were available in a category for the ingredient

PEGylated Alkyl Glycerides – Search Terms

67762-35-0
70377-91-2
103819-44-9
103819-45-0
103819-46-1
124046-50-0
124046-52-2
180254-52-8
186511-05-7

PubMed – April 10, 2014

(PEG OR (polyethylene AND glycol) OR (polyoxyethylene AND oxide) OR polyoxyethylene OR POE OR PEO) AND ((almond OR (apricot AND kernel) OR avocado OR babassu OR (caprylic AND capric) OR ((cocoa OR shea OR shorea) AND butter) OR corn OR (evening AND primrose) OR (hydrogenated AND fish) OR macadamia OR mango OR mink OR moringa OR mushroom OR olive OR palm OR (passilora AND seed) OR safflower OR soy OR sunflower OR tsubakiate) AND glyceride*) OR cocoglyceride OR (coco AND glyceride)) – 127 hits/0 useful

PEGylated AND alkyl AND glyceride – 0 hits

*glyceride AND ((ethylene AND glycol) OR epoxide) – 219 hits/1 useful

labrasol – 190 hits/3 useful

SciFinder – April 14, 2014

Substance Identifier search – 11 hits via names and CAS numbers/no references found
Research Topic search – PEG alkyl glycerides; glyceride ethylene glycol; glyceride epoxide; PEG Glycerides; PEG Almond Glycerides; PEG Apricot Kernel Glycerides; PEG Avocado Glycerides; PEG Babassu Glycerides; PEG Caprylic/Capric Glycerides; Labrasol; PEG Cocoa Butter Glycerides; PEG Coco glycerides; PEG Corn Glycerides; PEG Evening Primrose Glycerides; PEG Hydrogenated Corn Glycerides; PEG Macadamia Glycerides; PEG Mango Glycerides; PEG Mink Glycerides; PEG Moringa Glycerides; PEG Mushroom Glycerides; PEG Olive Glycerides; PEG Palm Glycerides; PEG Palm Kernel Glycerides; PEG Passiflora Glycerides; PEG Passiflora Edulis Seed Glycerides; PEG Passiflora Incarnata Seed Glycerides; PEG Safflower Glycerides; PEG Shea Butter Glycerides; PEG Shorea Butter Glycerides; PEG Soy Glycerides; PEG Sunflower Glycerides; PEG Tsubakiate Glycerides – all with document-type limiters – 1461 hits/ 14 useful

ECHA – REACH - April 15, 2014

by CAS No – 0
by name – 0

ChemPortal

by CAS No – 0
by name – 0

COSMOS – May 1, 2014

by CAS No – 0
by name – 0

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INTRODUCTION

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

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

PEGylated alkyl glycerides are mono-, di-, and/or tri-glycerides that have been modified with a specific number of 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[1] (Table 1).

Five of the ingredients included in this review, i.e. PEG-7 glyceryl cocoate, PEG-30 glyceryl cocoate, PEG-40 glyceryl cocoate, PEG-78 glyceryl cocoate, and PEG-80 glyceryl cocoate, previously have been reviewed. In 1999, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded these ingredients were safe as used in rinse-off products and safe at up to 10% in leave-on products; according to the Discussion of that report, the basis of the concentration limit for leave-on products was the ocular and sensitization data.[2] It has been 15 years since that safety assessment was published and, according to CIR Procedures, the Panel needs to determine whether or not a re-review is warranted. Rather than initiate a separate re-review, it is proposed that these ingredients be included in this safety assessment of PEGylated alkyl glycerides because of structural similarity. Additionally, PEG-3 glyceryl cocoate was not included in the 1999 safety assessment, and it is proposed that this ingredient also be included in the current safety assessment. Unpublished data on PEG-7 glyceryl cocoate have been submitted by industry and are included in this safety assessment; additionally, where appropriate, information from the 1999 report is included in this safety assessment, as indicated by *italicized text*.

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 non-irritating.[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 equivalents of ethylene oxide to reach 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 sub-fraction of PEGylated oils. PEGylated oils mostly contain PEGylated triglycerides and some PEGylated fatty acids (i.e., not attached to a mole-

cule 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, is comprised mostly of ***tri***glycerides, wherein the six 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, a PEGylated alkyl glyceride, PEG-6 almond glycerides, is comprised mostly of ***mono-*** and ***di***glycerides, wherein six 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, i.e., 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 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 some of the starting material may be present as residual impurities. Therefore, a data summary and the conclusion of each relevant report are provided[4-11] (Table 2). Previous CIR reports were available on all component oils except hydrogenated corn oil (although a report on corn oil was available), hydrogenated fish oil, mushroom oil, and *Passiflora incarnate* oil. Additionally, the conclusion and a data summary from the PEGylated oils[3] report are provided (Table 2). Finally, CIR currently is reviewing the safety of glycerin.

CHEMISTRY

Definition and Structure

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

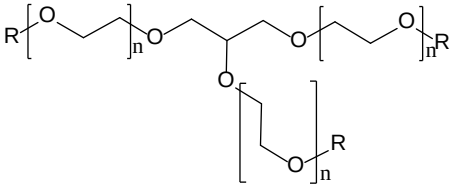


Figure 1. generic PEGylated alkyl glyceride structure, wherein R is hydrogen or the fatty acids declared in the name or found in the source material, and the sum of all cases of n is "X" in PEG-"X"

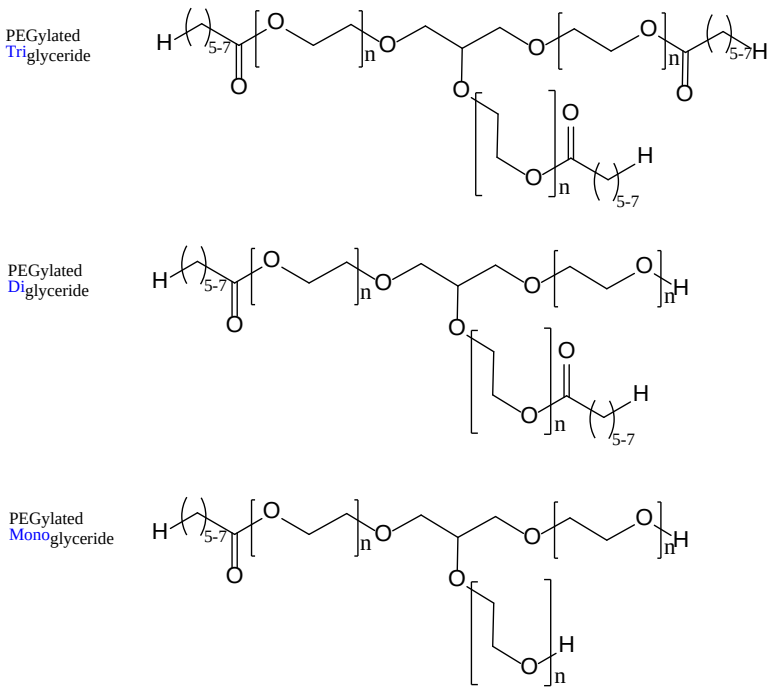


Figure 2. PEG-6 caprylic/capric glycerides, wherein the sum of all instances of "n" is 6 (i.e., "PEG-6").

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.[12,13] 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.

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 (e.g., 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.[12] 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 (e.g., 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 and Physical 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. Owing to the combination of polar and non-polar functional groups, most of these ingredients are soluble in some organic solvents and are at least dispersible in water, if not soluble (Table 3). The fatty acid compositions of the oils that comprise the alkylated glycerides are provided in Table 4.

Methods of Manufacture

PEG-8 caprylic/capric glycerides can be obtained by partial alcoholysis 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.[14,15]

PEG-11 avocado glycerides,[16] PEG-9 cocoglycerides,[17] and PEG-10 olive glycerides[18] are produced by the reaction of their respective oil with ethylene oxide. 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. PEGs 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; 1,4-dioxane is a known animal carcinogen.[19] The 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 remove it from the ingredient before blending into cosmetic formulations.[20,21]

Raw material information sheets for PEG-11 avocado glycerides,[16] PEG-9 cocoglycerides,[17] and PEG-10 olive glycerides[18] 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.

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 (i.e., esters of capric or caprylic acid with PEG-8; not glycerides), and 20% free PEG-8.[22] It is reported to contain ≤10 ppm 1,4-dioxane, <1 ppm ethylene oxide, and <10 ppm heavy metals (Pb).[23,24]

USE

Cosmetic

Most of the PEGylated alkyl glycerides are reported to function as a skin conditioning agent – emollient and as a surfactant – emulsifying agent[1] (Table 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 reported to act as a surfactant - solubilizing agent or surfactant – cleansing agent.

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,[25] 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),[26-28] 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, i.e., 858; the majority of these uses (713) are in rinse-off formulations.[25] PEG-6 caprylic/capric glycerides is reported to be used in 548 formulations, again 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 results of the concentration of use survey conducted by the Council indicate the highest leave-on concentrations reported are 6% PEG-7 glyceryl cocoate in an "other" fragrance preparation and 3.2% PEG-60 almond glycerides in a leave-on body and hand product. PEG-7 glyceryl cocoate and PEG-60 almond glycerides also have the highest rinse-off concentrations of use reported, i.e., 6.9% in "other" personal cleanliness products and 6.5% in "other" skin care preparation, respectively.

The PEG glyceryl cocoates have increased in use. In 1996, PEG-6 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 cocoate is used mostly in rinse-off formulations.[2,25] 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). At the time of the original safety assessment, concentration of use data were not available from the FDA.

One ingredient is used in products that could be incidentally ingested (i.e., PEG-75 cocoa butter is reported to be used in two lipstick formulations) and a few of the ingredients are used near the eye (e.g., 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 glyceride in a pump spray suntan product. In practice, 95 to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[29,30] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[31,32]

The PEGylated alkyl glycerides named in this safety assessment are listed in the European Union inventory of cosmetic ingredients.[33]

Non-Cosmetic

PEG-8 caprylic/capric glycerides has use as a pharmaceutical excipient.[34]

A mixture of mono-, di- and tri-glycerides and PEG mono- and di-esters 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 400-3000 molecular weight PEG are approved for use as an indirect food additive 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 200-4600 molecular weight 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 11.5-53% PEG-8 caprylic/capric glycerides, 3-70% isostearyl isostearate, 8-35% polyglyceryl-6 isostearate, and 7-65% water increased delivery of lidocaine up to four times compared to an oil/water emulsion vehicle, and increased the delivery of prilocaine hydrochloride almost ten times compared to a hydrogel.[22] 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 non-selective β-adrenergic antagonist, through porcine skin. The flux of carvedilol from a PEG-8 caprylic/capric glycerides vehicle (i.e., 14.28 $\mu g/cm^2/h$) was 8.6 times greater than that obtained with the control vehicle (i.e., 1.66 $\mu g/cm^2/h$) composed of phosphate buffered saline containing 40% v/v PEG 400.[35] However, when used as a penetration enhancer and 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 non-polar cyclic oligopeptide, through excised rat skin.[36]

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 large molecular weight; however, the amount of kahalalide F retained and permeated through the skin was much greater with dimethyl sulfoxide.[37] 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-8 caprylic/capric glycerides has an oral LD_{50} of 22 g/kg in rats.[38] *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 three 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% ethyoxydiglycol.[39] (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/day test article for 4 wks. A negative control group of 10 rats/sex received 20 ml/kg/day 1% (w/v) hydroxyethylcellulose 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 content and related activities were evaluated.

The test article was relatively well-tolerated at 5 ml/kg/day, and this volume was considered the no-observable adverse effect level (NOAEL). Adverse effects were observed with the greater dose volumes, and the main effects were observed in the liver, kidneys, and adrenal glands. One female of the 20 ml/kg/day 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/day animals, there was an increase in clinical signs of toxicity, including ptyalism, 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; five of the ten males and three of the nine 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 CYP was reported. Some similar effects were reported in animals given 10 ml/kg/day, but not at the same rate of incidence.

No adverse effects were observed in dogs that were dosed orally for 13 wks with 1.0 g/kg/day PEG-8 caprylic/capric glycerides.[38] (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.[40] 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%.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on reproductive and developmental toxicity of PEGylated alkyl glycerides were not found in the published literature, nor were unpublished data provided.

GENOTOXICITY

PEG-10 olive glycerides was not mutagenic in an Ames test.[18] (No details were provided.)

Genotoxicity studies of other PEGylated alkyl glycerides were not found in the published literature, nor were additional unpublished data provided.

CARCINOGENICITY

Carcinogenicity data of 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 non-human and human studies, and these ingredients generally were not irritants or sensitizers (Table 7). A microemulsion of 1.3% diclofenac epolamine w/w in 30% propylene glycol monocaprylate, 50% PEG-8 caprylic/capric glycerides/ethoxydiglycol (1:2 w/w), and 20% water was not irritating to rat skin,[41] *50% PEG-7 glyceryl cocoate was not irritating to mouse skin*,[2] formulations containing 4% PEG-6 caprylic/capric glycerides[42] and PEG-10 olive glycerides (3% active matter)[18] were not irritating to rabbit skin, and *50% PEG-7 glyceryl cocoate*[2] *and* undiluted PEG-7 glyceryl cocoate were not irritating to guinea pig skin.[43] *However, in one study, PEG-7 glyceryl cocoate was mildly irritating to rabbit skin.*[2] Undiluted PEG-7 glyceryl cocoate[43] and PEG-10 olive glycerides (as 50% active matter)[18] were not sensitizers in guinea pigs.

In clinical testing, PEG-20 almond glyceride (5.0% aq.),[44] a formulation containing 4% PEG-6 caprylic/capric glycerides,[45] formulations containing 8 or 11% glyceryl cocoate,[46-48] and a formulation containing 1% PEG-75 shea butter glycerides[49] were not sensitizers in human repeated insult patch tests. Additionally, PEG-10 olive glycerides (2% active matter) was nonirritating to mildly irritating,[18] and the cutaneous irritation potential of a formulation containing 1% PEG-75 shea butter was practically zero.[50] *PEG-7 glyceryl cocoate, at concentrations up to 100%, was not irritating.*[2]

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 humans.*

Ocular

In a hen's egg test utilizing the chorioallantoic membrane, a formulation containing 11% PEG-7 glyceryl cocoate had practically no irritation potential,[51] and concentrations of 10, 50, and 100% PEG-7 glyceryl cocoate were slightly irritating[52] (Table 8). PEG-10 sunflower glyceride was a non-irritant in a chorioallantoic membrane vascular assay.[53] In rabbits, *10% aq. PEG-7 glyceryl cocoate*[2] and formulations containing 4% PEG-6 caprylic/capric glycerides[54] and up to 3% PEG-8 caprylic/capric glycerides were not ocular irritants;[55] 5% PEG-8 caprylic/capric glycerides was a slight irritant to rabbit eyes. In clinical testing, a formulation containing 1% PEG-75 shea butter did not induce ocular irritation in a tolerance test.[50]

Mucous Membrane

PEG-10 olive glycerides, 3% active matter, did not irritate the mucous membrane.[18] (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.[56] Twenty-one female subjects bathed in a bubble bath using a "quarter-size amount" of the test material for 10-20 min daily for one week.

SUMMARY

This report addresses the safety of 60 PEGylated alkyl glycerides as used in cosmetics. PEGylated alkyl glycerides are mono-, di-, and/or tri-glycerides that have been modified with a specific number of 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. PEG-7 glyceryl cocoate has the most reported uses, i.e., 858, followed by PEG-6 caprylic/capric glycerides with 548 reported uses; the majority of uses for both of these ingredients is in rinse-off formulations. The highest concentrations of use reported for products resulting in leave-on dermal exposure are 6% PEG-7 glyceryl cocoate in other fragrance preparations and 3.2% PEG-60 almond glycerides in a body and hand product. PEG-7 glyceryl cocoate and PEG-60 almond glycerides also have the highest rinse-off concentrations of use reported, i.e., 6.9% in "other" personal cleanliness products and 6.5% in "other" skin care preparation, respectively. The frequency of use of PEG-7 glyceryl cocoate increased from 173 reported uses to 858 reported uses.

PEG-8 caprylic/capric glycerides can be a dermal penetration enhancer.

In rats, PEG-8 caprylic/capric glycerides had an oral LD_{50} of 22 g/kg and PEG-15 glyceryl isostearate has an oral LD_{50} of 29.76 ml/kg. In a 4-wk study in rats, the NOAEL for a blend of 40% PEG-8 caprylic/capric glycerides, 40% apricot kernel oil PEG-6 esters, and 20% ethyoxydiglycol was 5 ml/kg/day. Test-article related effects were reported in the kidneys, livers, and gastrointestinal systems of animals dosed with 20 ml/g/day; effects were also observed in animals given 10 ml/kg/day, but they did not occur at the same rate of incidence. In a 4-wk 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 wks with 1.0 g/kg/day PEG-8 caprylic/capric glycerides.

PEG-10 olive glycerides was not mutagenic in an Ames test.

The irritation and sensitization potentials of several PEGylated alkyl glycerides were evaluated in non-human and human studies, and these ingredients were not irritants or sensitizers. A microemulsion of 1.3% diclofenac epolamine w/w in 30% propylene glycol monocaprylate, 50% PEG-8 caprylic/capric glycerides/ethoxydiglycol (1:2 w/w), and 20% water was not irritating to rat skin, a formulations containing 4% PEG-6 caprylic/capric glycerides and PEG-10 olive glycerides (3% active matter) were not irritating to rabbit skin, and undiluted PEG-7 glyceryl cocoate was not irritating to guinea pig skin. Undiluted PEG-7 glyceryl cocoate and PEG-10 olive glycerides (as 50% active matter) were not sensitizers in guinea pigs.

In clinical testing, PEG-20 almond glyceride (5.0% aq.), a formulation containing 4% PEG-6 caprylic/capric glycerides, formulations containing 8 or 11% glyceryl cocoate, and a formulation containing 1% PEG-75 shea butter glycerides were not sensitizers in human repeated insult patch tests. Additionally, PEG-10 olive glycerides (2% active matter) was not irritating to mildly irritating, and the cutaneous irritation potential of a formulation containing 1% PEG-75 shea butter was practically nil.

In a hen's egg test utilizing the chorioallantoic membrane, a formulation containing 11% PEG-7 glyceryl cocoate had practically no irritation potential, and concentrations of 10, 50, and 100% PEG-7 glyceryl cocoate were slightly irritating. PEG-10 sunflower glyceride was a non-irritant in a chorioallantoic membrane vascular assay. 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. In clinical testing, a formulation containing 1% PEG-75 shea butter 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 reproductive and developmental toxicity, and carcinogenicity of PEGylated alkyl glycerides were not found in the published literature, nor were unpublished data provided. Moreover, genotoxicity data also were generally absent.

TABLES

Table 1. Definitions and functions of the ingredients in this safety assessment

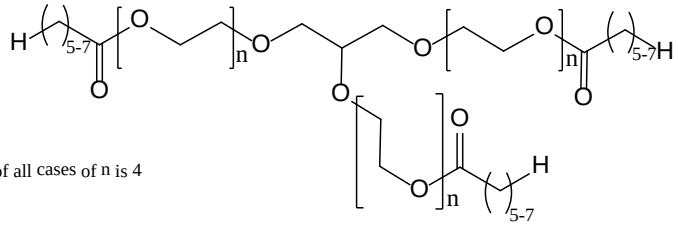
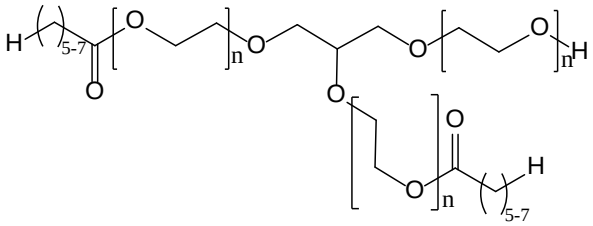
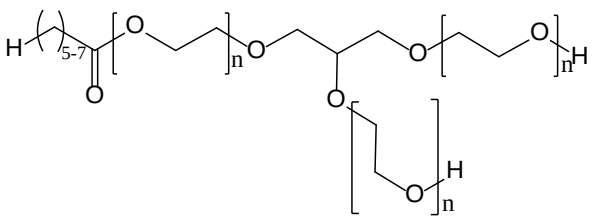
Ingredient (CAS No.)	Definition[1]	Function(s)[1]
PEG-6 Almond Glycerides [124046-50-0; generic]	a polyethylene glycol derivative of the mono- and diglycerides from almond oil with an average of 6 moles of ethylene oxide; *wherein R in Figure 1 is hydrogen or the fatty acid residues from almond oil, where at least one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 sum of all cases of n is 4  	skin-conditioning agent - emollient; surfactant – emulsifying agent

Table 1. Definitions and functions of the ingredients in this safety assessment

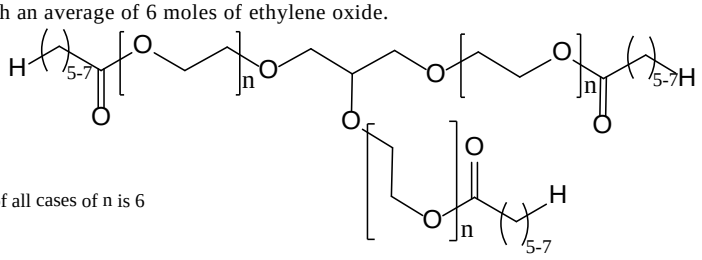
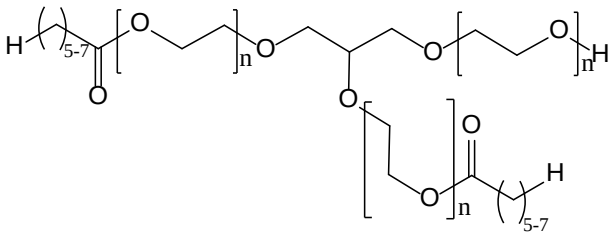
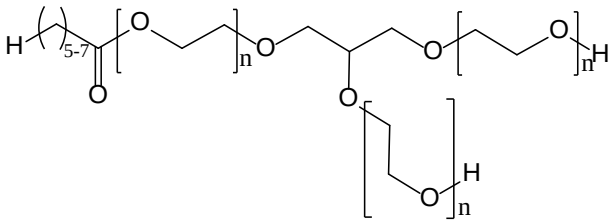
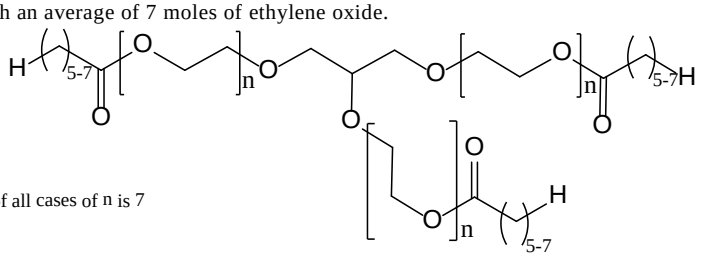
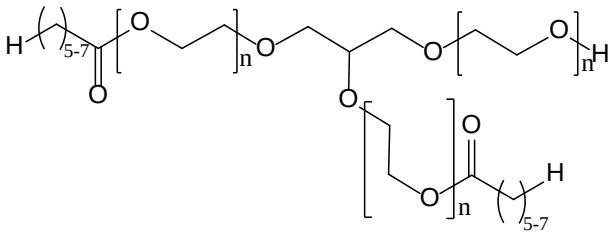
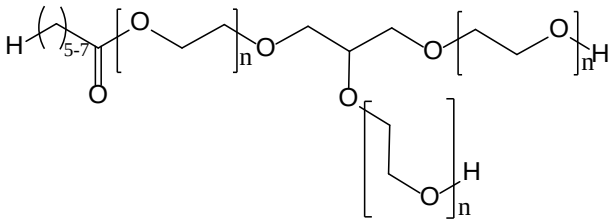
Ingredient (CAS No.)	Definition[1]	Function(s)[1]
PEG-6 Caprylic/Capric Glycerides 361459-38-3[57]	a polyethylene glycol derivative of a mixture of mono-, di-, and triglycerides of caprylic and capric acids with an average of 6 moles of ethylene oxide.  wherein the sum of all cases of n is 6  	skin-conditioning 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 sum of all cases of n is 7  	skin-conditioning agent - emollient; surfactant – emulsifying agent

Table 1. Definitions and functions of the ingredients in this safety assessment

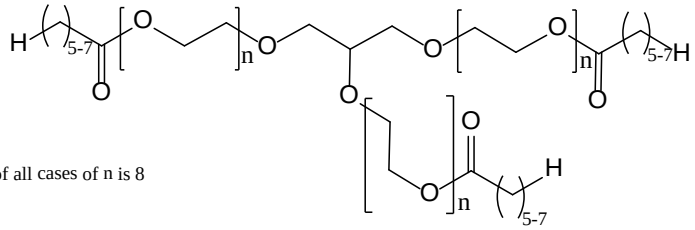
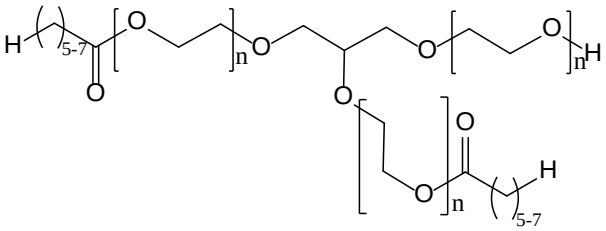
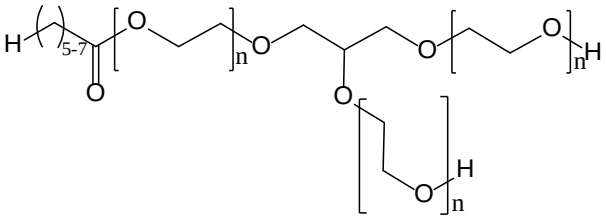
Ingredient (CAS No.)	Definition[1]	Function(s)[1]
PEG-8 Caprylic/Capric Glycerides	a polyethylene glycol derivative of a mixture of mono-, di-, and triglycerides of caprylic and capric acids with an average of 8 moles of ethylene oxide.  wherein the sum of all cases of n is 8  	skin-conditioning agent - 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 one R (and no more than two) is a fatty acid, and the 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 one R is a fatty acid, and the sum of all cases of n is 75*	skin-conditioning agent - emollient; surfactant – emulsifying agent
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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R is a fatty acid, and the 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	PEG-60 Corn Glycerides is 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 one R is a fatty acid, and the sum of all cases of n is 60* *Corn Glycerides is a mixture of mono, di and triglycerides 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the sum of all cases of n is 60*	surfactant – emulsifying agent; surfactant – solubilizing agent

Table 1. Definitions and functions of the ingredients in this safety assessment

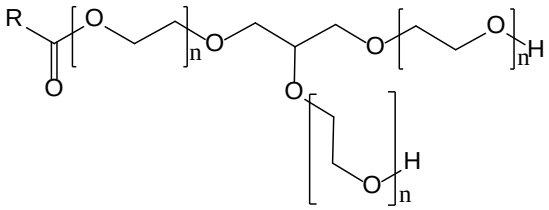
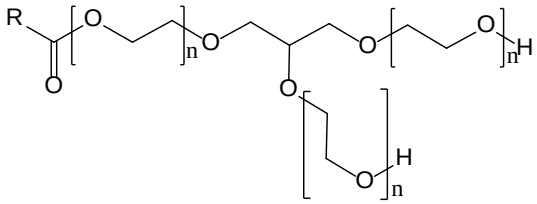
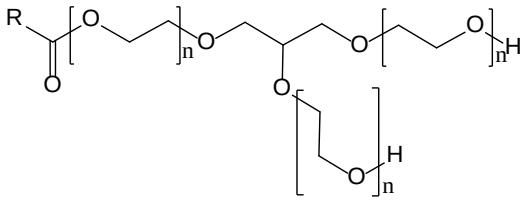
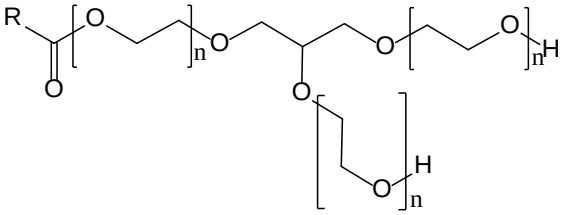
Ingredient (CAS No.)	Definition[1]	Function(s)[1]
PEG-3 Glyceryl Cocoate	the polyethylene glycol ether of glyceryl cocoate that conforms generally to the structure below; *the polyethylene glycol derivative of the monoglyceride of coconut oil with an average ethoxylation value of 3*  *wherein RC(O) represents the fatty acid residues from coconut oil, and the 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 sum of all cases of n is 7.*	skin-conditioning agent - emollient; surfactant – emulsifying agent
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 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 sum of all cases of n is 40.*	surfactants - cleansing agent; surfactants - solubilizing agent

Table 1. Definitions and functions of the ingredients in this safety assessment

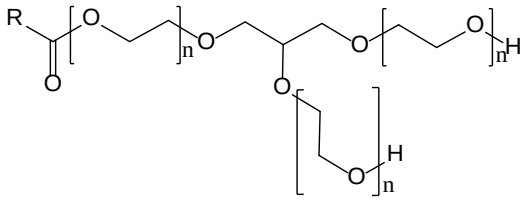
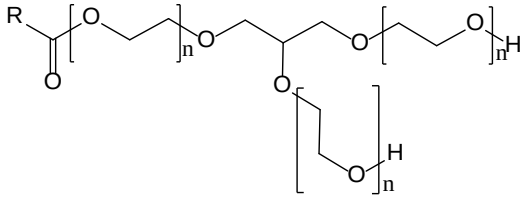
Ingredient (CAS No.)	Definition[1]	Function(s)[1]
PEG-78 Glyceryl Cocoate 68201-46-7(generic)	the polyethylene glycol ether of glyceryl cocoate that conforms generally to the structure below; *the polyethylene glycol derivative of the monoglyceride of coconut oil with an average ethoxylation value of 78*  *wherein RC(O) represents the fatty acid residues from coconut oil, and the 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 sum of all cases of n is 80.*	surfactants - cleansing agent; surfactants - solubilizing agent
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 one R is a fatty acid, and the 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 one R is a fatty acid, and the 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 one R is a fatty acid, and the 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 one R is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the sum of all cases of n is 42*	skin-conditioning agent - emollient; surfactant – emulsifying agent

Table 1. Definitions and functions of the ingredients in this safety assessment

Ingredient (CAS No.)	Definition[1]	Function(s)[1]
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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the sum of all cases of n is 10*	skin-conditioning agent - emollient; surfactant – emulsifying agent
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 one R (and no more than two) is a fatty acid, and the 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 one R is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the sum of all cases of n is 12*	skin-conditioning agent - emollient; surfactant – emulsifying agent
PEG-45 Palm Kernel Glycerides 68606-12-2;[58] 124046-52-2 [generic]	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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R is a fatty acid, and the 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 one R is a fatty acid, and the 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[59]	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 one R (and no more than two) is a fatty acid, and the sum of all cases of n is 35*	skin-conditioning agent – miscellaneous; surfactant – emulsifying agent; surfactant – solubilizing agent

Table 1. Definitions and functions of the ingredients in this safety assessment

Ingredient (CAS No.)	Definition[1]	Function(s)[1]
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 one R (and no more than two) is a fatty acid, and the sum of all cases of n is 75*	skin-conditioning agent - emollient; surfactant – emulsifying agent
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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the 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 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 one R (and no more than two) is a fatty acid, and the 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 one R (and no more than two) is a fatty acid, and the sum of all cases of n is 60*	surfactant – cleansing agent

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 ~5700 mg/kg/ day in a rat dominant lethal assay) or carcinogenic (up to 0.25 ml/week 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/day, 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;	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	5

Table 2. Summaries of previous CIR safety assessments

Ingredient(s)	Conclusion	Summary	Reference
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		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.	
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 two generation feeding studies. Application of undiluted test material to rabbits produced no to mild irritation. A 4% solution in ethanol were not sensitizers in guinea pigs.	[6]
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, anti-oxidant, 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 glyceride 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(o)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. Non-human 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]
Safflower Oil	see Plant-Derived Fatty Acid Oils	The pure oil produced slight to moderate comedogenicity. However, products containing up to 5 percent 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 12-dimethylbenz(a)anthracene in rats.	[11]

Table 2. Summaries of previous CIR safety assessments

Ingredient(s)	Conclusion	Summary	Reference
PEGylated Oils	PEGylated oils are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating. (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 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% w/w 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 non-irritating in rabbit eyes.	3

Table 3. Chemical and Physical Properties

Property	Description	Reference
	PEG-11 Avocado Glycerides	
physical appearance	brown liquid yellow, liquid to pasty yellowish to brown liquid with characteristic odor	60 61 62
solubility	soluble in water	61
pH value (10% in water; 25ºC)	5.0-7.0	62
saponification value	60-80 mg KOH/g	62
iodine value	25-37 g iodine/100 g	62
surfactant-type	non-ionic	61
	PEG-20 Almond Glycerides	
physical appearance	yellow liquid with a characteristic odor	63
	PEG-42 Babassu Glycerides	
physical appearance	clear to slightly hazy yellow liquid	64
	PEG-6 Caprylic/Capric Glycerides	
physical appearance	clear yellow liquid	57,65
solubility	soluble in water, cosmetic alcohol, and 1,2-propylene glycol; insoluble in paraffin oil and isopropyl myristate; dispersible in glycerol	66
acid value	<2	57,65
	PEG-8 Caprylic/Capric Glycerides	
physical appearance	pale yellow oily liquid with a faint odor	15,23
mean molecular wt	200-400	14,15
solubility	very soluble in ethanol (96º), chloroform, methylene chloride; soluble in water; insoluble in mineral oils freely soluble in methylene chloride; dispersible in hot water	23 15
specific gravity (20ºC; D20/4)	1.060 – 1.070	23

Table 3. Chemical and Physical Properties

Property	Description	Reference
refractive index (20ºC)	1.450 – 1.470	23
saponification value	85 – 105 mg KOH/g	23
acid value	≤2.0	23,24
fatty acid composition	caproic acid (C6): ≤2.0% caprylic acid (C8): 50-80% capric acid (C10): 20-50% lauric acid (C12): ≤3.0% myristic acid (C14): ≤1.0%	23,24
free glycerol content	≤5%	23
hydrophilic-lipophilic balance (HLB)	14	38
	PEG-9 Cocoglycerides	
physical appearance	yellow, liquid to pasty	67
solubility	soluble in water	67
HLB	13	67
surfactant-type	non-ionic	67
	PEG-60 Corn Glycerides	
physical appearance	liquid	68
surfactant-type	non-ionic	68
	PEG-60 Evening Primrose Glycerides	
physical appearance	soft, pale paste	69
	PEG-7 Glyceryl Cocoate	
physical appearance	*clear, pale yellow oil with a mild fatty odoer*	2
solubility	*soluble in water and ethanol; insoluble in mineral oil*	2
hydrophile-lipophile balance	*15*	2
hydroxyl value	*172-187*	2
saponification value	*90-100*	2
acid value	*5.0 max*	2
iodine value	*5.0 max*	2
	PEG-16 Macadamia Glycerides	
physical appearance	liquid	70
affinity	hydrophilic	71
HLB	12-14	71
hydroxyl value	90-130 mg KOH/g	70
saponification value	45-60 mg KOH/g	70
	PEG-70 Mango Glycerides	
physical appearance	solid	72
solubility	water-dispersible	73
surfactant-type	non-ionic	73
HLB	16-18	72,73
acid value	1.5	73
saponification value	14-20 mg KOH/g	73
	PEG-10 Olive Glycerides	
physical appearance	yellow, liquid to pasty yellowish-brown paste with characteristic odor	74 75
solubility	soluble in water solubility, 2.5% in water – almost clear to turbid solubility, 10% in isopropyl alcohol - clear	74 75
pH value (10% in water; 25ºC)	5.0-7.0	75
acid value	max 4.0 mg KOH/g	75
saponification value	52-72 mg KOH/g	75
iodine value	26-36 g iodine/100 g	75
		75
affinity	hydrophilic	76
surfactant-type	ionic	74
HLB	13	74
	PEG-45 Palm Kernel Glycerides	
physical appearance	clear liquid	58
surfactant-type	non-ionic	77
	PEG-75 Shea Butter Glycerides	
physical appearance	waxy solid	78
solubility	water-dispersible	72

Table 3. Chemical and Physical Properties

Property	Description	Reference
pH	5.5-8.5	78
surfactant-type	non-ionic	72
HLB	16-18	78
	PEG-35 Soy Glycerides	
physical appearance	solid or paste	59
solubility	soluble in water	59
surfactant-type	non-ionic	59
	PEG-10 Sunflower Glycerides	
physical appearance	liquid	79
solubility	soluble in water; dispersible in oil	80
refractive index	1.460	81
pH	6.9	81
surfactant-type	hydrophilic	80
HLB	8-10	81
hydroxyl value	135-160 mg KOH/g	79
acid value	0-1.5 mg KOH/g	79
saponification value	60-80 mg KOH/g	79

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 to 8		5-9	
Capric (C10)				4 to 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 to 5	34-36	1-3	0-4.5
Oleic (C18:1)	62-86	58-65.7 (total 18:1)	67-72	10 to 12	30-40	5-8	19 – 49
Linoleic (C18:2)	20-30	29-33 28.5 (undef. 18:2)	10 to 12	1 to 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%							

Table 4 Total fatty acid composition of plant-derived fatty acid oils and of butters (%)

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[82]	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[83]	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	0000	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				

Table 5. Frequency and concentration of use according to duration and type of exposure

	# of Uses[25]	*Max. Conc. of Use (%)*[26-28]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26-28]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26-28]
	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**	**0.01-6.9**
Duration of Use						
Leave-On	*15*	*NR*	*2*	*NR*	*124*	*0.02-6*
Rinse Off	*5*	*NR*	*NR*	*NR*	*713*	*0.01-6.9*
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; 0.18-5.5[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	0.01-6.9
Deodorant (underarm)	NR	NR	NR	NR	14[a]	not spray: 3; pump spray: 2
Hair - Non-Coloring	5	NR	NR	NR	146	0.18-5.5
Hair-Coloring	NR	NR	NR	NR	11	1.8-4.6
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

Table 5. Frequency and concentration of use according to duration and type of exposure

	# of Uses[25]	*Max. Conc. of Use (%)*[26-28]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26-28]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26-28]
	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
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]	NR	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

Table 5. Frequency and concentration of use according to duration and type of exposure

	# of Uses[25]	*Max. Conc. of Use (%)*[26-28]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26-28]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26-28]
	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

* 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

NR – none reported

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

Table 7 . Dermal irritation and sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ALTERNATIVE STUDIES		
PEG-8 caprylic/capric glycerides	35% in an ME also containing 10% isostearylic isostearate and 35% polyclyceryl-6 isostearate	male Wistar rat skin	1 ml of the ME or water was applied to the skin sample for 20 h in a Franz-type diffusion cell	low potential for skin irritancy the ME did not perturb the skin barrier	22
			NON-HUMAN		
PEG-6 caprylic/capric glycerides	4% in formulation, 0.5 ml	3 NZW rabbits/sex	4-h occlusive patch applied to shaved intact skin	not corrosive; mildly irritating	42
PEG-8 caprylic/capric glycerides	ME containing 1.3% diclofenac epolamine w/w in 30% propylene glycol monocaprylate, 50% PEG-8 caprylic/capric glycerides/ethoxydiglycol (1:2 w/w), and 20% water	3 albino Wistar rats	100 µl was applied for 24 h to the left ear of each rat	not an irritant no erythema	41
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-h occlusive patches; each animal was patched with 2 concentrations	no irritation at any concentration	43
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 h*	*no reaction*	2
PEG-7 glyceryl cocoate	*50% in Vaseline*	*4 male NZW rabbits*	*24-h patch test*	*slight reaction; reaction score of ¾*	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 h*	*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 h and scored at and 48 24 h*	*skin had reddening directly after rinsing; no irritation observed after 24 h*	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 wk later; 48-h occlusive patches were applied over the intradermal injection sites; the test site was pretreated with 10% SLS in petrolatum the day before patching 2 wks after topical induction, the challenge was performed with 24-h occlusive patches applied to a previously untreated site of test animals and to control animals	not a sensitizer	43
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	18

Table 7 . Dermal irritation and sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
PEG-10 olive glycerides	50% active matter	guinea pigs, number not provided	sensitization study; no details provided	not an irritant or sensitizer	18
			HUMAN		
PEG-20 almond glycer-ide	5.0% aq; 0.4 ml	93 subjects	occlusive HRIPT; nine 24-h patches were applied to a site on the upper arm 3x/wk for 3 wks; the 24-h challenge patch was applied after a 17 day non-treatment period	not a sensitizer	44
PEG-6 caprylic/capric glycerides	4% in formulation	81 subjects	HRIPT; 24-h patch were applied to a site on the arm 3x/wk for 3 wks the challenge patch was applied after a 10 day non-treatment period	not a sensitizer	45
PEG-7 glyceryl cocoate	8% in formulation applied neat; 0.1 g	103 subjects	semi-occlusive HRIPT; nine 24-h patches were applied to a site on the back 3x/wk for 3 wks; the 24-h challenge patch was applied after a 10-15 day non-treatment period	not a sensitizer	46
PEG-7 glyceryl cocoate	8% in formulation applied neat; 0.1 g	103 subjects (same subjects as above)	semi-occlusive HRIPT, followed the same protocol as above	not a sensitizer	47
PEG-7 glyceryl cocoate	11% in formulation; 0.2 g	205 subjects	semi-occlusive HRIPT; nine 24-h patches were applied to a site on the back 3x/wk for 3 wks; the 24-h challenge patch was applied after a 10-15 day non-treatment period	not a sensitizer one subject had definite erythema and edema (++) at the 2nd induction reading and was removed from the study	48
PEG-7 glyceryl cocoate	*50%*	*4 subjects*	*24-h 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-10 olive glycerides	2% active matter	not stated	Duhring-chamber test; no details provided	not irritating to mildly irritating	18
PEG-75 shea butter glycerides	1% in formulation	10 subjects	cutaneous tolerance test; product was applied to the whole face., including the eyes, 2x/day for 5 days	cutaneous irritant potential is “practically nil”	50
PEG-75 shea butter glycerides	1% in formulation; tested neat; 0.2 g	219 subjects	semi-occlusive HRIPT; nine 24-h patches were applied to a site on the back 3x/wk for 3 wks; the 24-h challenge patch was applied after a 2-wk non-treatment period	not a sensitizer 2 subjects had ± reactions during induction (one on D1; one on D7) 5 subjects had ±/1 reactions at challenge	49

Abbreviations: FCA – Freund’s complete adjuvant; HRIPT – human repeated insult patch test; ME – microemulsion; NZW – New Zealand White; 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 eggs	HET-CAM	practically no irritation potential mean score 1.25/32	51
PEG-7 glyceryl cocoate	10 and 50% in water and undiluted, 0.3 ml	chicken eggs	HET-CAM	slight irritant	52
PEG-7 glyceryl cocoate	100-1468 µg/ml	human keratinocytes (HaCaT)	NRU	cytotoxic to the HaCaT cells, resulting in a median MRU-50 value of 427 µg/ml; considered no classified (≥750 is classified as non-irritant, and <110 is classified as a severe irritant)	84
PEG-10 sunflower glyceride	neat; 40 µl	DeKalb eggs	CAMVA	non-irritant RC_{50} was 80% (>5.0% is a non-irritant)	53
			NON-HUMAN 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	54
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 4x/day for 7 days	0.5-3% was not irritating 5% was a slight irritant	55
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, 2x/day for 5 days	no ocular irritation; ocular irritation rate of 3/2000	50

Abbreviations: CAMVA – chorioallantoic membrane vascular assay (CAMVA); HET-CAM – hen's egg test utilizing the chorioallantoic membrane; NRU – neutral red uptake; NZW – New Zealand White; RC_{50} – theoretical concentration producing a positive reaction in 50% of treated eggs

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PEG-20 ALMOND GLYCERIDES	05A - Hair Conditioner	4
PEG-20 ALMOND GLYCERIDES	05F - Shampoos (non-coloring)	1
PEG-20 ALMOND GLYCERIDES	05G - Tonics, Dressings, and Other Hair Grooming Aids	2
PEG-20 ALMOND GLYCERIDES	10A - Bath Soaps and Detergents	2
PEG-20 ALMOND GLYCERIDES	12A - Cleansing	1
PEG-20 ALMOND GLYCERIDES	12J - Other Skin Care Preps	1
PEG-60 ALMOND GLYCERIDES	01A - Baby Shampoos	2
PEG-60 ALMOND GLYCERIDES	02D - Other Bath Preparations	1
PEG-60 ALMOND GLYCERIDES	03D - Eye Lotion	4
PEG-60 ALMOND GLYCERIDES	03E - Eye Makeup Remover	1
PEG-60 ALMOND GLYCERIDES	03F - Mascara	1
PEG-60 ALMOND GLYCERIDES	04A - Cologne and Toilet waters	1
PEG-60 ALMOND GLYCERIDES	04B - Perfumes	1
PEG-60 ALMOND GLYCERIDES	05A - Hair Conditioner	1
PEG-60 ALMOND GLYCERIDES	05F - Shampoos (non-coloring)	38
PEG-60 ALMOND GLYCERIDES	05G - Tonics, Dressings, and Other Hair Grooming Aids	15
PEG-60 ALMOND GLYCERIDES	05H - Wave Sets	2
PEG-60 ALMOND GLYCERIDES	05I - Other Hair Preparations	7
PEG-60 ALMOND GLYCERIDES	06D - Hair Shampoos (coloring)	1
PEG-60 ALMOND GLYCERIDES	06F - Hair Lighteners with Color	1
PEG-60 ALMOND GLYCERIDES	06G - Hair Bleaches	4
PEG-60 ALMOND GLYCERIDES	10A - Bath Soaps and Detergents	11
PEG-60 ALMOND GLYCERIDES	10E - Other Personal Cleanliness Products	9
PEG-60 ALMOND GLYCERIDES	11A - Aftershave Lotion	1
PEG-60 ALMOND GLYCERIDES	11G - Other Shaving Preparation Products	1
PEG-60 ALMOND GLYCERIDES	12A - Cleansing	14
PEG-60 ALMOND GLYCERIDES	12C - Face and Neck (exc shave)	22
PEG-60 ALMOND GLYCERIDES	12D - Body and Hand (exc shave)	2
PEG-60 ALMOND GLYCERIDES	12F - Moisturizing	11
PEG-60 ALMOND GLYCERIDES	12G - Night	2
PEG-60 ALMOND GLYCERIDES	12H - Paste Masks (mud packs)	2
PEG-60 ALMOND GLYCERIDES	12I - Skin Fresheners	2
PEG-60 ALMOND GLYCERIDES	12J - Other Skin Care Preps	6
PEG-192 APRICOT KERNEL GLYCERIDES	05B - Hair Spray (aerosol fixatives)	4
PEG-192 APRICOT KERNEL GLYCERIDES	05I - Other Hair Preparations	20
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	01A - Baby Shampoos	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	01C - Other Baby Products	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	02A - Bath Oils, Tablets, and Salts	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	02B - Bubble Baths	6
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	02D - Other Bath Preparations	11
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	03B - Eyeliner	11
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	03E - Eye Makeup Remover	5
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	03F - Mascara	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	04A - Cologne and Toilet waters	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	04B - Perfumes	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	04E - Other Fragrance Preparation	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	05E - Rinses (non-coloring)	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	05F - Shampoos (non-coloring)	64
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	05G - Tonics, Dressings, and Other Hair Grooming Aids	4
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	05I - Other Hair Preparations	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	07I - Other Makeup Preparations	2
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	10A - Bath Soaps and Detergents	191
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	10C - Douches	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	10E - Other Personal Cleanliness Products	128
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	11A - Aftershave Lotion	47
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	11G - Other Shaving Preparation Products	4
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	12A - Cleansing	36

PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	12C - Face and Neck (exc shave)	5
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	12D - Body and Hand (exc shave)	5
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	12F - Moisturizing	8
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	12G - Night	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	12H - Paste Masks (mud packs)	1
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	12I - Skin Fresheners	2
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	12J - Other Skin Care Preps	3
PEG-6 CAPRYLIC/CAPRIC GLYCERIDES	13A - Suntan Gels, Creams, and Liquids	2
PEG-6 CAPRYLIC/CAPRIC TRIGLYCERIDE	10A - Bath Soaps and Detergents	2
PEG-7 CAPRYLIC/CAPRIC GLYCERIDES	12A - Cleansing	2
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	02A - Bath Oils, Tablets, and Salts	1
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	02D - Other Bath Preparations	1
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	05I - Other Hair Preparations	1
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	10E - Other Personal Cleanliness Products	2
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	12A - Cleansing	1
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	12C - Face and Neck (exc shave)	9
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	12D - Body and Hand (exc shave)	2
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	12F - Moisturizing	3
PEG-8 CAPRYLIC/CAPRIC GLYCERIDES	12J - Other Skin Care Preps	2
PEG-75 COCOA BUTTER	04B - Perfumes	1
PEG-75 COCOA BUTTER	05A - Hair Conditioner	2
PEG-75 COCOA BUTTER	05F - Shampoos (non-coloring)	3
PEG-75 COCOA BUTTER	07E - Lipstick	2
PEG-75 COCOA BUTTER	07I - Other Makeup Preparations	1
PEG-75 COCOA BUTTER	10E - Other Personal Cleanliness Products	1
PEG-75 COCOA BUTTER	12F - Moisturizing	10
PEG-3 GLYCERYL COCOATE	12D - Body and Hand (exc shave)	2
PEG-7 GLYCERYL COCOATE	01A - Baby Shampoos	5
PEG-7 GLYCERYL COCOATE	01B - Baby Lotions, Oils, Powders, and Creams	1
PEG-7 GLYCERYL COCOATE	01C - Other Baby Products	4
PEG-7 GLYCERYL COCOATE	02A - Bath Oils, Tablets, and Salts	4
PEG-7 GLYCERYL COCOATE	02B - Bubble Baths	9
PEG-7 GLYCERYL COCOATE	02D - Other Bath Preparations	8
PEG-7 GLYCERYL COCOATE	03D - Eye Lotion	1
PEG-7 GLYCERYL COCOATE	03E - Eye Makeup Remover	10
PEG-7 GLYCERYL COCOATE	03G - Other Eye Makeup Preparations	1
PEG-7 GLYCERYL COCOATE	04E - Other Fragrance Preparation	1
PEG-7 GLYCERYL COCOATE	05A - Hair Conditioner	6
PEG-7 GLYCERYL COCOATE	05F - Shampoos (non-coloring)	122
PEG-7 GLYCERYL COCOATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	11
PEG-7 GLYCERYL COCOATE	05I - Other Hair Preparations	2
PEG-7 GLYCERYL COCOATE	06A - Hair Dyes and Colors (all types requiring caution statement	1
PEG-7 GLYCERYL COCOATE	06D - Hair Shampoos (coloring)	9
PEG-7 GLYCERYL COCOATE	06G - Hair Bleaches	1
PEG-7 GLYCERYL COCOATE	07I - Other Makeup Preparations	2
PEG-7 GLYCERYL COCOATE	08C - Nail Creams and Lotions	1
PEG-7 GLYCERYL COCOATE	10A - Bath Soaps and Detergents	342
PEG-7 GLYCERYL COCOATE	10B - Deodorants (underarm)	14
PEG-7 GLYCERYL COCOATE	10C - Douches	1
PEG-7 GLYCERYL COCOATE	10E - Other Personal Cleanliness Products	89
PEG-7 GLYCERYL COCOATE	11A - Aftershave Lotion	9

PEG-7 GLYCERYL COCOATE	11E - Shaving Cream	1
PEG-7 GLYCERYL COCOATE	11G - Other Shaving Preparation Products	6
PEG-7 GLYCERYL COCOATE	12A - Cleansing	114
PEG-7 GLYCERYL COCOATE	12C - Face and Neck (exc shave)	32
PEG-7 GLYCERYL COCOATE	12D - Body and Hand (exc shave)	18
PEG-7 GLYCERYL COCOATE	12F - Moisturizing	11
PEG-7 GLYCERYL COCOATE	12G - Night	2
PEG-7 GLYCERYL COCOATE	12H - Paste Masks (mud packs)	6
PEG-7 GLYCERYL COCOATE	12I - Skin Fresheners	1
PEG-7 GLYCERYL COCOATE	12J - Other Skin Care Preps	13
PEG-30 GLYCERYL COCOATE	01C - Other Baby Products	1
PEG-30 GLYCERYL COCOATE	05F - Shampoos (non-coloring)	22
PEG-30 GLYCERYL COCOATE	07C - Foundations	1
PEG-30 GLYCERYL COCOATE	10A - Bath Soaps and Detergents	6
PEG-30 GLYCERYL COCOATE	10E - Other Personal Cleanliness Products	5
PEG-30 GLYCERYL COCOATE	12A - Cleansing	9
PEG-40 GLYCERYL COCOATE	02D - Other Bath Preparations	1
PEG-40 GLYCERYL COCOATE	03E - Eye Makeup Remover	2
PEG-40 GLYCERYL COCOATE	04E - Other Fragrance Preparation	1
PEG-40 GLYCERYL COCOATE	05F - Shampoos (non-coloring)	3
PEG-40 GLYCERYL COCOATE	10A - Bath Soaps and Detergents	6
PEG-40 GLYCERYL COCOATE	12A - Cleansing	10
PEG-80 GLYCERYL COCOATE	05F - Shampoos (non-coloring)	1
PEG-80 GLYCERYL COCOATE	10A - Bath Soaps and Detergents	2
PEG-80 GLYCERYL COCOATE	10E - Other Personal Cleanliness Products	8
PEG-16 MACADAMIA GLYCERIDES	10A - Bath Soaps and Detergents	3
PEG-16 MACADAMIA GLYCERIDES	10E - Other Personal Cleanliness Products	1
PEG-16 MACADAMIA GLYCERIDES	12A - Cleansing	1
PEG-16 MACADAMIA GLYCERIDES	12F - Moisturizing	1
PEG-16 MACADAMIA GLYCERIDES	12J - Other Skin Care Preps	2
PEG-70 MANGO GLYCERIDES	05B - Hair Spray (aerosol fixatives)	4
PEG-70 MANGO GLYCERIDES	05G - Tonics, Dressings, and Other Hair Grooming Aids	4
PEG-70 MANGO GLYCERIDES	05I - Other Hair Preparations	22
PEG-70 MANGO GLYCERIDES	10E - Other Personal Cleanliness Products	1
PEG-10 OLIVE GLYCERIDES	05G - Tonics, Dressings, and Other Hair Grooming Aids	
PEG-45 PALM KERNEL GLYCERIDES	02A - Bath Oils, Tablets, and Salts	1
PEG-45 PALM KERNEL GLYCERIDES	02D - Other Bath Preparations	8
PEG-45 PALM KERNEL GLYCERIDES	05B - Hair Spray (aerosol fixatives)	4
PEG-45 PALM KERNEL GLYCERIDES	05F - Shampoos (non-coloring)	1
PEG-45 PALM KERNEL GLYCERIDES	05H - Wave Sets	1
PEG-45 PALM KERNEL GLYCERIDES	05I - Other Hair Preparations	1
PEG-45 PALM KERNEL GLYCERIDES	07I - Other Makeup Preparations	1
PEG-45 PALM KERNEL GLYCERIDES	10A - Bath Soaps and Detergents	16
PEG-45 PALM KERNEL GLYCERIDES	12A - Cleansing	1
PEG-45 PALM KERNEL GLYCERIDES	12C - Face and Neck (exc shave)	5
PEG-45 PALM KERNEL GLYCERIDES	12D - Body and Hand (exc shave)	2
PEG-45 PALM KERNEL GLYCERIDES	12J - Other Skin Care Preps	2

PEG-75 SHEA BUTTER GLYCERIDES	02A - Bath Oils, Tablets, and Salts	1
PEG-75 SHEA BUTTER GLYCERIDES	05A - Hair Conditioner	1
PEG-75 SHEA BUTTER GLYCERIDES	05B - Hair Spray (aerosol fixatives)	1
PEG-75 SHEA BUTTER GLYCERIDES	05F - Shampoos (non-coloring)	1
PEG-75 SHEA BUTTER GLYCERIDES	05I - Other Hair Preparations	2
PEG-75 SHEA BUTTER GLYCERIDES	10A - Bath Soaps and Detergents	8
PEG-75 SHEA BUTTER GLYCERIDES	10E - Other Personal Cleanliness Products	6
PEG-75 SHEA BUTTER GLYCERIDES	12A - Cleansing	2
PEG-75 SHEA BUTTER GLYCERIDES	12D - Body and Hand (exc shave)	1
PEG-75 SHEA BUTTER GLYCERIDES	12F - Moisturizing	1
PEG-50 SHEA BUTTER	01C - Other Baby Products	1
PEG-50 SHEA BUTTER	08B - Cuticle Softeners	1
PEG-50 SHEA BUTTER	10E - Other Personal Cleanliness Products	1
PEG-50 SHEA BUTTER	12D - Body and Hand (exc shave)	1
PEG-50 SHEA BUTTER	12F - Moisturizing	1
PEG-35 SOY GLYCERIDES	12A - Cleansing	1
PEG-10 SUNFLOWER GLYCERIDES	02B - Bubble Baths	1
PEG-10 SUNFLOWER GLYCERIDES	05F - Shampoos (non-coloring)	5
PEG-10 SUNFLOWER GLYCERIDES	05G - Tonics, Dressings, and Other Hair Grooming Aids	2
PEG-10 SUNFLOWER GLYCERIDES	10A - Bath Soaps and Detergents	1
PEG-10 SUNFLOWER GLYCERIDES	11G - Other Shaving Preparation Products	1
PEG-10 SUNFLOWER GLYCERIDES	12A - Cleansing	1
PEG-13 SUNFLOWER GLYCERIDES	05G - Tonics, Dressings, and Other Hair Grooming Aids	1

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Final Report on the Safety Assessment of PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate[1]

PEGs Glyceryl Cocoate polymers are the polyethylene glycol ethers of glyceryl cocoate. They function as skin conditioning agents, emollients, surfactants, nonionic emulsifying agents, and solubilizing agents in cosmetic formulations. Only limited data on the safety of PEG-7 Glyceryl Cocoate were found, and no data were available on the higher molecular weight polymers in this group. Data from previous safety assessments of Polyethylene Glycol (PEG), and several fatty acids (Stearic Acid, Oleic Acid, Lauric Acid, Palmitic Acid, and Myristic Acid) were considered relevant and added to the review. PEG has low oral and dermal toxicity. The fatty acids have slight oral toxicity, but little or no dermal toxicity. Dermal application of PEG-7 Glyceryl Cocoate at a concentration of SO% did not produce irritation in mice and guinea pigs, but did produce slight irritation in rabbits. Intracutaneous injection of PEG-7 Glyceryl Cocoate at a concentration of 10% did not produce sensitization. This same concentration was not an ocular irritant in animal tests. PEG-7 Glyceryl Cocoate was not phototoxic at a concentration of SO%. Although monoalkyl ethers of ethylene glycol are reproductive and developmental toxins, given the methods of manufacture of PEG-7 Glyceryl Cocoate, there is no likelihood of such compounds being present as impurities. The structure of the PEGs Glyceryl Cocoate polymers is such that it is unlikely that they would cause reproductive or developmental effects. PEG did not produce reproductive toxicity in oral toxicity studies. Oleic Acid in feed at a concentration of 15% did impair reproductive capacity in female rats, but growth and general health were not affected. No data were available on genotoxicity or carcinogenicity of PEGs Glyceryl Cocoate. PEG was not genotoxic. The fatty acids were generally not genotoxic, but positive results were seen for Oleic Acid in one assay. Neither PEG nor the fatty acids were carcinogenic in animals tests. Of concern was the possible presence of 1,4-dioxane and ethylene oxide impurities. The importance of using the necessary purification procedures to remove these impurities was stressed. In clinical studies PEG-7 Glyceryl Cocoate was neither a dermal irritant nor a photosensitizer. The principal clinical finding related to PEGs is based on data in burn patients—PEGs were mild irritant/sensitizers and there was evidence of nephrotoxicity. No such effects were seen in animal studies on intact skin. Cosmetic manufacturers should adjust product formulations containing Polyethylene Glycol to minimize any untoward effects when products are used on damaged skin. In recognition that PEG-7 Glyceryl Cocoate can enhance the skin penetration of other chemicals, care should also be exercised in using these ingredients in products where the penetration of other ingredients is aconcern. Based on the limited data on PEGs Glyceryl Cocoate and on safety assessments of other related ingredients, it was concluded that PEG-7, -30, -40, -70, and -80 Glyceryl Cocoate are safe as used in rinse-off products and safe at concentrations up to 10% in leave-on products.

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‘Reviewed by the Cosmetic Ingredient Review Expert Panel. Rebecca S. Lanigan, former Scientific Analyst and Writer, prepared this report. Address correspondence to Dr. F. Alan Andersen, Director, CIR, 1101 17th Street, NW, Suite 3 10, Washington, DC 20036, USA,

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INTRODUCTION

The PEGs Glyceryl Cocoate polymers serve a variety of functions in cosmetic formulations. PEG-7 Glyceryl Cocoate serves as a skin-conditioning agent, emollient, surfactant, and nonionic emulsifying agent in cosmetic formulations. PEG-30, -40, -78, and -80 Glyceryl Cocoate function as surfactants-cleansing agents and solubilizing agents. Because there are limited data specifically on PEG-7 Glyceryl Cocoate, and no data are available on PEG-30-80 Glyceryl Cocoate, the data concerning the PEGs and the C 12-C 18 fatty acids have been summarized in this review as an additional basis for the assessment of safety of PEG-7 Glyceryl Cocoate. Note that the different chain length PEGs are formed by condensing ethylene oxide and water, with the average number of moles of ethylene oxide used corresponding to the number in the name.

Polyethylene Glycol, Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid have been reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel and the Final Reports have been published. The following conclusions were made:

> PEG -6, -8, -32, -75, 150, -14M, and -20M are safe for use at the concentrations reflected in the Cosmetic Use section and in the product formulation safety test data included in the Final Report. The Expert Panel recommends that cosmetic formulations containing these PEGs not be used on damaged skin (Andersen 1993).
>
> Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid are safe in present practices of use and concentration in cosmetics (Elder 1987).

CHEMISTRY

Definition and Structure

PEG-7 Glyceryl Cocoate (CAS Nos. 66105-29- 1; 6820 1-46-7 [generic]) is a polyethylene glycol ether of Glyceryl Cocoate (q. v.). It generally conforms to the formula shown in Figure 1. where RCO-represents the coconut oil–derived fatty acids and n has the average value of 7 (Wenninger and McEwen 1997). PEG-30, -40, -78, and -80 Glyceryl Cocoate (CAS No.68201-46-7; generic) conform to the same formula shown in Figure 1: again, n has an average value equal to the number in the name.

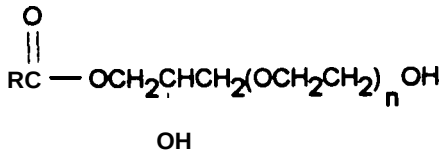

FIGURE 1
Chemical formula for PEGs Glyceryl Cocoate (Wenninger and McEwen 1997). RCO- represents the coconut oil-derived fatty acids and n has the average value corresponding to the PEG chain length.

Other names for PEG-7 Glyceryl Cocoate are Polyethylene Glycol (7) Glyceryl Monococoate Polyoxyethylene (7) Glyceryl Monococoate (Wenninger and McEwen 1997), Polyoxyethylated Glycerol Stearic Acid Ester (Provost, Herbots, and Kinget 1989), and Polyoxyethylene (7) Stearyl Partial Glyceride (Provost and Kinget 1988). This compound is also commonly known by the trade name Cetiol HE (Provost, Herbots, and Kinget 1988; Wenninger and McEwen 1997). Synonyms for PEGs Glyceryl Cocoate are Polyethylene Glycol (n) Glyceryl Monococoate, Polyethylene Glycol (n) Glyceryl Cocoate, and Polyoxyethylene (n) Glyceryl Cocoate. PEG-40 Glyceryl Cocoate is also known as Polyethylene Glycol 2000 Glyceryl Cocoate (Wenninger and McEwen 1997).

Physical and Chemical Properties

PEG-7 Glyceryl Cocoate is the partial ester of polyoxyethylated glycerol with stearic acid and has approximately seven ethylene oxide residues. It is a clear, pale yellow oil with a mild, fatty odor (Nikitakis and McEwen 1990). PEG-7 Glyceryl Cocoate has low viscosity (Henkel Corporation, 1996). PEG-7 Glyceryl Cocoate has a hydrophile-lipophile balance (HLB) value of 15 (Provost and Kinget 1988), indicating that the compound is water-dispersible or soluble (Balsam and Sagarin 1974). The HLB illustrates the simultaneous relative attraction of PEG-7 Glyceryl Cocoate for both water and oil. The compound forms spherical micelles in water when dispersed at concentrations at or above the critical micelle concentration. The micelles have a hydrophilic polar surface and lipophilic apolar center (Provost and Kinget 1988).

PEG-7 Glyceryl Cocoate is water and ethanol soluble, and is insoluble in mineral oil (Nikitakis and McEwen 1990). When PEG-7 Glyceryl Cocoate cools in water, hydrogen bonding between some of the water molecules and the ether oxygens of the oxyethylene groups occurs, resulting in hydration of PEG-7 Glyceryl Cocoate such that the bound water does not freeze (Provost 1989; Provost, Herbots, and Kinget 1990). The hydroxyl value for PEG-7 Glyceryl Cocoate is 172-187, and the saponification value 90-100. Iodine and acid values each have a maximum of 5.0 (Nikitakis and McEwen 1990). Table 1 is a summary of the compound's physical properties.

Analytical Methods

PEG-7 Glyceryl Cocoate can be determined by infrared spectroscopy (Nikitakis and McEwen 1990). When analyzed by differential scanning calorimetry, PEG-7 Glyceryl Cocoate undergoes a single, very broad, endothermal transition (Provost 1989; Provost, Herbots, and Kinget 1990) with an onset temperature of 0.7°C and a minimum temperature of −11.9°C (Provost, Herbots, and Kinget 1990).

Method of Manufacture

No information was available on the method of manufacture of PEGs Glyceryl Cocoate. PEGs are formed by condensing ethylene oxide and water, with the average number of moles of ethylene oxide polymerized indicated by the number in the name (Andersen 1993). Oleic, Stearic, Palmitic, Myristic, and Lauric Acids are generally produced by the hydrolysis of common animal and vegetable fats and oils, followed by fractionation of the resulting animal acids. Oleic Acid has been prepared from animal tallow and olive oil, and is a by product in the manufacture of Palmitic and Stearic Acids. Lauric Acid is commonly isolated from coconut oil. Palmitic Acid is produced by the hydrolysis and fractionation of palm oil, tallow oil, coconut oil, Japan Wax, Chinese vegetable tallow, and spermaceti. It is also a by-product in the manufacturing process for Stearic Acid. Myristic Acid is isolated from tall-oil fatty acids from 9-ketotetradecanoic acid,

TABLE 1
Physical properties of PEG-7 Glyceryl Cocoate

Property	Description	Reference
Physical	Clear; pale yellow oil; mild, fatty odor	Nikitakis and McEwen 1990
Solubility	Soluble in water and ethanol; insoluble in mineral oil	Nikitakis and McEwen 1990
Hydrophile-lipophile balance	15	Provost and Kinget 1988
Hydroxyl value	172-187	Nikitakis and McEwen 1990
Saponification value	90–100	Nikitakis and McEwen 1990
Acid value	Maximum of 5.0	Nikitakis and McEwen 1990
Iodine value	Maximum of 5.0	Nikitakis and McEwen 1990

by electrolysis of a methyl hydrogen adipate and decanoic acid mixture, by Maurer oxidation of myristanol or cetanol, or by the fractional distillation of hydrolyzed coconut oil, palm kernel oil, or coconut acids (Elder 1987).

Impurities

No information on the impurities that may be found in PEGs Glyceryl Cocoate is available. Silverstein et al. (1984) reported that PEG-6 may contain small amounts of monomer and dimers. The amounts were not quantified. Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75 (Hamburger, Azaz, and Donbrow 1975). The amount of peroxide in PEGs is dependent upon the molecular weight of the PEG and its age. The older the compound, the greater the concentration of peroxides. In a colorimetric assay used to determine the peroxide concentrations in several production lots of PEGs, PEG-6 and PEG-8 were each added to acidified potassium iodide solution, and the iodine liberated was titrated against a standard thiosulfate solution. PEG-6 had peroxide concentrations ranging from 1.4 to 9.3 μEq thiosulfate/ml glycol. PEG-8 had concentrations ranging from 3.24 to 5.7 μEq thiosulfate/ml glycol. The specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide (McGinity, Hill, and La Via 1975).

Ethoxylated surfactants may also contain 1,4-dioxane, a by-product of ethoxylation (Robinson and Ciurczak 1980). 1,4-Dioxane is a known animal carcinogen (Kociba et al. 1974; Hoch-Ligeti, Argus, and Arcos 1970; Argus, Arcos, and Hoch-Ligeti 1965). In the CIR safety assessment of the PEGs Stearate polymers, the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations (Elder 1983).

Fatty acids used in foods, drugs, and cosmetics normally exist as mixtures of several fatty acids, depending on the source and manufacturing process. The individual fatty acids predominate in the mixture, ranging from 74% (Oleic Acid) to 95% Myristic Acid. All contain varying amounts of unsaponifiable matter, and some grades contain glyceryl monoesters of fatty acids. Butylated hydroxytoluene may be added to all five fatty acid preparations as an antioxidant. In cosmetics containing unsaturated materials, the butylated hydroxytoluene concentration range is 0.01–0.1% (Elder 1987).

USE

Cosmetic

PEG-7 Glyceryl Cocoate serves as a skin-conditioning agent, emollient, surfactant. and emulsifying agent in cosmetic formulations. PEG-30 and -80 Glyceryl Cocoate function as surfactant-cleansing agents and solubilizing agents (Wenninger and McEwen 1997). In formulation data submitted to the Food and Drug Administration (FDA), PEG-7 Glyceryl Cocoate was listed as being in 173 cosmetic formulations (Table 2). PEG-30, -40, -78, and -80 Glyceryl Cocoate were used in 10, 5, 1, and 2 formulations, respectively (FDA 1996). Concentration of use data are no longer requested by FDA, but concentration of use data submitted by the cosmetic industry in 1984 stated that PEG-7 Glyceryl Cocoate was used at concentrations from 0.1 to 50% (FDA 1984). Recent data submitted by industry indicated that PEG-7 Glyceryl Cocoate was generally used in foam baths and shower baths to enhance moisturizing characteristics and that O.l-0.5% was typically used in cosmetic product formulations (Dewhirst Lorien Ltd. 1996). Two face cream formulations contained 0.03% PEG-7 Glyceryl Cocoate (Ivy Laboratories 1995), and one night cream contained 0.03% PEG-7 Glyceryl Cocoate (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1996).

PEG-7 Glyceryl Cocoate serves as an emulsifier in transparent oil-water (TOW) gels (Provost and Kinget 1988; Provost 1989; Provost, Herbots, and Kinget 1990; De Vos, Vervoort, and Kinget 1993a) which function as vehicles for skin care preparations (Provost and Kinget 1988; Provost, Herbots, and Kinget 1990). Concentrations of up to 30% (w/w) PEG-7 Glyceryl Cocoate are used in the preparation of the gels (Provost and Kinget 1988), and the compound is essential for the incorporation of oil into the gel structure (Provost and Kinget 1988; Provost 1989). The presence of the emulsifier allows TOW gels to retain their transparency, even when containing a relatively large amount of oil (Provost 1989).

International

PEG-7 Glyceryl Cocoate is listed in the ***Comprehensive Licensing Standards*** of ***Cosmetics by Category*** (CLS) and must conform to the standards of the ***Japanese Cosmetic Ingredient Codex*** (JCIC) (Yakuji Nippo, Ltd. 1994). It can be used without restriction in all CLS categories except eyeliners, lipsticks and lip creams, and dentifrices.

Noncosmetic

TOW gels serve as vehicles for topical treatment of dermatological diseases using pharmaceutical preparations (Provost and Kinget 1988). TOW gels formed using PEG-7 Glyceryl Cocoate release both hydro- and lipophilic drugs at a relatively high rate and enable them to penetrate isolated human epidermis at rates similar to those from other dermatological vehicles (Provost 1989). TOW gels containing PEG-7 Glyceryl Cocoate adhere to mucosae, wet wounds, and other hydrophilic supports (Provost, Herbots, and Kinget 1988). Nonionic surfactants (such as PEG-7 Glyceryl Cocoate) act as penetration enhancers, conditioning the stratum comeum to enable and promote drug diffusion by reversibly inserting into the lipid structure, thereby disrupting lipid packing, and lowering the transition temperature of human stratum comeum (De Vos, Vervoort and Kinget 1993b).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Distribution

Gastrointestinal absorption of PEGs is dependent on the molecular weight of the compound. In general, the greater the

TABLE 2
Product formulation data (FDA 1996)

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-7 Glyceryl Cocoate		
Baby shampoos	23	1
Other baby products	37	2
Bath oils, tablets, salts	147	5
Bubble baths	211	8
Other bath preparations	166	6
Eye makeup remover	95	1
Other eye makeup preparations	136	1
Hair conditioners (noncoloring)	715	1
Shampoos (noncoloring)	972	22
Tonics, dressings, and other hair grooming aids	604	1
Hair dyes and colors	1612	58
Bath soaps and detergents	372	6
Douches	19	1
Other personal cleanliness products	339	10
Aftershave lotion	268	3
Other shaving preparations products	63	2
Cleansing	820	13
Face and neck (excluding shaving)	300	4
Body and hand (excluding shaving)	1012	7
Moisturizing	942	2
Paste masks (mud packs)	300	3
Skin fresheners	244	2
Other skin care preparations	810	11
Suntan gels, creams, and liquids	196	2
Other suntan preparations	68	1
1996 total		**173**
PEG-30 Glyceryl Cocoate		
Other baby products	37	1
Other eye makeup preparations	136	1
Hair straighteners	50	1
Permanent waves	434	2
Shampoos (noncoloring)	972	4
Cleansing	820	1
1996 totals		**10**
PEG-40 Glyceryl Cocoate		
Bath oils, tablets, and salts	147	1
Bubble baths	211	1
Eye makeup remover	95	2
Cleansing	820	1
1996 total		**5**
PEG-78 Glyceryl Cocoate		
Cleansing	820	1
1996 total		**1**
PEG-SO Glyceryl Cocoate		
Shampoos (noncoloring)	972	2
1996 total		2

molecular weight of the PEG compound, the lesser the absorption that occurs. In both oral and intravenous studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and feces. In a study with human bum patients, monomeric ethylene glycol was isolated in the serum following topical exposure to a PEG-based antimicrobial cream, indicating that PEGs are readily absorbed through damaged skin (Andersen 1993).

Increasing fatty acid chain length slighly decreased the digestibility of fatty acids. Stearic Acid was the most poorly absorbed of the common fatty acids. Dietary fatty acids are absorbed in micellar aggregates and transported esterified to glycerol in chylomicrons and very low density lipoproteins. Oleic, Palmitic, Myristic, and Stearic Acids are primarily transported via the lymphatic system. Lauric Acid is transported by the lymphatic and (as a free fatty acid) portal systems. Fatty acids originating from the adipose tissue stores are either bound to serum albumin or remain unesterified in the blood. Oleic Acid has been reported to penetrate the skin of rats. Within 10 min of topical application, fluorescence from absorbed Oleic Acid was found in the epidermal cell layers of skin removed from treated rats. The path of penetration was suggested to be via the hair follicles. Minute amounts of Oleic Acid were visualized in the blood vessels. Skin permeability increased with the lipophilic nature of the compound. Radioactivity was present in the heart, liver, lungs, spleen, kidneys, muscles, intestine, adrenal glands, blood, lymph, and adipose, mucosal, and dental tissues after administration of radioactive Oleic, Palmitic, and Stearic acids. Uptake and transport of fatty acids into the brain have been observed. Free fatty acids readily cross the placental barrier in rabbits, guinea pigs, rats, and humans. Fatty acids taken up by tissues are either stored as triglycerides or oxidized for energy via #?-oxidation and tricarboxylic acid cycle pathways (Elder 1987).

ANIMAL TOXICOLOGY

Acute Toxicity

Rats were given PEG-7 Glyceryl Cocoate by gavage and 10 rats were tested. Administration of 19.9 mg/kg did not produce signs of toxicity (Henkel Corporation 1996).

Results of toxicity studies with rats, rabbits, and dogs indicate that PEGs have low oral and dermal toxicity. In general, the higher molecular weight PEGs appear to be less toxic than the lower molecular weight PEGs in oral studies. Acute oral LD50s for PEGs in rabbits were 17.3 g/kg (100% PEG-6) and 76 g/kg (100% PEG-75). In acute dermal toxicity studies, no deaths were reported in groups of rabbits dosed with undiluted PEG-6 (20 ml/kg) or 40% PEG-20M (20 ml/kg) (Andersen 1993).

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids had slight acute oral toxicity in rats given 15-19 g/kg doses or cosmetic formulations containing the acids. In studies using albino rats, the acute oral LD50 of Oleic Acid was >2 1.5 ml/kg; the LD50 of both Palmitic Acid and Myristic Acid was > 10.0 g/kg. Little or no apparent toxicity was produced by topical application of Oleic, Palmitic, and Stearic Acid to the skin of rabbits, mice, or guinea pigs (Elder 1987).

Short-Term Toxicity

No evidence of toxicity was observed in a group of rabbits that received daily topical applications of PEG-20M (0.8 g/kg/day) for 30 days, with the exception of transient, mild erythema. The only evidence of systemic toxicity that resulted from dermal exposure was renal failure in rabbits that received repeated applications of an antimicrobial cream containing 63% PEG-6, 5% PEG-20, and 32% PEG-75 to excised skin sites for 7 days (Andersen 1993).

Chicks given 5% Oleic Acid or 50% Stearic Acid in feed for 4 weeks had no adverse effects. Rats given high-fat diets containing 5% Stearic Acid had decreased clotting time, moderate hyperlipemia, and severe phlebothrombosis following initiation by an intravenous injection of ***Salmonella*** *typhosa* lipopolysaccharide. Hyperlipemia was observed in rats fed diets containing 4.6 g/kg/day Palmitic Acid for 6 weeks. A microscopic "foreign body reaction" was observed in adipose tissue in rats given 50% Stearic Acid in feed for 8 weeks. In a 9-week study, rats given high-fat diets (6% Stearic Acid) had severe aortic atherosclerosis and thrombosis after induction by *S. typhosa* lipopolysaccharide; high mortality was observed. In short-term dermal studies using mice and rabbits, Oleic Acid, Lauric Acid, Palmitic Acid, and Myristic Acid (concentrations up to 30%) caused transient erythema, desquamation, follicular keratosis, follicular epidermal hyperplasia, or slight irritation. Stearic Acid at concentrations of 20–50% caused slight edema and desquamation (Elder 1987).

Subchronic Toxicity

In subchronic, 90-day oral toxicity studies using groups of albino rats, the largest (PEG-20M) and smallest (PEG-6) molecular weight PEGs tested neither induced toxicity nor death when administered daily at concentrations of 4% or less; PEG-20M was administered in the diet and PEG-6 in drinking water. In a dermal toxicity study, no evidence of toxicity was observed in a group of rabbits that received daily applications of PEG-6 5 days per week (2 ml/kg/day) for 18 weeks (Andersen 1993).

In a 24-week study using rats, a "foreign body reaction" was observed in the perigonadal fat and the reversible formation of lipogranulomas was observed following the administration of 50 g/kg/day of Stearic Acid in feed. Anorexia, severe pulmonary infection, and high mortality were observed in rats given diets containing 3000 ppm Stearic Acid for 30 weeks (Elder 1987).

Chronic Toxicity

Toxic effects also were not observed in groups of dogs that received PEG-8, PEG -32, and PEG-75 at concentrations of 2% in the diet for 1 year (Andersen 1993).

Dermal Irritation and Sensitization

Kastner (1977) compared the topical irritancy potential of fatty or fat-derived cosmetic ingredients, including 50% PEG-7

Glyceryl Cocoate (in Vaseline) on the skin of various animals (four per group) in 24-hour skin patch tests. Patches were applied to the shaved backs of adult male New Zealand White rabbits, male Pirbright White guinea pigs (average weight 300 g), and male and female adult mutant hairless mice. Porous leucoplastic fixed the patches to the guinea pigs and hairless mice. All test sites were observed at 24 hours (when the patches were removed) and 48 hours. Any reactions were then rated and placed into reaction classes 1–5, with 5 having the highest skin irritation potential. Rabbits had the greatest sensitivity to PEG-7 Glyceryl Cocoate, with a class 3 reaction (slight, with the resulting rash fading). Guinea pigs and hairless mice failed to react to PEG-7 Glyceryl Cocoate, and were classified in the lowest reaction group.

PEG-7 Glyceryl Cocoate was applied to the intact and abraded skin of three albino rabbits in a Draize primary irritation test. The test material caused moderate erythema and mild edema. The primary irritation index was 1.66, and PEG-7 Glyceryl Cocoate was classified as a mild dermal irritant. In a second study, PEG-7 Glyceryl Cocoate was applied to the clipped skin of two rabbits. The test sites were rinsed after 1 hour and scored at 24 hours and 48 hours. Directly after removal of PEG-7 Glyceryl Cocoate, the treated skin sites had slight reddening that could not be seen after 24 hours (Kastner 1977).

A 10% solution of PEG-7 Glyceryl Cocoate was given to five male Pirbright White W58 guinea pigs by 10 intracutaneous injections into the paravertebral depilated skin at intervals of two days. The test volume of each injection was 0.1 ml. A challenge injection (10% concentration, 0.1 ml test volume) was given 14 days after the last induction injection. Guinea pigs given PEG-7 Glyceryl Cocoate had sharply demarcated necrotic changes of the skin (about the size of a pea), but no general signs. These changes subsided during the 14-day interval. Body weight gain of the treated animals was comparable to controls. No other reactions were noted at the sites of the necrotic foci. No evidence of sensitization was observed (Henkel Corp. 1996).

The PEGs were not irritating to the skin of rabbits or guinea pigs, and PEG-75 was not a sensitizer. In skin irritation tests, undiluted PEG-6 was applied to the skin of rabbits for 4 hours and 50% PEG-75 was applied to guinea pigs for 4 days and to rabbits over a 13-week period. In the guinea pig skin sensitization test, PEG-75 was tested at a concentration of 0.1% (Andersen 1993).

Various concentrations of Oleic Acid, Stearic Acid, Palmitic Acid, Myristic Acid, and Lauric Acid produced minimal to mild erythema in primary skin irritation studies using rabbits, but were mainly nonirritating. Cosmetic formulations containing Stearic Acid and Oleic Acid were not sensitizing to female Hartley guinea pigs when tested at concentrations of 5.08% (Oleic Acid), and 3.5% and 1.0% (Stearic Acid) (Elder 1987).

Ocular Irritation

PEG-7 Glyceryl Cocoate at a concentration of 10% (aqueous) did not produce ocular irritation when instilled into the conjunctival sac of two rabbits (Henkel Corp. 1996).

PEGs-6 and -75 did not cause cornea1 injuries when instilled (undiluted, 0.5 ml) into the conjunctival sac of rabbits. PEG-8 (35% solution, 0.1 ml) and PEG-32 (melted in water bath, 0.1 ml) induced mild ocular irritation in rabbits (Andersen 1993).

Oleic Acid, Stearic Acid, Lauric Acid, Palmitic Acid, and Myristic Acid were nonirritating to the eyes of rabbits in ocular irritation studies using Draize procedures (Elder 1987).

Phototoxicity

PEG-7 Glyceryl Cocoate at a concentration of 50% was coated onto the dorsal skin of hairless mice (five per group). Treated skin sites were exposed to ultraviolet (UV) radiation in a single 30-minute session; the mice were kept 50 cm from the UV lamp during exposure. Control A received the vehicle (olive oil) and control B did not receive either the test material or the vehicle prior to UV exposure. The mice were examined at 6, 24, 30, 48, and 96 hours after exposure. No local or general signs of phototoxicity were observed during the study. Measurements of skin thickness indicated that all mice had swelling that peaked at 30 hours after exposure and subsided by 66 hours. No differences in swelling or skin thickness were observed in treated mice compared to controls (Henkel Corp. 1996).

Photosensitization

Cosmetic formulations containing 2.8% Stearic Acid were not photosensitizing when tested using male Hartley guinea pigs. The concentrations of the product formulations tested ranged from 25–100% (in water) (Elder 1987).

Comedogenicity

The comedogenicity of UVA-irradiated and nonirradiated Oleic Acid at a concentration of 99% was evaluated using Japanese and New Zealand White rabbits. After 18 hours of irradiation, a significant increase in lipid peroxide level of Oleic Acid was observed. A test volume of 2 ml of the irradiated Oleic Acid was applied topically to the ventral surface of one ear per rabbit each day for 2 weeks. An equal volume of nonirradiated Oleic Acid was applied to the other ear. Both Oleic Acid and its peroxides induced fairly large cornedones. The lipid peroxide concentration was positively correlated with the degree of comedone formation (Elder 1987).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Ethylene Glycol and Its Ethers

It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers (e.g., methoxyethanol, a.k.a. ethylene glycol monomethyl ether) are reproductive and developmental toxins. The CIR Expert Panel undertook a separate, limited scope review of these compounds in order to assess the possibility that PEG-derived cosmetic ingredients could present similar concerns (CIR 1996). In summary, it was concluded that the ethylene glycol monoalkyl ethers are not toxic.

but rather, that one or more alcohol or aldehyde dehydrogenase metabolites are toxic. From the available data, it was also concluded that the toxicity of the monoalkyl ethers is inversely proportional to the length of the alkyl chain (methyl is more toxic than ethyl than propyl than butyl, etc.).

The PEGs Glyceryl Cocoate polymers, however, are the partial esters of polyoxyethylated glycerol with stearic acid, and as such, are chemically different from the alkyl ethers. Thus, the Panel concluded no reproductive or developmental hazard is posed by these compounds.

Polyethylene Glycol

No adverse reproductive effects occurred during subchronic (90 days) and chronic (2 years) oral toxicity studies of PEG-6-32 and PEG-75. In the subchronic study, PEG-75 was tested at a dose of 0.23 g/kg/day. In the chronic study, PEG-75 was tested at doses up to 0.062 g/kg/day and, PEG-6-32, at doses up to 1.69 g/kg/day (Andersen 1993).

Fatty Acids

No adverse effects on growth or general health were observed in rats given 15% Oleic Acid in feed for 10–16 weeks; however, reproductive capacity of treated female rats was impaired (Elder 1987).

MUTAGENICITY

PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test; the maximum test concentration in both studies was 1%. In the unscheduled DNA synthesis assay, a statistically significant increase in radioactive thymidine incorporation into rat hepatocyte nuclei was noted only at the highest concentration tested (0.1% PEG-8). PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay when tested at concentrations up to 150 g/l (Andersen 1993).

Oleic Acid (100–500 μg/ml), Lauric Acid (1 O-200 @g/ml), and Stearic Acid (up to 500 μg/ml) did not induce mitotic aneuploidy and crossing over of chromosomes in the D_6 strain of ***Saccharomyces cerevisiae.*** Stearic Acid was nonmutagenic in ***Salmonella typhimurium*** strains TA98, TA100, TA1535, TA1537, and TA1538, with or without metabolic activation. Concentrations of Oleic Acid from 2.5-10.0 μg/ml induced higher incidences of aneuploidy and tetraploidy in a genotoxicity assay using V79 Chinese hamster lung fibroblasts, compared to controls. The mean number of sister chromatid exchanges per metaphase was similar to controls. Oleic, Lauric, Stearic, and Palmitic Acids inhibited the mutagenicity of several compounds (e.g., N-nitrosodialkylamines) in modified Ames tests using ***Escherichia*** *coli* and ***S. typhimurium*** (Elder 1987).

CARCINOGENICITY

All of the carcinogenicity data available on the PEGs was specifically on PEG-8, which was used as a solvent control for a number of studies. PEG-8 was not carcinogenic when administered orally to mice (30 weeks of dosing), intraperitoneally to rats (6 months of dosing), subcutaneously (20 weeks of dosing to rats; 1 year of dosing to mice), or when injected into the gastric antrum of guinea pigs over a period of 6 months (Andersen 1993).

No malignant tumors were induced by repeated subcutaneous injections of l-16.5 mg Oleic Acid per injection using female BALB/c or Swiss-Webster mice. Repeated subcutaneous injections of Lauric Acid (25-50 mg/injection), Palmitic Acid (25-50 mg/injection), or Stearic Acid (up to 82 mg/injection) did not increase the incidence of carcinomas, sarcomas, and lymphomas in mice. In oral studies, mice fed a diet containing up to 200 mg of Oleic Acid had intestinal and gastric tumors, and feeding of up to 50 g/kg/day of Stearic Acid was noncarcinogenic (Elder 1987).

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Kastner (1977) applied patches containing 50% PEG-7 Glyceryl Cocoate to the upper arms of four volunteers for 24 hours. Test sites were evaluated at patch removal and at 24 hours later. Any reactions were rated and placed into reaction classes l-5, with 5 having the greatest skin irritation potential. The subjects failed to react to 50% PEG-7 Glyceryl Cocoate and were classified in the lowest reaction group.

No evidence of dermal irritation was observed after PEG-7 Glyceryl Cocoate was applied (concentration not given) with a test plaster to the forearms of five subjects for 1 hour. In another study, undiluted PEG-7 Glyceryl Cocoate was applied to 40 volunteers in a primary irritation patch test. No skin irritation was observed (Henkel Corp. 1996).

In clinical studies, PEG-6 and PEG-8 induced mild sensitization in 9% and 4% of 23 male subjects tested, respectively. However, later production lots of PEG-6, as well as PEG-75, did not cause reactions in any of the 100 male and 100 female subjects tested. A product formulation containing 3% PEG-8 induced minimal to mild irritation (induction phase) in over 75% of 90 volunteers participating in a skin irritation and sensitization study. Responses (not classified) were noted in 22 subjects at the 24 hours challenge reading. Cases of systemic toxicity and contact dermatitis in bum patients were attributed to PEG-based topical ointments. The ointment that induced systemic toxicity contained 63% PEG-6, 5% PEG-20, and 32% PEG-75 (Andersen 1993).

Oleic, Myristic, and Stearic Acids at concentrations of 100% or 40–50% in mineral oil were nonirritating in primary and cumulative dermal irritation studies. Mild to intense erythema was observed in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies that tested cosmetic formulations containing 2-93% Oleic, Palmitic, Myristic, or Stearic Acid. These results were generally not related to the fatty acid concentration in the formulations, however.

Formulations containing up to 13% Oleic, Lauric, Palmitic, or Stearic Acid were not sensitizing (Elder 1987).

Ocular Irritation

Mascara formulations containing 2-3% Oleic Acid did not produce ocular irritation in two 3-week exaggerated use studies (Elder 1987).

Photosensitization

The photosensitization of a SPF 15 facial cream containing 0.03% PEG-7 Glyceryl Cocoate was determined using 28 adult volunteers. The minimal erythema dose (MED) of each subject was determined by exposing one side of the midback (1 -cm-diameter circular exposure areas) to a series of exposures in 25% increments from a 150-watt xenon arc solar simulator. Each volunteer then underwent the induction phase of testing. The facial cream was applied as an 80 mg dose to a 2 x 2–cm skin site on the lower back. The sites were covered with 2 x 2–cm squares of nonabsorbing cotton cloth, which was fastened to the skin with overlapping strips of occlusive tape. The patches were removed after 24 hours. The test sites were exposed to three MEDs from the xenon arc solar simulator. The sites were left uncovered for 48 hours, and the patches were reapplied for 24 hours to the same sites under an occlusive dressing. The patches were removed and the skin sites were exposed to an additional three MEDs. This procedure was repeated twice weekly for 3 weeks. Ten to 14 days after the last induction exposure, the volunteers received a single challenge exposure. The facial cream was applied (80 mg) in duplicate to untreated 2 x 2–cm skin sites on the opposite side of the lower back. The sites were covered with an occlusive dressing for 24 hours. One set of patches was removed, and each site was irradiated with 4 J/cm^2 of UVA, obtained by filtering the exit beam from the solar simulator to eliminate UVB wavelengths. The duplicate set of patches was unirradiated and served as control unexposed treated sites. All test sites were examined for photosensitization reactions at 48 hours and 72 hours. Of the 28 volunteers, two were dropped from the study for reasons unrelated to the test procedure. The only reactions observed during induction included mild erythema, desquamation, and tanning; these reactions were attributed to the repeated exposures to three MEDs. No signs of photosensitization were observed following challenge in any of the 26 test subjects (Ivy Laboratories 1995).

A second facial cream (SPF 15) containing 0.3% PEG-7 Glyceryl Cocoate was tested using the same procedures. Thirty-one subjects participated in the study; six withdrew from the study during induction. Mild erythema, desquamation, and tanning occurred during induction, and no signs of photosensitization were observed during challenge (Ivy Laboratories 1996).

Formulations containing up to 13% Oleic, Lauric, Palmitic, or Stearic Acid were not photosensitizing (Elder 1987).

SUMMARY

PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate are the polyethylene glycol (PEG) ethers of glyceryl cocoate. The PEGs Glyceryl Cocoate function as skin-conditioning agents, emollients, surfactants, nonionic emulsifying agents, and solubilizing agents in cosmetic formulations. In 1996, the PEGs Glyceryl Cocoate were reported to be used in 19 1 cosmetic products. PEG-7 Glyceryl Cocoate was reportedly used in cosmetic formulations at concentrations of 0.1–0.5%.

PEG-7 Glyceryl Cocoate is used as an emulsifier in TOW gels, which serve as vehicles for topical pharmaceutical preparations. TOW gels that contain PEG-7 Glyceryl Cocoate release hydro- and lipophilic drugs at a relatively high rate and enable them to penetrate isolated human epidermis at rates similar to those from other dermatological vehicles. The gels adhere to mucosae, wet wounds, and other hydrophilic supports. In general, nonionic surfactants act as penetration enhancers by conditioning the stratum comeum to enable and promote drug diffusion.

Limited data on the safety of PEG-7 Glyceryl Cocoate were found. No data on the other PEGs Glyceryl Cocoate were available. Most of the available safety test data are summaries from the previous safety assessments on PEG-6 through -20M, Stearic Acid, Oleic Acid, Lauric Acid, Palmitic Acid, and Myristic Acid.

No specific absorption, metabolism, or distribution data on the PEGs Glyceryl Cocoate were available. In oral and intravenous studies, no metabolism of PEG was observed and the administered PEGs were excreted unchanged in the urine and feces. PEGs are absorbed through damaged skin. In general, fatty acids (such as Stearic Acid) are readily absorbed and distributed in humans. Fatty acids can traverse the placental barrier.

Treatment of rats with 19.9 mg/kg PEG-7 Glyceryl Cocoate by gavage produced no signs of toxicity. PEGs have low oral and dermal toxicity. Oleic, Lauric, Palmitic, Myristic, and Stearic Acids have slight oral toxicity. Little or no apparent toxicity was produced by topical application of the fatty acids. In subchronic and chronic feeding studies, no adverse effects were reported following administration of the PEGs. High mortality, anorexia, and severe pulmonary infection were observed in rats given 3000 ppm Stearic Acid in feed for 30 weeks.

PEG-7 Glyceryl Cocoate at a concentration of 50% did not produce dermal irritation in a single-insult patch test using mice and guinea pigs; slight irritation was observed in rabbits. In a second primary irritation study, PEG-7 Glyceryl Cocoate was a mild dermal irritant in rabbits. Intracutaneous injections of 10% PEG-7 Glyceryl Cocoate in guinea pigs caused necrotic changes of the skin, but no signs of sensitization. The PEGs were not irritating to the skin of rabbits or guinea pigs, and PEG-75 was not a sensitizer. The fatty acids were mainly nonirritating, but various concentrations of Oleic, Stearic, Palmitic, Myristic, and Lauric Acids produced minimal to mild erythema in primary irritation studies. Cosmetic formulations containing 1–5.08% Stearic Acid and Oleic Acid were nonsensitizing. PEG-7 Glyceryl Cocoate was not an ocular irritant when tested at a

concentration of 10% using rabbits. Undiluted PEG-6 and PEG-75 were not irritating to the eyes of rabbits, and the fatty acids were not ocular irritants.

PEG-7 Glyceryl Cocoate was not phototoxic at a concentration of 50%, and Stearic Acid at a concentration of 2.8% in formulation was not photosensitizing. Oleic Acid and its UVA-induced peroxides induced the formation of fairly large comedones after topical application to sites on the ventral surface of rabbit ears.

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, PEG-7 Glyceryl Cocoate is the partial ester of polyoxyethylated glycerol with stearic acid. It was considered unlikely that the PEGs Glyceryl Cocoate would cause reproductive or developmental effects based on their structural characteristics. The PEGs did not produce reproductive or developmental toxicity in subchronic or chronic oral toxicity studies. Reproductive capacity was impaired in female rats given 15% Oleic Acid in feed for 10–16 weeks, but growth and general health were not affected adversely.

No specific genotoxicity or carcinogenicity data were available on the PEGs Glyceryl Cocoate. PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test. PEG- 150 was not mutagenic in the mouse lymphoma forward mutation assay. Oleic Acid, Lauric Acid, and Stearic Acid did not induce mitotic aneuploidy or crossing over of chromosomes in ***Saccharomyces cerevisiae.*** Stearic Acid was nonmutagenic in the Ames test. Oleic Acid induced aneuploidy and tetraploidy in Chinese hamster lung fibroblasts. Oleic, Lauric, Palmitic, and Stearic Acids inhibited the mutagenicity of N-nitrosodialkylamines in modified Ames tests. PEG-8 was noncarcinogenic in rats, guinea pigs, and mice after 30 weeks to 1 year of treatment by various routes. Daily subcutaneous injection of l-16.5 mg Oleic Acid produced no malignant tumors in mice. Intestinal and gastric tumors occurred in mice given 200 mg/day dietary Oleic Acid. Stearic Acid given at up to 50 g/kg/day in feed was not carcinogenic in mice.

In clinical studies, PEG-7 Glyceryl Cocoate was not a dermal irritant or photosensitizer. PEG-6 and PEG-8 produced mild sensitization. Bum patients receiving a PEG-based topical ointment had signs of systemic toxicity and contact dermatitis. SPF 15 facial creams containing 0.3% PEG-7 Glyceryl Cocoate did not produce signs of photocontact allergenicity during clinical trials. Oleic, Myristic, and Stearic Acids did not cause irritation in primary and cumulative dermal irritation studies. Cosmetic formulations containing the fatty acids were not sensitizers, photosensitizers, or ocular irritants.

DISCUSSION

The CIR Expert Panel has previously reviewed the safety of the PEGs in cosmetics, as well as the safety of Lauric, Stearic, Oleic, Palmitic, and Myristic Acids. Although little safety data were available on the PEGs Glyceryl Cocoate polymers, the Expert Panel concluded that the limited data provided on PEG-7 Glyceryl Cocoate and the data from the previous reports were adequate to support the safety of the PEGs Glyceryl Cocoate polymers in cosmetics. As discussed earlier in this report, the possibility of reproductive and developmental effects was determined not to be of concern. The PEGs Glyceryl Cocoate polymers were considered safe as used in rinse-off products and safe up to 10% in leave-on products. The concentration limit for leave-on products was based on the ocular and sensitization data provided in this report. Any party seeking to modify or remove the concentration limit should provide safety test data on the PEGs Glyceryl Cocoate polymers.

The CIR Expert Panel was concerned about the sensitization and toxicity potential of the PEGs Glyceryl Cocoate polymers when applied to damaged skin. This concern arose because of positive results in patch tests and incidences of nephrotoxicity in bum patients treated with an antimicrobial cream that contained PEG-6, PEG-20, and PEG-75. PEG was the causative agent in both animal and human studies; no evidence of systemic toxicity or sensitization was found in studies with intact skin. The Expert Panel concluded that cosmetic formulations containing PEG should not, therefore, be used on damaged skin.

Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. The cosmetic industry should continue to use the necessary procedures to remove these impurities from the PEGs Glyceryl Cocoate ingredients before blending them into cosmetic formulations.

The Expert Panel recognized that PEG-7 Glyceryl Cocoate can enhance the skin penetration of other chemicals, and recommends that care should be exercised in using the PEGs Glyceryl Cocoate in cosmetic products where the penetration of other ingredients is a concern.

CONCLUSION

On the basis of the available animal and clinical data presented in this report and in other reports on related ingredients, the CIR Expert Panel concludes that PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate are safe as used in rinse-off products and safe up to 10% in leave-on products.

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Amended Safety Assessment of PEGylated Oils as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review Expert Panel (the Panel) considered the safety of PEGylated oils, which function primarily as surfactants, in cosmetic products. The Panel reviewed relevant animal and human data provided in this safety assessment, and concluded that the 130 chemically related PEGylated oils were safe as cosmetic ingredients in the present practices of use and concentration when formulated to be non-irritating.

INTRODUCTION

In 1997, the Cosmetic Ingredient Review (CIR) published the safety assessment on PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil with the conclusion "PEG-30, -33, -35, -36, and -40 castor oil are safe for use in cosmetics at concentrations up to 50% and that PEG-30 and -40 hydrogenated castor oil are safe for use at concentrations up to 100%."[1] These PEGylated castor oils function primarily as surfactants in cosmetic products.

Since the original review, numerous additional studies were published related to the noncosmetic use of PEG-35 castor oil and PEG-40 hydrogenated castor oil (trade names Cremophor EL and Cremophor RH, respectively) in drug delivery systems. The few of these studies that appear relevant to assessing the safety of PEGylated oils in cosmetics are summarized in this safety assessment. Overall, single-dose and repeated-dose toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, dermal and ocular irritation, and sensitization and photosensitization data were available.

Because of similarities in chemical structure and cosmetic function, the PEGylated oils listed in Table 1 have been added to the safety assessment of PEG-30 castor oil to comprise a group of 130 cosmetic ingredients.. These cosmetic ingredients include components that have been previously reviewed and concluded to be safe for use by the CIR Expert Panel, most notably the recent safety assessments on plant-derived fatty acid oils, polyethylene glycols (PEGs) with an average of 4 moles of ethylene oxide or greater, and alkyl PEG ethers. The ingredients, their conclusions, a summary of the findings, and published citations are found in Table 2.

CHEMISTRY

The definitions of the PEGylated oils can be found in Table 3.

Just as oils and other PEGylated materials are mixtures, PEGylated oils are mixtures. As most natural source oils are primarily triglycerides (and mono- and diglycerides) and fatty acids, PEGylated oils are primarily PEGylated glycerides, along with some PEGylated fatty acids. 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.[2,3] For example, the primary component of castor oil, the ricinoleate triglyceride, is ethoxylated as shown in Figure 1, wherein n is equal to the number of ethylene oxide repeat units and need not be the same at all places of the molecule. It should be noted that n is not equal to X. In other words, wherein the value of X in PEG-X is equal to 2 (e.g., PEG-2 Castor Oil), n is not equal to 2. Instead, X represents the number of stoichiometric equivalents of ethylene oxide that were added to one stoichiometric equivalent of castor oil. 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.[2] Furthermore, when ethylene oxide reacts with castor oil 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 or acid groups.

While castor oil triglycerides are primarily (approximately 87%) composed of ricinoleic acid residues, approximately 7% are oleic acid, 3% are linoleic acid, 2% are palmitic acid, 1% are stearic acid, and a trace are dihydroxysteric acid.[1] Thus, these PEGylated castor oil ingredients, and all of the PEGylated oil ingredients, are rather complex mixtures of structurally related molecules.

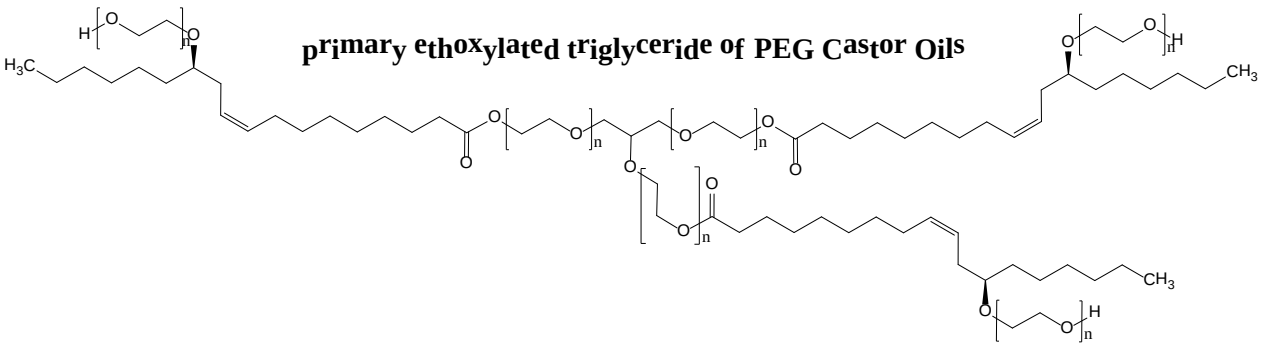

Figure 1. Glyceryl triricinoleyl polyethylene glycol

The available free fatty acids found in castor oil, and the other oils, may also be esterified by the ethoxylation process, as seen in Figure 2 (and etherified with ethylene oxide groups if there are any reactive alcohol functionalities on the fatty acids).

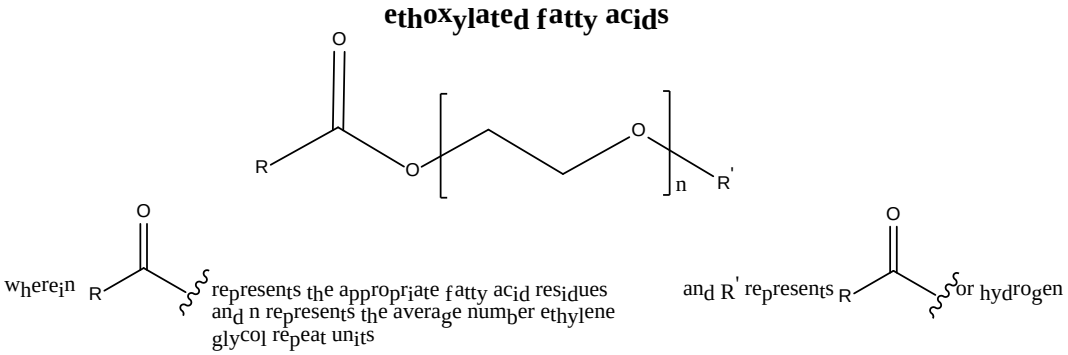

Figure 2. Fatty acid esterification

Some of the ingredients in this report have been hydrogenated. For example, hydrogenation of castor oil primarily results in the reduction of the Ω-9 unsaturation of ricinoleate triglycerides (and the Ω-9 unsaturation of any free ricinoleic fatty acids).[2] Accordingly, hydrogenated castor oil is principally 12-hydroxystearic triglyceride. The resultant ethoxylated triglyceride, therefore, differs from that of PEGylated non-hydrogenated castor oil only in the loss of these double bonds, as seen in Figure 3.

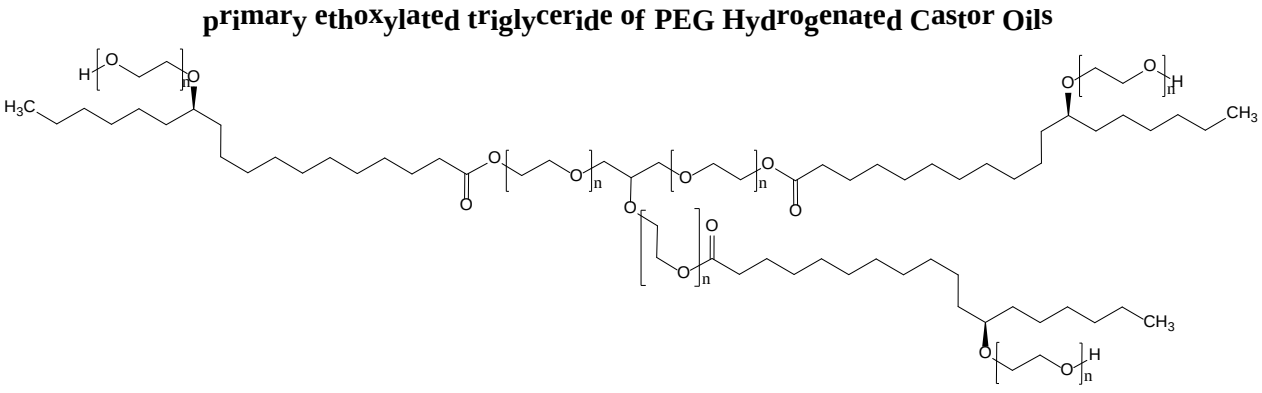

Figure 3. Glyceryl 12-hydroxystearyl polyethylene glycol

Physical and Chemical Properties

Physical and chemical properties of PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil can be found in the original safety assessment.[1] A supplier reports that PEG-30,-35, and-40 are pale yellow viscous liquids at 30° C and have a maximum water content of 0.2%.[4] PEG-40 hydrogenated castor oil is reported to be a waxy liquid at 30° C and also has a maximum water content of 0.2%.

Impurities

PEGs 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. 1,4-Dioxane is a known animal carcinogen.[5] 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 PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations.[6,7]

USE

Cosmetic

Table 4a presents the historical and current product formulation data for PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil. These PEGylated castor oils function primarily as surfactants (emulsifying or solubilizing agents) in cosmetic formulations.[8] According to information supplied to the Food and Drug Administration's (FDA) Voluntary Cosmetic Registration Program (VCRP) database by industry in 1997, PEG-40 hydrogenated castor oil had the most uses at 268, with the majority of the uses reported in leave-on products with a dermal exposure route.[1] The ingredient with the second most uses was PEG-40 castor oil with 170 uses, most in leave-on products with a dermal exposure route. An industry survey reported use concentrations for PEG-40 hydrogenated castor oil and PEG-40 castor oil of $\leq$ 10% and $\leq$ 5%, respectively. Currently, the FDA's VCRP database indicates that uses have decreased for PEG-30 castor oil, PEG-40 castor oil, and PEG-30 hydrogenated castor oil, with the most significant decrease occurring for PEG-40 castor oil, which now has 95 reported uses.[9] Increases in use are reported for the remaining PEGylated castor oils from the original report. The most significant increase is for PEG-40 hydrogenated castor oil, which now has 2107 reported uses (up from 268 uses). In a recent survey of use concentrations, PEG-40 hydrogenated castor oil had a maximum use concentration range of 7.0 x 10^{-5}% to 22%, with 22% reported in leave-on non-coloring hair products.[10] PEG-30 castor oil had a maximum use concentration of 0.1% in a rinse-off non-coloring hair product.

Table 4b presents the current product formulation data for the cosmetic ingredients that were added to the PEGylated oil safety assessment. Currently, the VCRP database indicates that, of the additional ingredients, PEG-60 hydrogenated castor oil has the most uses (349) with the majority in leave-on products with a dermal exposure route.[9] The maximum use concentration range for PEG-60 hydrogenated castor oil was 4.0 x 10^{-5}% to 18%, with the 18% reported in leave-on non-coloring hair products.[11] Olive oil PEG-7 esters had the second most reported uses (97). The maximum use concentration range for olive oil PEG-7 esters was 0.05% to 97%, with the 97% reported in a rinse-off (shaving) product.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were available. For example, PEG-33 castor oil is reported to be used in 41 formulations, but no use concentration data were available. In other cases, no reported uses were received from the VCRP, but a use concentration was provided in the industry survey. For example, PEG-25 castor oil was not reported in the VCRP database to be in use, but the industry survey indicated that it is used in leave-on formulations at maximum concentrations ranging from 3%-17%. It should be presumed that PEG-25 castor oil is used in at least one cosmetic formulation.

PEGylated oils were reported to be used in fragrance products, hair sprays, deodorants, and indoor tanning preparations and could possibly be inhaled. For example, PEG-60 castor oil was reported to be used in aerosol hair sprays at maximum concentrations up to 16%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.[12-15] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[13,14] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[14] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

The PEGylated oils are not restricted from use in any way under the rules governing cosmetic products in the European Union.[16]

Non-Cosmetic

PEG-30 castor oil and PEG-40 hydrogenated castor oil may be used as nonionic surfactants in oral, topical, and parenteral drug delivery systems.[3,4,17-23] PEGylated castor oil derivatives may also be used in animal feeds and textiles.[4]

PEG-30, -33, -35, -36, and -40 castor oil have been approved by the FDA as indirect food additives in adhesives and components of coatings (21 CFR § 175.105 and §175.300) and packaging and food contact surfaces (21 CFR §176.210, §177.2800). PEG-30 and -40 hydrogenated castor oil are approved as direct food additives (21 CFR §73.1) as well as in indirect food additives in packaging and food contact surfaces (21 CFR §177.2800).

TOXICOKINETICS

Toxicokinetics data were available from earlier CIR safety assessments supporting the safety of alkyl PEG ethers and castor oil. These data are summarized in Table 2.

Absorption, Distribution, Metabolism, Excretion

The disposition of PEG-35 castor oil was determined in 31 cancer patients treated with a 1-h infusion of paclitaxel (87.8 mg PEG-35 castor oil per mg drug).[24] Dose levels of PEG-35 castor oil ranged from 70 to 100 mg/m^2. Plasma concentrations were measured. Clearance of PEG-35 castor oil appeared to be independent of infusion duration and the administered dose in the range studied (P =0.797). Exposure measures increased in near proportion to an increase in dose. PEG-35 castor oil had a half-life and clearance of 35.7 $\pm$ 18.9 h and 0.216 $\pm$ 0.075 L/h, respectively ($P < 0.00001$). The volume of distribution at steady state was 9.48 $\pm$ 2.59 L and indicated limited distribution of the excipient outside of the central compartment. These results were compared to those of the excipient Tween 80, which had a shorter terminal half-life (0.607 $\pm$ 0.245 h) and total plasma clearance (7.70 $\pm$ 2.90 L/h). The other values were similar. The study concluded that use of PEG-35 castor oil as a formulation vehicle could result in drug interaction and excipient-related toxic side effects due to its relatively low rates of elimination.

Penetration Enhancement

A study of the development of a topical gel for treatment of acne vulgaris reports that various types of PEGs are hydrophilic penetration enhancers and are used in topical dermatological preparations.[17] The authors selected PEG-40 hydrogenated castor oil because of its properties as a very hydrophilic, non-ionic solubilizer for fat-soluble vitamins A, D, E, and K, and for its stability and clarity in alcohol solution.

In a study evaluating vehicle effects on in vitro skin permeation of model drugs caffeine and testosterone, apricot kernel oil PEG-6 esters facilitated the flux and diffusivity of caffeine across the stratum corneum, when compared to propylene glycol.[25]

TOXICOLOGICAL STUDIES

Acute Toxicity

Dermal and oral acute and repeated dose toxicity data were available from earlier CIR safety assessments supporting the safety of alkyl PEG ethers and castor oil. These data are summarized in Table 2**.**

Intravenous – Non-Human

PEG-X CASTOR OIL

Castor oil with an unspecified number of stoichiometric equivalents of ethylene oxide (generically listed as Cremophor) mixed with dimethyl acetamide (DMA) was evaluated as a vehicle in a diabetes drug.[26] The mixture was composed of 23%-45% DMA/10%-12% Cremophor in water and the dose volume was 1.67 to 3 ml/kg. Groups of 3 New Zealand White rabbits received intravenously the test material, saline, insulin, or N-methyl-2-pyrrolidone (NMP) into the marginal ear vein. Blood was drawn just before injection and again at 0.25, 0.5, 1, 2, 4, and 24 h after injection to determine glycemia values. Glycemia after injection with the DMA/Cremophor mixture remained stable and within the normal range of 3.6 to 5.0 mM. These results were comparable to those for the rabbits that received saline. In addition, the test material did not elicit irritation at the site of injection.

PEG-60 HYDROGENATED CASTOR OIL

The toxicity of PEG-60 hydrogenated castor oil was evaluated in male and female Beagle dogs, male and female cynomolgus monkeys, male New Zealand White rabbits, male Hartley guinea pigs, and male Sprague Dawley rats.[27] The test material was injected intravenously to groups of 3 dogs at 0.625, 1.25, 2.5, or 10 mg/kg; in groups of 3 monkeys or 5 rabbits at 50 or 100 mg/5 ml/kg; and in groups of 5 guinea pigs, and 5 rats at 10 or 100

mg/5 ml/kg. Blood pressure was monitored in the dogs before the injection and 10, 30, and 60 min after injection. Blood was taken from all animals to measure plasma histamine levels. In dogs, further histopathological examinations were performed on mast cells in the liver and skin. Clinical signs of toxicity were observed until 60 min after injection in all animals.

In dogs injected with 1.25, 2.5 or 10 mg/kg of the test material, blood pressure decreased and flush, swelling and itching were observed. Additionally, in the 10 mg/kg dose group, a decrease in spontaneous activity was observed. An increase in plasma histamine levels was observed in the 2.5 and 10 mg/kg dose groups. Degranulation was observed after injection in the mast cells of the skin, but not in the liver. No signs of toxicity were observed in monkeys, rabbits, guinea pigs or rats and there was no change in plasma histamine levels. The toxicity of PEG-60 hydrogenated castor oil may be species specific.[27]

Repeated Dose Toxicity

PEG-35 CASTOR OIL

Several in situ rat studies investigated the effects of the use of Cremophor EL (PEG-35 castor oil) as a vehicle in intravenous drugs.[28-31] Reduction of muscle mitochondria, increase in myocardial lipid peroxidation, acidosis, weight loss, and cholestatic effects have been observed at perfusion concentrations of 100 µg/L.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity data were available from earlier CIR safety assessments supporting the safety of PEGS, castor oil, and alkyl PEG ethers. These data are summarized in Table 2.

GENOTOXICITY

Genotoxicity data were available from earlier CIR safety assessments supporting the safety of castor oil, PEGs, and alkyl PEG ethers. These data are summarized in Table 2.

PEG-60 HYDROGENATED CASTOR OIL

The genotoxic potential of PEG-60 hydrogenated castor oil was studied in a reverse mutation test in *Salmonella typhimurium* strains TA100, TA98, TA1535, and TA1537 and in *Escherichia coli* strain WP2uvrA, with and without metabolic activation.[32] The test concentrations ranged from 313-5000 µg/plate. The positive controls were 9-aminoacridine, sodium azide, 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide, and 2-aminoanthracene. No biologically relevant increases in revertant colony numbers were observed in any test strain at any concentration, with or without metabolic activation. Controls yielded expected results. The study concluded that PEG-60 hydrogenated castor oil was not genotoxic.

The research study above also investigated the genotoxic potential of PEG-60 hydrogenated castor oil in a chromosome aberration study with Chinese hamster V79 cells, with and without metabolic activation.[32] The test concentrations ranged from 313-5000 µg/ml. The positive controls were mitomycin C and dimethylnitrosamine. The test material without metabolic activation had dose-related inhibition of cell proliferation after 24- and 48-h treatments. With metabolic activation, the test material induced only slight inhibition of cell proliferation even at the highest concentration after 6 h treatment. PEG-60 hydrogenated castor oil did not induce chromosome aberrations at any dose, with or without metabolic activation. The controls yielded expected results. The study concluded that PEG-60 hydrogenated castor oil was not genotoxic.

The same study also researched the genotoxic potential of PEG-60 hydrogenated castor oil in a mouse micronucleus test using BDF1 male and female mice.[32] A dose range finding experiment preceded the main study. In the main study, groups of 5 mice of each sex received single intraperitoneal injections of 2000 mg/kg body weight PEG-60 hydrogenated castor oil. Control groups received physiological saline or mitomycin C. Bone marrow cells were collected at 24, 48, or 72 h. The number of micronucleated erythrocytes in 1000 polychromatic erythrocytes and the number of polychromatic erythrocytes in 1000 erythrocytes were recorded for each mouse. In the dose range-finding study, no deaths occurred. In the main study, no treatment-related mortalities or clinical signs of toxicity were observed. No significant increase of micronucleated polychromatic erythrocytes or significant decrease of the ratio of polychromatic to normochromatic erythrocytes were observed in male or female mice that received the test material. The controls yielded expected results. The study concluded that PEG-60 hydrogenated castor oil was not genotoxic.

CARCINOGENICITY

Carcinogenicity data were available from earlier CIR safety assessments supporting the safety of PEGs and alkyl PEG ethers. These data are summarized in Table 2.

IRRITATION AND SENSITIZATION

Irritation

Irritation data were available from earlier CIR safety assessments supporting the safety of PEGs, mink oil, and plant-derived fatty acid oils. These data are summarized in Table 2.

Dermal – Non-Human

PEG-35 CASTOR OIL

A skin irritation study of a pharmaceutical microemulsion that contained 20% w/w PEG-35 castor oil was performed in male guinea pigs (strain not specified).[33] The hair on the backs of the guinea pigs was removed 24 h before treatment, and the animals were divided into a group with intact skin and a group with skin injury from scarification. These groups were again subdivided into single and multiple applications. There were a total of 5 guinea pigs in each subgroup. All guinea pigs received the test material and a control cream. Single application animals were treated for 24 h and the test sites were inspected for erythema and edema 1, 24, 48, and 72 h after material removal. Multiple-application animals were treated for 24 h, followed by assessment for skin irritation 1 h after material removal, in a total of 7 applications. The test sites were observed for an additional 3 days after the last application. While very slight irritation was observed on average at the 1-h observation point in guinea pigs treated with multiple applications with damaged skin, the average scores were still in the range that was considered to indicate "no irritation". No irritation was observed in any of the single-application animals or in the intact skin of the multiple-application animals. It was concluded that single and multiple applications of the microemulsion that contained 20% w/w PEG-35 castor oil did not cause irritation effects in guinea pigs.

PEG-40 HYDROGENTATED CASTOR OIL

A dermal irritation test was performed in mice (species and number not described) to investigate the potential irritancy of a microemulsion that contains 20% PEG-40 hydrogenated castor oil.[23] A single dose of 10 µl of the test microemulsion was applied to the left ear of the mouse. The right ear served as a control. The mice were observed for development of erythema for 6 days. No signs of irritation were observed in the mice. The authors concluded that the formulation containing 20% PEG-40 hydrogenated castor oil would probably not irritate human skin.

The dermal irritancy potential of a microemulsion gel system that contained 20.66% PEG-40 hydrogenated castor oil as a surfactant was studied in male albino rats using the Draize method.[34] Animals were divided into 3 groups of 6: a negative control (no treatment), a positive control (0.8% aq. formalin), and the test formulation. The rats received a dose of 0.5 g of the formulation on a 5-cm^2 area on the shaved dorsal side daily for 3 consecutive days. Signs of erythema and edema were monitored daily for 3 days. After 3 days, the rats were killed and skin samples were taken for histopathological examination. No signs of irritation were observed in the test formulation. The controls yielded expected results. Histopathological examination found no apparent signs of skin irritation. The study concluded that the test formulation that contained 20.66% PEG-40 hydrogenated castor oil was not a skin irritant.

Ocular

PEG-35 CASTOR OIL

Several different formulations of a potential glaucoma drug in a nanoemulsion were tested for ocular irritation potential.[35] A few of these formulations contained PEG-35 castor oil as a surfactant. Groups of 6 New Zealand albino rabbits received test formulations that contained 0%-13% PEG-35 castor oil. In each rabbit, the right eye received 50 µl of the tested formulation, while the left eye was used as a control. The rabbits received the test formulation every 2.5 h through a period of 7.5 h per day for 3 successive days and once on the fourth day. Eyes were examined according to the Draize method 1 and 24 h after the last instillation. The eyelids, cornea, iris, conjunctiva, and anterior chamber were inspected for inflammation or other toxic reactions. The eyes were then stained with fluorescein and examined under UV light to verify possible corneal lesion. A few nanoemulsion formulations that contained up to 13.5% PEG-35 castor oil were found to be non-irritating and tolerated well by the rabbit eye. Cross sections from the corneas of rabbits' eye after application of the tested formulations together with a control section showed that both corneal structure and integrity were unaffected by treatment.

Sensitization

Sensitization data were available from earlier CIR safety assessments support the safety of PEGs, mink oil, plant-derived fatty acid oils, and alkyl PEG ethers. These data are summarized in Table 2.

CLINICAL USE

Case Studies

PEG-35 CASTOR OIL

A 40-year-old female undergoing chemotherapy treatment for breast cancer had a cutaneous lupus erythematous-like reaction within 24 h of intravenous administration of the drug paclitaxel that contained the diluent, PEG-35 castor oil.[36]

When treatment was switched to a formulation of paclitaxel bound to albumin, without PEG-35 castor oil, no lupus-like reactions were observed. The case study concluded that PEG-35 castor oil induced the lupus-like reaction and suggested that previously reported incidences of lupus-like reaction in chemotherapy patients was from this diluent and not from the chemotherapeutic agent.

PEG-7 HYDROGENATED CASTOR OIL

A 73-year-old male was reported to have an eczematous rash on the face and neck after use of a sunscreen lotion.[37] The patient was patch tested with an extended British Contact Dermatitis Society standard series, medicament series, facial series, photoallergic series, and the sunscreen. A positive reaction was elicited only with the patient's sunscreen, both on nonirradiated and irradiated skin. When tested with the individual ingredients of the sunscreen, a positive reaction occurred to 10% PEG-7 hydrogenated castor oil in petrolatum (+ on days 2 and 4). Negative reactions were observed to the remaining sunscreen ingredients.

PEG-60 HYDROGENATED CASTOR OIL

A 27-year-old male undergoing maintenance chemotherapy for acute myeloblastic leukemia developed a high-grade fever and erythroblastopenia within 6 h of after intravenous administration of the chemotherapy drugs that included enocitabine.[38] The enocitabine product contained PEG-60 hydrogenated castor oil. When enocitabine was administered alone, the same symptoms reoccurred. Co-culturing the patient's bone marrow with enocitabine or PEG-60 hydrogenated castor oil found significant growth inhibition of late erythroid progenitors in the presence of the patient's IgG. The researchers of the study believe that PEG-60 hydrogenated castor oil acted as a hapten and caused the immunological suppression of the growth of erythroid progenitors through a hypersensitive reaction mediated by IgG.

SUMMARY

This report is a re-review of PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil that has been expanded to include additional PEGylated castor oils and other PEGylated plant-derived oils. Data from the original report on the PEGylated castor oils have been summarized in Table 2. This summary only contains newly identified information on the original ingredients and the expanded ingredients.

Just as oils and other PEGylated materials are mixtures, PEGylated oils are mixtures. As most natural source oils are primarily triglycerides (and mono- and diglycerides) and fatty acids, PEGylated oils are primarily PEGylated glycerides, along with some PEGylated fatty acids.

PEGs 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.

The PEGylated castor oils function primarily as surfactants that function as emulsifying or solubilizing agents in cosmetic formulations. Of the 130 PEGylated oil ingredients described as cosmetic ingredients, only 35 have uses reported by either the FDA's VCRP database or the Personal Care Products Council. Current FDA data indicate that PEG-40 hydrogenated castor oil has the largest number of reported uses, 2107, with a maximum use concentration range of 7.0×10^{-5}% to 22%, with the 22% reported 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. PEGylated castor oil derivatives may also be used in animal feeds and textiles. PEG-30, -33, -35, -36, and -40 castor oil have been approved by the FDA as indirect food additives in adhesives and 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.

The toxicity of PEG-60 hydrogenated castor oil was evaluated in male and female Beagle dogs, male and female cynomolgus monkeys, male New Zealand White rabbits, male Hartley guinea pigs, and male Sprague Dawley rats. Toxicity, including decreased blood pressure, flush, swelling, itching, and increase histamine levels, was observed in dogs injected with 1.25, 2.5 or 10 mg/kg of the test material. No signs of toxicity were observed in monkeys, rabbits, guinea pigs or rats.

Several rat studies investigated the effects of the use of Cremophor EL (PEG-35 castor oil) as a vehicle in intravenous drugs. Effects on cardiac and skeletal function have been observed at a concentration of 100 µg/L.

The genotoxic potential of PEG-60 hydrogenated castor oil was studied in a reverse mutation test, in a chromosome aberration study, and in a mouse micronucleus test: the studies concluded that PEG-60 hydrogenated castor oil was not genotoxic.

A study of single and multiple applications of a microemulsion that contained 20% w/w PEG-35 castor oil did not cause irritation effects in guinea pigs. A dermal irritation test performed in mice concluded that a formulation containing 20% PEG-40 hydrogenated castor oil would probably not irritate human skin. A study of the dermal irritancy potential of a microemulsion gel system in rats concluded that the test 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 non-irritating in rabbit eyes.

Case studies of adverse events occurring in cancer patients were reported following use of chemotherapy drugs that contained PEG-35 castor oil and PEG-60 hydrogenated castor oil. Another case study reported an adverse dermatological event following use of a sunscreen containing PEG-7 hydrogenated castor oil.

DISCUSSION

Overall, toxicokinetics, single-dose and repeated-dose toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, dermal and ocular irritation, and sensitization data were available for PEG castor oils. Similarly, extensive supportive data exist for the components of the PEGylated oils, which are complex mixtures of the etherification and transesterifcation products of fatty acid glycerides and fatty acids derived from the identified plant source with the equivalents of ethylene oxide to reach the desired PEG length. PEG compounds will be present unattached to glycerides or fatty acid groups. Because of this unique chemistry, the Panel determined that the available data in previous safety assessments of PEGs and of plant-derived fatty acids supported the safety of PEGylated oils in a “read-across” fashion.

The Panel expressed concern regarding the possible presence of ethylene oxide and trace amounts of 1,4-dioxane as impurities in any cosmetic ingredient containing a PEG moiety. They stressed that the cosmetic industry should continue to use the necessary purification procedures to remove these impurities from the ingredient before blending it into cosmetic formulations.

The Panel also expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

A safety assessment of diethylene glycol (aka PEG-2) has not been completed. A safety assessment of the PEGs group of ingredients, however, includes PEG-4, which was found to be safe for use in cosmetics. Since PEG-4 is a mixture that includes PEG-2, PEG-2 also would be safe for use in cosmetics.

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

The Panel looked at changes in the pattern of use and concentration of use since the original safety assessment of PEG castor oils and noted that the earlier safety assessment had specified safe up to 50% use concentration. As PEG castor oils and the rest of the PEGylated oils now are used at concentrations below 50% in leave-on products, the Panel determined that concentration limits need no longer be specified. Products using these ingredients should be formulated to be non-irritating

The Panel noted that adverse reactions have been reported for PEG-35 castor oil used as a vehicle in intravenous drugs. Because this route of exposure does not occur from cosmetic use, the Panel considered that such data were not relevant to assessing the safety of the ingredient in cosmetics.

The Panel discussed the issue of incidental inhalation exposure from fragrance products, hair sprays, deodorants, and indoor tanning preparations. There were no inhalation toxicity data available. These ingredients are reportedly used at concentrations up to 16% in cosmetic products that may be aerosolized (i.e., cosmetic sprays) and in other products that may become airborne (i.e., cosmetic powders). The Panel noted that 95% – 99% of

droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. In addition, the Panel considered other data available to characterize the potential for PEGylated Oils and related ingredients to cause reproductive, developmental, and carcinogenic effects in animals (as described in the original safety assessment of PEG castor oils) and dermal irritation and sensitization. They noted the low systemic toxicity at high doses in several acute and repeat exposure studies, little or no irritation or sensitization in multiple tests of dermal exposure and in clinical studies, little or no irritation in multiple ocular tests, the absence of genotoxicity in bacterial and mammalian test systems, and no reproductive or developmental toxicity or carcinogenicity in animal feeding studies. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the 130 PEGylated oil ingredients listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating. This conclusion supersedes the earlier conclusion issued by the Expert Panel in 1997.

PEG-2 Castor Oil*
PEG-3 Castor Oil*
PEG-4 Castor Oil*
PEG-5 Castor Oil*
PEG-8 Castor Oil*
PEG-9 Castor Oil
PEG-10 Castor Oil*
PEG-11 Castor Oil*
PEG-15 Castor Oil*
PEG-16 Castor Oil*
PEG-20 Castor Oil*
PEG-25 Castor Oil
PEG-26 Castor Oil*
PEG-29 Castor Oil*
PEG-30 Castor Oil
PEG-33 Castor Oil
PEG-35 Castor Oil
PEG-36 Castor Oil
PEG-40 Castor Oil
PEG-44 Castor Oil*
PEG-50 Castor Oil
PEG-54 Castor Oil*
PEG-55 Castor Oil*
PEG-60 Castor Oil
PEG-75 Castor Oil*
PEG-80 Castor Oil*
PEG-100 Castor Oil*
PEG-200 Castor Oil*
PEG-18 Castor Oil Dioleate*
PEG-60 Castor Oil Isostearate*
PEG-2 Hydrogenated Castor Oil
PEG-5 Hydrogenated Castor Oil*
PEG-6 Hydrogenated Castor Oil*
PEG-7 Hydrogenated Castor Oil
PEG-8 Hydrogenated Castor Oil*
Hydrogenated Castor Oil PEG-8 Esters*
PEG-10 Hydrogenated Castor Oil
PEG-16 Hydrogenated Castor Oil
PEG-20 Hydrogenated Castor Oil
PEG-25 Hydrogenated Castor Oil
PEG-30 Hydrogenated Castor Oil
PEG-35 Hydrogenated Castor Oil
PEG-40 Hydrogenated Castor Oil
PEG-45 Hydrogenated Castor Oil
PEG-50 Hydrogenated Castor Oil
PEG-54 Hydrogenated Castor Oil*
PEG-55 Hydrogenated Castor Oil*
PEG-60 Hydrogenated Castor Oil
PEG-65 Hydrogenated Castor Oil*
PEG-80 Hydrogenated Castor Oil
PEG-100 Hydrogenated Castor Oil
PEG-200 Hydrogenated Castor Oil*
PEG-5 Hydrogenated Castor Oil Isostearate*
PEG-10 Hydrogenated Castor Oil Isostearate*
PEG-15 Hydrogenated Castor Oil Isostearate*
PEG-20 Hydrogenated Castor Oil Isostearate*
PEG-30 Hydrogenated Castor Oil Isostearate*
PEG-40 Hydrogenated Castor Oil Isostearate*
PEG-50 Hydrogenated Castor Oil Isostearate*
PEG-58 Hydrogenated Castor Oil Isostearate*
PEG-20 Hydrogenated Castor Oil Laurate*
PEG-30 Hydrogenated Castor Oil Laurate*
PEG-40 Hydrogenated Castor Oil Laurate*
PEG-50 Hydrogenated Castor Oil Laurate*
PEG-60 Hydrogenated Castor Oil Laurate*
PEG-20 Hydrogenated Castor Oil PCA Isostearate*
PEG-30 Hydrogenated Castor Oil PCA Isostearate*
PEG-40 Hydrogenated Castor Oil PCA Isostearate
PEG-60 Hydrogenated Castor Oil PCA Isostearate*
PEG-50 Hydrogenated Castor Oil Succinate
Potassium PEG-50 Hydrogenated Castor Oil Succinate*
Sodium PEG-50 Hydrogenated Castor Oil Succinate*
PEG-5 Hydrogenated Castor Oil Triisostearate*
PEG-10 Hydrogenated Castor Oil Triisostearate*
PEG-15 Hydrogenated Castor Oil Triisostearate*
PEG-20 Hydrogenated Castor Oil Triisostearate
PEG-30 Hydrogenated Castor Oil Triisostearate*
PEG-40 Hydrogenated Castor Oil Triisostearate
PEG-50 Hydrogenated Castor Oil Triisostearate*
PEG-60 Hydrogenated Castor Oil Triisostearate*
Adansonia Digitata Seed Oil PEG-8 Esters*
Almond Oil PEG-6 Esters*
Almond Oil PEG-8 Esters *
Apricot Kernel Oil PEG-6 Esters
Apricot Kernel Oil PEG-8 Esters*
Apricot Kernel Oil PEG-40 Esters*
Argan Oil PEG-8 Esters*
Avocado Oil PEG-8 Esters*
Avocado Oil PEG-11 Esters
Bertholletia Excelsa Seed Oil PEG-8 Esters*
Borage Seed Oil PEG-8 Esters*
Coconut Oil PEG-10 Esters
Corn Oil PEG-6 Esters*
Corn Oil PEG-8 Esters*
Grape Seed Oil PEG-8 Esters
Hazel Seed Oil PEG-8 Esters*

Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters
Jojoba Oil PEG-8 Esters
Jojoba Oil PEG-150 Esters*
Linseed Oil PEG-8 Esters*
Macadamia Ternifolia Seed Oil PEG-8 Esters*
Mango Seed Oil PEG-70 Esters*
Mink Oil PEG-13 Esters*
Olive Oil PEG-6 Esters*
Olive Oil PEG-7 Esters
Olive Oil PEG-8 Esters*
Olive Oil PEG-10 Esters
Orbignya Oleifera Seed Oil PEG-8 Esters*
Palm Oil PEG-8 Esters*
Passiflora Edulis Seed Oils PEG-8 Esters*
Peanut Oil PEG-6 Esters*
PEG-75 Crambe Abyssinica Seed Oil*
PEG-75 Meadowfoam Oil
Pumpkin Seed Oil PEG-8 Esters*
Rapeseed Oil PEG-3 Esters*
Rapeseed Oil PEG-20 Esters*
Raspberry Seed Oil PEG-8 Esters*
Safflower Seed Oil PEG-8 Esters*
Schinziophyton Rautanenii Kernel Oil PEG-8 Esters*
Sclerocarya Birrea Seed Oil PEG-8 Esters*
Sesame Seed Oil PEG-8 Esters*
Soybean Oil PEG-8 Esters*
Soybean Oil PEG-20 Esters*
Soybean Oil PEG-36 Esters*
Sunflower Seed Oil PEG-8 Esters*
Sunflower Seed Oil PEG-32 Esters*
Sweet Almond Oil PEG-8 Esters*
Watermelon Seed Oil PEG-8 Esters*
Wheat Germ Oil PEG-40 Butyloctanol Esters*
Wheat Germ Oil PEG-8 Esters*

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

TABLES AND FIGURES

Table 1. PEGylated Oils

PEG-2 Castor Oil
PEG-3 Castor Oil
PEG-4 Castor Oil
PEG-5 Castor Oil
PEG-8 Castor Oil
PEG-9 Castor Oil
PEG-10 Castor Oil
PEG-11 Castor Oil
PEG-15 Castor Oil
PEG-16 Castor Oil
PEG-20 Castor Oil
PEG-25 Castor Oil
PEG-26 Castor Oil
PEG-29 Castor Oil
PEG-30 Castor Oil
PEG-33 Castor Oil
PEG-35 Castor Oil
PEG-36 Castor Oil
PEG-40 Castor Oil
PEG-44 Castor Oil
PEG-50 Castor Oil
PEG-54 Castor Oil
PEG-55 Castor Oil
PEG-60 Castor Oil
PEG-75 Castor Oil
PEG-80 Castor Oil
PEG-100 Castor Oil
PEG-200 Castor Oil
PEG-18 Castor Oil Dioleate
PEG-60 Castor Oil Isostearate
PEG-2 Hydrogenated Castor Oil
PEG-5 Hydrogenated Castor Oil
PEG-6 Hydrogenated Castor Oil
PEG-7 Hydrogenated Castor Oil
PEG-8 Hydrogenated Castor Oil
Hydrogenated Castor Oil PEG-8 Esters
PEG-10 Hydrogenated Castor Oil
PEG-16 Hydrogenated Castor Oil
PEG-20 Hydrogenated Castor Oil
PEG-25 Hydrogenated Castor Oil
PEG-30 Hydrogenated Castor Oil
PEG-35 Hydrogenated Castor Oil
PEG-40 Hydrogenated Castor Oil
PEG-45 Hydrogenated Castor Oil
PEG-50 Hydrogenated Castor Oil
PEG-54 Hydrogenated Castor Oil
PEG-55 Hydrogenated Castor Oil
PEG-60 Hydrogenated Castor Oil
PEG-65 Hydrogenated Castor Oil
PEG-80 Hydrogenated Castor Oil
PEG-100 Hydrogenated Castor Oil
PEG-200 Hydrogenated Castor Oil
PEG-5 Hydrogenated Castor Oil Isostearate
PEG-10 Hydrogenated Castor Oil Isostearate
PEG-15 Hydrogenated Castor Oil Isostearate
PEG-20 Hydrogenated Castor Oil Isostearate
PEG-30 Hydrogenated Castor Oil Isostearate
PEG-40 Hydrogenated Castor Oil Isostearate
PEG-50 Hydrogenated Castor Oil Isostearate
PEG-58 Hydrogenated Castor Oil Isostearate
PEG-20 Hydrogenated Castor Oil Laurate
PEG-30 Hydrogenated Castor Oil Laurate
PEG-40 Hydrogenated Castor Oil Laurate
PEG-50 Hydrogenated Castor Oil Laurate
PEG-60 Hydrogenated Castor Oil Laurate
PEG-20 Hydrogenated Castor Oil PCA Isostearate
PEG-30 Hydrogenated Castor Oil PCA Isostearate
PEG-40 Hydrogenated Castor Oil PCA Isostearate
PEG-60 Hydrogenated Castor Oil PCA Isostearate
PEG-50 Hydrogenated Castor Oil Succinate
Potassium PEG-50 Hydrogenated Castor Oil Succinate
Sodium PEG-50 Hydrogenated Castor Oil Succinate
PEG-5 Hydrogenated Castor Oil Triisostearate
PEG-10 Hydrogenated Castor Oil Triisostearate
PEG-15 Hydrogenated Castor Oil Triisostearate
PEG-20 Hydrogenated Castor Oil Triisostearate
PEG-30 Hydrogenated Castor Oil Triisostearate
PEG-40 Hydrogenated Castor Oil Triisostearate
PEG-50 Hydrogenated Castor Oil Triisostearate
PEG-60 Hydrogenated Castor Oil Triisostearate
Adansonia Digitata Seed Oil PEG-8 Esters
Almond Oil PEG-6 Esters
Almond Oil PEG-8 Esters
Apricot Kernel Oil PEG-6 Esters
Apricot Kernel Oil PEG-8 Esters
Apricot Kernel Oil PEG-40 Esters
Argan Oil PEG-8 Esters
Avocado Oil PEG-8 Esters
Avocado Oil PEG-11 Esters
Bertholletia Excelsa Seed Oil PEG-8 Esters
Borage Seed Oil PEG-8 Esters
Coconut Oil PEG-10 Esters
Corn Oil PEG-6 Esters
Corn Oil PEG-8 Esters
Grape Seed Oil PEG-8 Esters
Hazel Seed Oil PEG-8 Esters
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters
Jojoba Oil PEG-8 Esters
Jojoba Oil PEG-150 Esters
Linseed Oil PEG-8 Esters
Macadamia Ternifolia Seed Oil PEG-8 Esters
Mango Seed Oil PEG-70 Esters
Mink Oil PEG-13 Esters
Olive Oil PEG-6 Esters
Olive Oil PEG-7 Esters
Olive Oil PEG-8 Esters
Olive Oil PEG-10 Esters
Orbignya Oleifera Seed Oil PEG-8 Esters
Palm Oil PEG-8 Esters
Passiflora Edulis Seed Oils PEG-8 Esters
Peanut Oil PEG-6 Esters
PEG-75 Crambe Abyssinica Seed Oil
PEG-75 Meadowfoam Oil
Pumpkin Seed Oil PEG-8 Esters
Rapeseed Oil PEG-3 Esters
Rapeseed Oil PEG-20 Esters
Raspberry Seed Oil PEG-8 Esters
Safflower Seed Oil PEG-8 Esters
Schinziophyton Rautanenii Kernel Oil PEG-8 Esters
Sclerocarya Birrea Seed Oil PEG-8 Esters
Sesame Seed Oil PEG-8 Esters
Soybean Oil PEG-8 Esters
Soybean Oil PEG-20 Esters
Soybean Oil PEG-36 Esters
Sunflower Seed Oil PEG-8 Esters
Sunflower Seed Oil PEG-32 Esters
Sweet Almond Oil PEG-8 Esters
Watermelon Seed Oil PEG-8 Esters
Wheat Germ Oil PEG-40 Butyloctanol Esters
Wheat Germ Oil PEG-8 Esters

Table 2. Summaries of previous CIR safety assessments.

Ingredient(s)	Conclusion	Summary	Reference
PEGylated Castor Oils	PEG-30, -33, -35, -36, and -40 castor oil are safe for use in cosmetics at concentrations up to 50% and PEG-30 and -40 hydrogenated castor oil are safe for use at concentrations up to 100%	PEG Castor Oils and PEG Hydrogenated Castor Oils are used as skin conditioning agents and as surfactants (emulsifying and/or solubilizing agents). Results from animal studies indicate very high acute LD_{50} values. Repeated exposure studies of PEG-30 Castor Oil and PEG-35 Castor Oil with intravenous exposure of 0.5 ml/kg produced some evidence of toxicity in dogs, but intramuscular injection with 1 ml of 50% PEG-35 Castor Oil and oral studies with up to 5% PEG-40 Castor Oil and PEG-40 Hydrogenated Castor Oil were negative. No ocular irritation was observed in studies in rabbits. Some irritation was observed in animals when applied undiluted, but no sensitization was found on challenge in guinea-pig studies using up to 50% PEG-35 Castor Oil. No evidence of developmental toxicity was seen in mice and rat feeding studies at up to 100,000 ppm. These ingredients, tested as vehicle controls, produced no mutagenic or carcinogenic effect. Clinical data were generally negative for irritation and sensitization.	1
Ricinus Communis (Castor) Oil and Hydrogenated Castor Oil	Safe for use in cosmetics in the present practices of use and concentration	Castor oil, its salts and esters function primarily as skin-conditioning agents, emulsion stabilizers, and surfactants in cosmetics. The principle component of castor oil, ricinoleic acid, penetrated rat skin at only 5% of applied material. These ingredients are not acute or repeated dose toxicants at concentrations up to 10%. Undiluted castor oil was an irritant in several animal studies. Castor oil was not genotoxic in bacterial (up to 10,000 µg/plate) or mammalian test systems (up to 10%). No dose-related reproductive toxicity was found in mice fed up to 10% castor oil for 13 weeks. Castor oil is not a significant skin irritant, sensitizer, or photosensitizer in human clinical tests, but it was a mild ocular irritant.	39
Plant-Derived Fatty Acid Oils	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.	40
Triethylene Glycol and Polyethylene Glycols (PEGs) $\geq$ 4	Safe for use in cosmetics in the present practices of use and concentration	PEGS function primarily as binders, humectants, and solvents in cosmetic ingredients. In general, PEGs are not oral toxicants, with acute oral LD_{50} values in rodents ranging from 15 to 22 g/kg. Minimal dermal irritation and sensitization with undiluted PEGs has been observed. PEGs are not genotoxic (up to ~5700 mg/kg/day in a rat dominant lethal assay) or carcinogenic (up to 0.25 ml/week 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/day, providing a margin of safety.	41

Table 2. Summaries of previous CIR safety assessments.

Ingredient(s)	Conclusion	Summary	Reference
Simmondsia Chinensis (Jojoba) Seed Oil	Safe for use in cosmetics in the present practices of use and concentration	Simmondsia Chinensis (Jojoba) Seed Oil and the hydrogenated oil function primarily as hair and skin conditioning agents. The oil was not an acute oral toxicant to mice or rats (LD_{50} generally greater than 5.0 g/kg). The wax was not toxic when applied dermally at doses up to 0.5g/kg to the shaved backs of guinea pigs in repeated exposure tests. Simmondsia Chinensis (Jojoba) Seed Oil may be a slight ocular irritant. None of the tested ingredients were genotoxic (up to 100 mg/plate) and there were no structural alerts for carcinogenicity. No carcinogenicity, reproductive or developmental toxicity data were available. In clinical tests, Simmondsia Chinensis (Jojoba) Seed Oil (up to 100%) was neither a significant dermal irritant, nor a sensitizer. Simmondsia Chinensis (Jojoba) Seed Oil (up to 20%) and Jojoba Alcohol (up to 100%) were not phototoxic.	42
Mink Oil	Safe for use in cosmetics in the present practices of use and concentration	Mink oil functions primarily as a hair-conditioning agent, skin-conditioning agent, and surfactant. This ingredient does not absorb significant UVA or UVB radiation. Mink oil is not an acute oral toxicant (LD_{50} > 64 cc/kg) in rats. Non-human 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.	43
Akyl PEG Ethers	Safe for use in cosmetics in the present practices of use and concentration when formulated to be non-irritating	These ingredients primarily function in cosmetics as surfactants, and some have additional functions as skin conditioning agents, fragrance ingredients, and emulsion stabilizers. Alkyl PEG ethers are readily absorbed through the skin of guinea pigs and rats and through the intestinal mucosa of rats, and they are quickly eliminated from the body through the urine, feces, and expired air. Some alkyl PEG ethers, such as ceteareths and oleths, have been reported to enhance the penetration of certain compounds through the skin. Acute oral toxicity data were available for with the LD_{50} ranging from 1 mg/kg to >10,000 mg/kg, while dermally, the data available indicated the LD_{50} values were mostly >2000 mg/kg for these families of ingredients. Multiple repeated dose feeding studies have been performed. These ingredients were not carcinogenic at concentrations up to 1% in diet. Most of the alkyl PEG ethers produced ocular irritation at concentrations of 5% and greater and dermal irritation at 1000 mg/kg/day and greater in studies with animals; however they were not sensitizers in guinea pigs. These ingredients were not reproductive or developmental toxicants and were not genotoxic in in vivo or in vitro assays. In clinical studies, many of the alkyl PEG ethers were irritants but not sensitizers.	44

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[8](*italicized text has been generated by CIR*)
PEGylated Castor Oils & PEGylated Hydrogenated Castor Oils	
PEG-2 Castor Oil 61791-12-6 (generic to any number PEG Castor Oil, i.e. PEG-X Castor Oil)	PEG-2 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil, with an average of 2 moles of ethylene oxide. *PEG-2 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with two equivalents of ethylene oxide.*
PEG-3 Castor Oil 61791-12-6 (generic)	PEG-3 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 3 moles of ethylene oxide. *PEG-3 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with three equivalents of ethylene oxide.*
PEG-4 Castor Oil 61791-12-6 (generic)	PEG-4 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 4 moles of ethylene oxide. *PEG-4 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with four equivalents of ethylene oxide.*
PEG-5 Castor Oil 61791-12-6 (generic)	PEG-5 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 5 moles of ethylene oxide. *PEG-5 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with five equivalents of ethylene oxide.*
PEG-8 Castor Oil 61791-12-6 (generic)	PEG-8 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 8 moles of ethylene oxide. *PEG-8 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with eight equivalents of ethylene oxide.*
PEG-9 Castor Oil 61791-12-6 (generic)	PEG-9 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 9 moles of ethylene oxide. *PEG-9 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with nine equivalents of ethylene oxide.*
PEG-10 Castor Oil 61791-12-6 (generic)	PEG-10 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 10 moles of ethylene oxide. *PEG-10 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with ten equivalents of ethylene oxide.*
PEG-11 Castor Oil 61791-12-6 (generic)	PEG-11 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 11 moles of ethylene oxide. *PEG-11 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with eleven equivalents of ethylene oxide.*
PEG-15 Castor Oil 61791-12-6 (generic)	PEG-15 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 15 moles of ethylene oxide. *PEG-15 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with fifteen equivalents of ethylene oxide.*
PEG-16 Castor Oil 61791-12-6 (generic)	PEG-16 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 16 moles of ethylene oxide. *PEG-16 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with sixteen equivalents of ethylene oxide.*
PEG-20 Castor Oil 61791-12-6 (generic)	PEG-20 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 20 moles of ethylene oxide. *PEG-20 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with twenty equivalents of ethylene oxide.*
PEG-25 Castor Oil 61791-12-6 (generic)	PEG-25 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 25 moles of ethylene oxide. *PEG-25 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with twenty-five equivalents of ethylene oxide.*
PEG-26 Castor Oil 61791-12-6 (generic)	PEG-26 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 26 moles of ethylene oxide. *PEG-26 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with twenty-six equivalents of ethylene oxide.*
PEG-29 Castor Oil 61791-12-6 (generic)	PEG-29 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 29 moles of ethylene oxide. *PEG-29 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with twenty-nine equivalents of ethylene oxide.*
PEG-30 Castor Oil 61791-12-6 (generic)	PEG-30 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 30 moles of ethylene oxide. *PEG-30 Castor Oil is a mixture of the etherification product of castor oil glycerides and the esterification product of the fatty acids from castor oil, with one end of a polyethylene glycol chain, averaging thirty ethylene glycol repeat units in length.*
PEG-33 Castor Oil 61791-12-6 (generic)	PEG-33 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 33 moles of ethylene oxide. *PEG-33 Castor Oil is a mixture of the etherification product of castor oil glycerides and the esterification product of the fatty acids from castor oil, with one end of a polyethylene glycol chain, averaging thirty-three ethylene glycol repeat units in length.*
PEG-35 Castor Oil 61791-12-6 (generic)	PEG-35 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 35 moles of ethylene oxide. *PEG-35 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with thirty-five equivalents of ethylene oxide.*
PEG-36 Castor Oil 61791-12-6 (generic)	PEG-36 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 36 moles of ethylene oxide. *PEG-36 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with thirty-six equivalents of ethylene oxide.*
PEG-40 Castor Oil 61791-12-6 (generic)	PEG-40 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 40 moles of ethylene oxide. *PEG-40 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with forty equivalents of ethylene oxide.*
PEG-44 Castor Oil 61791-12-6 (generic)	PEG-44 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 44 moles of ethylene oxide. *PEG-44 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with forty-four equivalents of ethylene oxide.*
PEG-50 Castor Oil 61791-12-6 (generic)	PEG-50 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 50 moles of ethylene oxide. *PEG-50 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with fifty equivalents of ethylene oxide.*
PEG-54 Castor Oil 61791-12-6 (generic)	PEG-54 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 54 moles of ethylene oxide. *PEG-54 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with fifty-four equivalents of ethylene oxide.*

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[8](*italicized text has been generated by CIR*)
PEG-55 Castor Oil 61791-12-6 (generic)	PEG-55 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 55 moles of ethylene oxide. *PEG-55 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with fifty-five equivalents of ethylene oxide.*
PEG-60 Castor Oil 61791-12-6 (generic)	PEG-60 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 60 moles of ethylene oxide. *PEG-60 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with sixty equivalents of ethylene oxide.*
PEG-75 Castor Oil 61791-12-6 (generic)	PEG-75 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 75 moles of ethylene oxide. *PEG-75 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with seventy-five equivalents of ethylene oxide.*
PEG-80 Castor Oil 61791-12-6 (generic)	PEG-80 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 80 moles of ethylene oxide. *PEG-80 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with eighty equivalents of ethylene oxide.*
PEG-100 Castor Oil 61791-12-6 (generic)	PEG-100 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 100 moles of ethylene oxide. *PEG-100 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with one-hundred equivalents of ethylene oxide.*
PEG-200 Castor Oil 61791-12-6 (generic)	PEG-200 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 200 moles of ethylene oxide. *PEG-200 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with two hundred equivalents of ethylene oxide.*
Diesters	
PEG-18 Castor Oil Dioleate	PEG-18 Castor Oil Dioleate is the oleic acid diester of ethoxylated castor oil in which the average ethoxylation value is 18.
PEG-60 Castor Oil Isostearate	PEG-60 Castor Oil Isostearate is the ester of Isostearic Acid and PEG-60 Castor Oil.
Hydrogenated	
PEG-2 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-2 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 2 moles of ethylene oxide. *PEG-2 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with two equivalents of ethylene oxide.*
PEG-5 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-5 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 5 moles of ethylene oxide. *PEG-5 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with five equivalents of ethylene oxide.*
PEG-6 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-6 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 6 moles of ethylene oxide. *PEG-6 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with six equivalents of ethylene oxide.*
PEG-7 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-7 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 7 moles of ethylene oxide. *PEG-7 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with seven equivalents of ethylene oxide.*
PEG-8 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-8 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 8 moles of ethylene oxide. *PEG-8 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with eight equivalents of ethylene oxide.*
PEG-10 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-10 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 10 moles of ethylene oxide. *PEG-10 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with ten equivalents of ethylene oxide.*
PEG-16 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-16 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 16 moles of ethylene oxide. *PEG-16 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with sixteen equivalents of ethylene oxide.*
PEG-20 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-20 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 20 moles of ethylene oxide. *PEG-20 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with twenty equivalents of ethylene oxide.*
PEG-25 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-25 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 25 moles of ethylene oxide. *PEG-25 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with twenty-five equivalents of ethylene oxide.*
PEG-30 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-30 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 30 moles of ethylene oxide. *PEG-30 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with thirty equivalents of ethylene oxide.*
PEG-35 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-35 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 35 moles of ethylene oxide. *PEG-35 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with thirty-five equivalents of ethylene oxide.*
PEG-40 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-40 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 40 moles of ethylene oxide. *PEG-40 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with forty equivalents of ethylene oxide.*
PEG-45 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-45 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 45 moles of ethylene oxide. *PEG-45 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with forty-five equivalents of ethylene oxide.*

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[8](*italicized text has been generated by CIR*)
PEG-50 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-50 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 50 moles of ethylene oxide. *PEG-50 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty equivalents of ethylene oxide.*
PEG-54 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-54 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 54 moles of ethylene oxide. *PEG-54 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty-four equivalents of ethylene oxide.*
PEG-55 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-55 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 55 moles of ethylene oxide. *PEG-55 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty-five equivalents of ethylene oxide.*
PEG-60 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-60 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 60 moles of ethylene oxide. *PEG-60 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with sixty equivalents of ethylene oxide.*
PEG-65 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-65 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 65 moles of ethylene oxide. *PEG-65 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with sixty-five equivalents of ethylene oxide.*
PEG-80 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-80 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 80 moles of ethylene oxide. *PEG-80 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with eighty equivalents of ethylene oxide.*
PEG-100 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-100 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 100 moles of ethylene oxide. *PEG-100 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with one hundred equivalents of ethylene oxide.*
PEG-200 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-200 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 200 moles of ethylene oxide. *PEG-200 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with two hundred equivalents of ethylene oxide.*
PEG-8 block added transester	
Hydrogenated Castor Oil PEG-8 Esters	Hydrogenated Castor Oil PEG-8 Esters is a product obtained by the transesterification of Hydrogenated Castor Oil and PEG-8.
PEGylated Hydrogenated Castor Oil Diesters	
PEG-5 Hydrogenated Castor Oil Isostearate	PEG-5 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 5.
PEG-10 Hydrogenated Castor Oil Isostearate	PEG-10 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 10.
PEG-15 Hydrogenated Castor Oil Isostearate	PEG-15 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 15.
PEG-20 Hydrogenated Castor Oil Isostearate	PEG-20 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 20.
PEG-30 Hydrogenated Castor Oil Isostearate	PEG-30 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 30.
PEG-40 Hydrogenated Castor Oil Isostearate	PEG-40 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 40.
PEG-50 Hydrogenated Castor Oil Isostearate	PEG-50 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 50.
PEG-58 Hydrogenated Castor Oil Isostearate	PEG-58 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 58.
PEG-20 Hydrogenated Castor Oil Laurate [868047-47-6, generic to all PEG-X Hydrogenated Castor Oil]	PEG-20 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 20
PEG-30 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-30 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 30.
PEG-40 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-40 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 40.
PEG-50 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-50 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 50.
PEG-60 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-60 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 60.

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[8](*italicized text has been generated by CIR*)
PEG-20 Hydrogenated Castor Oil PCA Isostearate	PEG-20 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-20 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-30 Hydrogenated Castor Oil PCA Isostearate	PEG-30 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-30 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-40 Hydrogenated Castor Oil PCA Isostearate	PEG-40 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-40 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-60 Hydrogenated Castor Oil PCA Isostearate	PEG-60 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-60 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-50 Hydrogenated Castor Oil Succinate	PEG-50 Hydrogenated Castor Oil Succinate is a polyethylene glycol derivative of the succinic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 50.
PEG-5 Hydrogenated Castor Oil Triisostearate [188734-82-9, generic to all PEG-X Hydrogenated Castor Oil Triisostearate]	PEG-5 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 5 moles of ethylene oxide.
PEG-10 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-10 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 10 moles of ethylene oxide.
PEG-15 Hydrogenated Castor Oil Triisostearate	PEG-15 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 15 moles of ethylene oxide.
PEG-20 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-20 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average ethoxylation value of 20.
PEG-30 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-30 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 30 moles of ethylene oxide.
PEG-40 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-40 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 40 moles of ethylene oxide.
PEG-50 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-50 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average of 50 moles of ethylene oxide.
PEG-60 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-60 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average of 60 moles of ethylene oxide.
Potassium PEG-50 Hydrogenated Castor Oil Succinate	Potassium PEG-50 Hydrogenated Castor Oil Succinate is the potassium salt of PEG-50 Hydrogenated Castor Oil Succinate.
Sodium PEG-50 Hydrogenated Castor Oil Succinate	Sodium PEG-50 Hydrogenated Castor Oil Succinate is the sodium salt of PEG-50 Hydrogenated Castor Oil Succinate.
Other PEG-X block added Oils	
Adansonia Digitata Seed Oil PEG-8 Esters	Adansonia Digitata Seed Oil PEG-8 Esters is the product obtained by the transesterification of Adansonia Digitata Seed Oil and PEG-8.
Almond Oil PEG-6 Esters	Almond Oil PEG-6 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Almond) Oil and PEG-6.
Almond Oil PEG-8 Esters	Almond Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Almond) Oil and PEG-8.
Apricot Kernel Oil PEG-6 Esters	Apricot Kernel Oil PEG-6 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-6.
Apricot Kernel Oil PEG-8 Esters	Apricot Kernel Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-8.
Apricot Kernel Oil PEG-40 Esters	Apricot Kernel Oil PEG-40 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-40.
Argan Oil PEG-8 Esters	Argan Oil PEG-8 Esters is the product obtained by the transesterification of Argania Spinosa Kernel Oil and PEG-8.
Avocado Oil PEG-8 Esters	Avocado Oil PEG-8 Esters is the product obtained by the transesterification of Persea Gratissima (Avocado) Oil and PEG-8.
Avocado Oil PEG-11 Esters	Avocado Oil PEG-11 Esters is the product obtained from the transesterification of Persea Gratissima (Avocado) Oil and PEG-11.
Bertholletia Excelsa Seed Oil PEG-8 Esters	Bertholletia Excelsa Seed Oil PEG-8 Esters is the product obtained from the transesterificaton of Bertholletia Excelsa Seed Oil and PEG-8.
Bitter Cherry Seed Oil PEG-8 Esters	Bitter Cherry Seed Oil PEG-8 Esters is a product obtained by the transesterification of Prunus Cerasus (Bitter Cherry) Seed Oil and PEG-8.
Borage Seed Oil PEG-8 Esters	Borage Seed Oil PEG-8 Esters is the product obtained by the transesterification of Borago Officinalis (Borage) Seed Oil and PEG-8.
Coconut Oil PEG-10 Esters	Coconut Oil PEG-10 Esters is a polyethylene glycol derivative of Cocos Nucifera (Coconut) Oil with an average of 10 moles of ethylene oxide.
Corn Oil PEG-6 Esters	Corn Oil PEG-6 Esters is a product obtained by the transesterification of Zea Mays (Corn) Oil and PEG-6.
Corn Oil PEG-8 Esters	Corn Oil PEG-8 Esters is a product obtained by the transesterification of Zea Mays (Corn) Oil and PEG-8.

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[8](*italicized text has been generated by CIR*)
Grape Seed Oil PEG-8 Esters	Grape Seed Oil PEG-8 Esters is the product obtained by the transesterification of Vitis Vinifera (Grape) Seed Oil and PEG-8.
Hazel Seed Oil PEG-8 Esters	Hazel Seed Oil PEG-8 Esters is the product obtained by the transesterification of Corylus Avellana (Hazel) Seed Oil and PEG-8.
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters is the product obtained by the transesterification of Hydrogenated Palm Kernel Oil, Hydrogenated Palm Oil and PEG-6.
Jojoba Oil PEG-8 Esters	Jojoba Oil PEG-8 Esters is the polyethylene glycol derivative of the acids and alcohols derived from Simmondsia Chinensis (Jojoba) Oil containing an average of 8 moles of ethylene oxide.
Jojoba Oil PEG-150 Esters	Jojoba Oil PEG-150 Esters is the polyethylene glycol derivative of the acids and alcohols derived from Simmondsia Chinensis (Jojoba) Oil containing an average of 150 moles of ethylene oxide.
Linseed Oil PEG-8 Esters	Linseed Oil PEG-8 Esters is the product obtained by the transesterification of Linum Usitatissimum (Linseed) Oil and PEG-8.
Macadamia Ternifolia Seed Oil PEG-8 Esters	Macadamia Ternifolia Seed Oil PEG-8 Esters is the product obtained by the transesterification of Macadamia Ternifolia Seed Oil and PEG-8.
Mango Seed Oil PEG-70 Esters	Mango Seed Oil PEG-70 Esters is the product obtained by the transesterification of Mangifera Indica (Mango) Seed Oil and PEG-70.
Mink Oil PEG-13 Esters	Mink Oil PEG-13 Esters is the product obtained by the transesterification of Mink Oil and PEG-13.
Olive Oil PEG-6 Esters	Olive Oil PEG-6 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-6.
Olive Oil PEG-7 Esters	Olive Oil PEG-7 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-7
Olive Oil PEG-8 Esters	Olive Oil PEG-8 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-8.
Olive Oil PEG-10 Esters	Olive Oil PEG-10 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-10.
Orbignya Oleifera Seed Oil PEG-8 Esters	Orbignya Oleifera Seed Oil PEG-8 Esters is the product obtained by the transesterification of Orbignya Oleifera Seed Oil and PEG-8.
Palm Oil PEG-8 Esters	Palm Oil PEG-8 Esters is the product obtained by the transesterification of Elaeis Guineensis (Palm) Oil and PEG-8.
Passiflora Edulis Seed Oils PEG-8 Esters	Passiflora Edulis Seed Oils PEG-8 Esters is a product obtained by the transesterification of a blend of Passiflora Edulis Seed Oil with PEG-8.
Peanut Oil PEG-6 Esters	Peanut Oil PEG-6 Esters is the product obtained by the transesterification of Arachis Hypogaea (Peanut) Oil and PEG-6.
PEG-75 Crambe Abyssinica Seed Oil	PEG-75 Crambe Abyssinica Seed Oil is a polyethylene glycol derivative of Crambe Abyssinica Seed Oil with an average of 75 moles of ethylene oxide. *PEG-75 Crambe Abyssinica Seed Oil is a mixture of the etherification and esterification products of crambe abyssinica seed oil glycerides and fatty acids from crambe abyssinica seed oil, with seventy-five equivalents of ethylene oxide.*
PEG-75 Meadowfoam Oil	PEG-75 Meadowfoam Oil is a polyethylene glycol derivative of Limnanthes Alba (Meadowfoam) Seed Oil with an average of 75 moles of ethylene oxide. *PEG-75 Meadowfoam Oil is a mixture of the etherification and esterification products of meadowfoam oil glycerides and fatty acids from meadowfoam oil, with seventy-five equivalents of ethylene oxide.*
Pumpkin Seed Oil PEG-8 Esters	Pumpkin Seed Oil PEG-8 Esters is the product obtained by the transesterification of Cucurbita Pepo (Pumpkin) Seed Oil and PEG-8.
Rapeseed Oil PEG-3 Esters	Rapeseed Oil PEG-3 Esters is the product obtained by the transesterification of Brassica Campestris (Rapeseed) Oil and PEG-3.
Rapeseed Oil PEG-20 Esters	Rapeseed Oil PEG-20 Esters is the product obtained by the transesterification of Brassica Campestris (Rapeseed) Oil and PEG-20.
Raspberry Seed Oil PEG-8 Esters	Raspberry Seed Oil PEG-8 Esters is the product obtained by the transesterification of Rubus Idaeus (Raspberry) Seed Oil and PEG-8.
Safflower Seed Oil PEG-8 Esters	Safflower Seed Oil PEG-8 Esters is the product obtained by the transesterification of Carthamus Tinctorius (Safflower) Seed Oil and PEG-8.
Schinziophyton Rautanenii Kernel Oil PEG-8 Esters	Schinziophyton Rautanenii Kernel Oil PEG-8 Esters is the product obtained by the transesterification of Schinziophyton Rautanenii Kernel Oil and PEG-8.
Sclerocarya Birrea Seed Oil PEG-8 Esters	Sclerocarya Birrea Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Sclerocarya Birrea Seed Oil.
Sesame Seed Oil PEG-8 Esters	Sesame Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Sesamum Indicum Seed Oil.
Soybean Oil PEG-8 Esters	Soybean Oil PEG-8 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-8.
Soybean Oil PEG-20 Esters	Soybean Oil PEG-20 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-20
Soybean Oil PEG-36 Esters	Soybean Oil PEG-36 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-36.
Sunflower Seed Oil PEG-8 Esters	Sunflower Seed Oil PEG-8 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and PEG-8.
Sunflower Seed Oil PEG-32 Esters	Sunflower Seed Oil PEG-32 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and PEG-32.
Sweet Almond Oil PEG-8 Esters	Sweet Almond Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Amygdalus (Sweet Almond) Oil and PEG-6.
Watermelon Seed Oil PEG-8 Esters	Watermelon Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Citrillus Lanatus (Watermelon) Seed Oil.

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[8](*italicized text has been generated by CIR*)
Wheat Germ Oil PEG-40 Butyloctanol Esters	Wheat Germ Oil PEG-40 Butyloctanol Esters is the product obtained by the reaction of a mixture of Triticum Vulgare (Wheat) Germ Oil (q.v.) and Butyloctanol with PEG-40. *Wheat Germ Oil PEG-40 Butyloctanol Esters is the transesterification product obtained by the reaction of a mixture of Triticum Vulgare (Wheat) Germ Oil with 2-butyloctanol and PEG-40.*
Wheat Germ Oil PEG-8 Esters	Wheat Germ Oil PEG-8 Esters is the product obtained by the transesterificaton of Triticum Vulgare (Wheat) Germ Oil and PEG-8.

Table 4a. Historical and current use and concentration of use data for PEG-30, -33, -35, -36, -40 Castor Oil and PEG-30 and-40 Hydrogenated Castor Oil.[1,9]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	PEG-30 Castor Oil				**PEG-33 Castor Oil**				**PEG-35 Castor Oil**			
Data Year	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**
Totals*	**77[a]**	**1**	**≥ 50[b]**	**0.1**	**13**	**41**	**NR**	**NR**	**4**	**35**	**NR**	**0.001-1**
Duration of Use												
Leave-On	NR	NR	[b]	NR	10	30	NR	NR	4	21	NR	0.005-1
Rinse-Off	73	1	[b]	0.1	3	11	NR	NR	NR	14	NR	0.001-1
Diluted for (Bath) Use	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type												
Eye Area	NR	NR	[b]	NR	NR	1	NR	NR	NR	2	NR	NR
Incidental Ingestion	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	[b]	NR	NR	NR	NR	NR	1	1	NR	NR
Incidental Inhalation-Powder	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	[b]	NR	8	35	NR	NR	3	24	NR	0.005
Deodorant (underarm)	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	1	[b]	0.1	5	6	NR	NR	1	11	NR	0.001-1
Hair-Coloring	72	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	0.2-0.4
Nail	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	[b]	NR	NR	NR	NR	NR	NR	1	NR	0.005
Baby Products	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR

	PEG-36 Castor Oil				**PEG-40 Castor Oil**				**PEG-30 Hydrogenated Castor Oil**			
Data Year	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**
Totals*	**3**	**6**	**NR**	**NR**	**170[c]**	**95**	**≤ 10[b]**	**NR**	**5**	**3**	**≤ 0.1[b]**	**0.06-10**
Duration of Use												
Leave-On	3	6	NR	NR	60	59	[b]	NR	2	1	[b]	0.06-2
Rinse Off	NR	NR	NR	NR	46	36	[b]	NR	3	2	[b]	2-10
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR	[b]	NR	NR	NR	[b]	NR
Exposure Type												
Eye Area	NR	NR	NR	NR	1	1	[b]	NR	NR	NR	[b]	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	[b]	NR	NR	NR	[b]	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	7	1	[b]	NR	1	NR	[b]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	[b]	NR	NR	NR	[b]	NR
Dermal Contact	3	6	NR	NR	74	63	[b]	NR	5	2	[b]	2-10
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	[b]	NR	1	NR	[b]	NR
Hair - Non-Coloring	NR	NR	NR	NR	33	29	[b]	NR	NR	NR	[b]	NR
Hair-Coloring	NR	NR	NR	NR	NR	2	[b]	NR	NR	1	[b]	NR
Nail	NR	NR	NR	NR	NR	1	[b]	NR	NR	NR	[b]	0.06
Mucous Membrane	NR	NR	NR	NR	2	14	[b]	NR	NR	NR	[b]	10
Baby Products	NR	NR	NR	NR	NR	NR	[b]	NR	NR	NR	[b]	NR

	PEG-40 Hydrogenated Castor Oil			
	1997	**2012**	**1997**	**2012**
Totals*	**268[d]**	**2107**	**≤ 5[b]**	**0.00007-22**
Duration of Use				
Leave-On	186	1319	[b]	0.0007-22
Rinse-Off	50	754	[b]	0.00007-14
Diluted for (Bath) Use	20	34	[b]	0.001-5
Exposure Type				
Eye Area	9	53	[b]	0.002-15
Incidental Ingestion	NR	4	[b]	0.9-4
Incidental Inhalation-Spray	31	279	[b]	0.003-6[e]
Incidental Inhalation-Powder	3	3	[b]	0.002
Dermal Contact	197	1461	[b]	0.00007-10
Deodorant (underarm)	2	27	[b]	0.02-4
Hair - Non-Coloring	54	537	[b]	0.008-22
Hair-Coloring	2	93	[b]	0.06-14
Nail	NR	4	[b]	0.8
Mucous Membrane	30	390	[b]	0.001-10
Baby Products	1	18	[b]	0.5-4

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

NR = Not reported

a Total includes4 uses listed under trade name of mixtures, exact duration of use and exposure type could not be determined.

b Breakdown not available.

c Total includes 63 uses listed under trade name of mixtures, exact duration of use and exposure type could not be determined.

d Total includes 11 uses listed under trade name, exact duration of use and exposure type could not be determined.

e 0.5% in a baby hair detangling spray; 0.003% in an other spray fragrance; 6% in an other pump spray fragrance; 0.02-0.4% in an aerosol hair spray; 0.2-0.7% in a pump hair spray; 0.5% in a tonic, dressing, and other hair grooming aids spray; 4% in an aerosol deodorant spray; 3% in a body and hand cream spray; 3% in a foot spray; and 2% in a skin freshener spray.

Table 4b. Frequency and concentration of use (2012) according to duration and type of exposure for expanded PEGylated Oils group.[9]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	PEG-9 Castor Oil		**PEG-25 Castor Oil**		**PEG-50 Castor Oil**	
Totals*	**1**	**0.3**	**NR**	**3-17**	**2**	**NR**
Duration of Use						
Leave-On	1	0.3	NR	3-17	2	NR
Rinse-Off	NR	NR	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1	NR	NR	3[a]	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	0.3	NR	3-17	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	PEG-60 Castor Oil		**PEG-2 Hydrogenated Castor Oil**		**PEG-7 Hydrogenated Castor Oil**	
Totals*	**NR**	**0.002-23**	**5**	**NR**	**11**	**0.05-8**
Duration of Use						
Leave-On	NR	0.04-23	5	NR	9	0.05-8
Rinse Off	NR	0.002-11	NR	NR	2	NR
Diluted for (Bath) Use	NR	6	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	0.08-1	5	NR	NR	5
Incidental Ingestion	NR	0.06-2	NR	NR	NR	8
Incidental Inhalation-Spray	NR	0.04-16[b]	NR	NR	4	NR
Incidental Inhalation-Powder	NR	0.2	NR	NR	NR	NR
Dermal Contact	NR	0.002-11	NR	NR	9	0.6-5
Deodorant (underarm)	NR	0.04-0.5	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.5-23	NR	NR	2	0.05
Hair-Coloring	NR	0.6-8	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.06-6	NR	NR	2	8
Baby Products	NR	NR	NR	NR	NR	NR

	PEG-10 Hydrogenated Castor Oil		**PEG-16 Hydrogenated Castor Oil**		**PEG-20 Hydrogenated Castor Oil**	
Totals*	**5**	**3**	**1**	**NR**	**5**	**0.05-0.5**
Duration of Use						
Leave-On	5	*3*	1	NR	4	0.05-0.5
Rinse-Off	NR	*NR*	NR	NR	1	NR
Diluted for (Bath) Use	NR	*NR*	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	1	NR	1	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	3	3	NR	NR	5	0.05-0.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	1	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 4b. Frequency and concentration of use (2012) according to duration and type of exposure for expanded PEGylated Oils group.[9]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	PEG-25 Hydrogenated Castor Oil		**PEG-35 Hydrogenated Castor Oil**		**PEG-45 Hydrogenated Castor Oil**	
Totals	**39**	**0.01-23**	**1**	**NR**	**2**	**NR**
Duration of Use						
Leave-On	34	0.01-23	1	NR	1	NR
Rinse Off	5	0.3	NR	NR	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	4	NR	1	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	16	0.01-2	1	NR	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	23	3-23	NR	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	3	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	1	NR

	PEG-60 Hydrogenated Castor Oil		**PEG-80 Hydrogenated Castor Oil**		**PEG-100 Hydrogenated Castor Oil**	
Totals*	**349**	**0.00004-18**	**4**	**NR**	**NR**	**0.02-4**
Duration of Use						
Leave-On	251	0.00004-18	3	NR	NR	0.02-3
Rinse-Off	94	0.00004-0.5	1	NR	NR	1-2
Diluted for (Bath) Use	4	NR	NR	NR	NR	4
Exposure Type						
Eye Area	9	3-5	NR	NR	NR	NR
Incidental Ingestion	1	6	NR	NR	NR	0.5
Incidental Inhalation-Spray	13	0.3-1[c]	NR	NR	NR	0.3[d]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	307	0.00004-5	4	NR	NR	0.02-4
Deodorant (underarm)	2	NR	NR	NR	NR	NR
Hair - Non-Coloring	41	0.3-18	NR	NR	NR	0.2-3
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	3	NR	NR	NR	NR
Mucous Membrane	37	0.004-6	NR	NR	NR	0.5-4
Baby Products	1	NR	NR	NR	NR	NR

	PEG-20 Hydrogenated Castor Oil Triisostearate		**PEG-40 Hydrogenated Castor Oil Triisostearate**		**PEG-50 Hydrogenated Castor Oil Succinate**	
Totals*	**3**	**NR**	**NR**	**0.002-0.003**	**NR**	**1-40**
Duration of Use						
Leave-On	3	NR	NR	NR	NR	40
Rinse-Off	NR	NR	NR	0.002-0.003	NR	1
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	3	NR	NR	NR	NR	1
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	0.002-0.003	NR	1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.003	NR	40
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	0.002-0.003	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 4b. Frequency and concentration of use (2012) according to duration and type of exposure for expanded PEGylated Oils group.[9]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	PEG-40 Hydrogenated Castor Oil PCA Isostearate		**Apricot Kernel Oil PEG-6 Esters**		**Avocado Oil PEG-11 Esters**	
Totals*	**2**	**NR**	**24**	**0.8-1**	**NR**	**0.1**
Duration of Use						
Leave-On	1	NR	23	0.8-1	NR	0.1
Rinse-Off	1	NR	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	1	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	1	1	NR	NR
Incidental Ingestion	NR	NR	4	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	20	0.8-1	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	NR	0.1
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	5	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Coconut Oil PEG-10 Esters		**Grape Seed Oil PEG-8 Esters**		**Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters**	
Totals*	**8**	**NR**	**18**	**NR**	**4**	**0.6-24**
Duration of Use						
Leave-On	2	NR	10	NR	4	0.6-24
Rinse-Off	6	NR	8	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	1	9-24
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1	NR	NR	0.6
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	16
Dermal Contact	2	NR	18	NR	4	0.6-24
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	6	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	6	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Jojoba Oil PEG-8 Esters		**Olive Oil PEG-7 Esters**		**Olive Oil PEG-10 Esters**	
Totals*	**40**	**0.5**	**97**	**0.05-97**	**NR**	**0.002-0.009**
Duration of Use						
Leave-On	26	NR	45	0.9-12	NR	0.002
Rinse Off	7	0.5	52	0.05-97	NR	0.003-0.009
Diluted for (Bath) Use	7	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	3	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.9	NR	NR
Incidental Inhalation-Spray	NR	NR	2	1[e]	NR	NR
Incidental Inhalation-Powder	1	NR	NR	NR	NR	NR
Dermal Contact	34	NR	74	0.1-97	NR	0.002-0.009
Deodorant (underarm)	NR	NR	1	NR	NR	NR
Hair - Non-Coloring	6	0.5	23	0.05-1	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	NR	22	0.1-0.9	NR	0.003-0.009
Baby Products	3	NR	1	NR	NR	NR

Table 4b. Frequency and concentration of use according to duration and type of exposure for expanded PEGylated Oils group.[9]

	# of Uses	*Max Conc of Use (%)*
	PEG-75 Meadowfoam Oil	
Totals*	**1**	**0.08**
Duration of Use		
Leave-On	1	0.08
Rinse-Off	NR	NR
Diluted for (Bath) Use	NR	NR
Exposure Type		
Eye Area	NR	NR
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	NR	0.08[f]
Incidental Inhalation-Powder	NR	NR
Dermal Contact	NR	NR
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	1	0.08
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
NR = Not reported
a 3% in a pump hair spray.
b 0.5% in a pump hair spray and 16% in an aerosol hair spray; 0.04% in an aerosol deodorant; and 0.4% in a face and neck cream spray.
c 0.3% in an aerosol Hairspray, 0.9% in a pump Hairspray, and 1% in a face and Neck cream spray
d0.3% in an aerosol other fragrance preparation.
e 1% in a pump spray
f 0.08% in a pump spray

Table 4c. Not reported to be in use

PEG-2 Castor Oil	PEG-15 Hydrogenated Castor Oil Isostearate	Corn Oil PEG-8 Esters
PEG-3 Castor Oil	PEG-20 Hydrogenated Castor Oil Isostearate	Hazel Seed Oil PEG-8 Esters
PEG-4 Castor Oil	PEG-30 Hydrogenated Castor Oil Isostearate	Jojoba Oil PEG-150 Esters
PEG-5 Castor Oil	PEG-40 Hydrogenated Castor Oil Isostearate	Linseed Oil PEG-8 Esters
PEG-8 Castor Oil	PEG-50 Hydrogenated Castor Oil Isostearate	Macadamia Ternifolia Seed Oil PEG-8 Esters
PEG-10 Castor Oil	PEG-58 Hydrogenated Castor Oil Isostearate	Mango Seed Oil PEG-70 Esters
PEG-11 Castor Oil	PEG-20 Hydrogenated Castor Oil Laurate	Mink Oil PEG-13 Esters
PEG-15 Castor Oil	PEG-30 Hydrogenated Castor Oil Laurate	Olive Oil PEG-6 Esters
PEG-16 Castor Oil	PEG-40 Hydrogenated Castor Oil Laurate	Olive Oil PEG-8 Esters
PEG-20 Castor Oil	PEG-50 Hydrogenated Castor Oil Laurate	Orbignya Oleifera Seed Oil PEG-8 Esters
PEG-26 Castor Oil	PEG-60 Hydrogenated Castor Oil Laurate	Palm Oil PEG-8 Esters
PEG-29 Castor Oil	PEG-20 Hydrogenated Castor Oil PCA Isostearate	Passiflora Edulis Seed Oils PEG-8 Esters
PEG-44 Castor Oil	PEG-30 Hydrogenated Castor Oil PCA Isostearate	Peanut Oil PEG-6 Esters
PEG-54 Castor Oil	PEG-60 Hydrogenated Castor Oil PCA Isostearate	PEG-75 Crambe Abyssinica Seed Oil
PEG-55 Castor Oil	Potassium PEG-50 Hydrogenated Castor Oil Succinate	Pumpkin Seed Oil PEG-8 Esters
PEG-75 Castor Oil	Sodium PEG-50 Hydrogenated Castor Oil Succinate	Rapeseed Oil PEG-3 Esters
PEG-80 Castor Oil	PEG-5 Hydrogenated Castor Oil Triisostearate	Rapeseed Oil PEG-20 Esters
PEG-100 Castor Oil	PEG-10 Hydrogenated Castor Oil Triisostearate	Raspberry Seed Oil PEG-8 Esters
PEG-200 Castor Oil	PEG-15 Hydrogenated Castor Oil Triisostearate	Safflower Seed Oil PEG-8 Esters
PEG-18 Castor Oil Dioleate	PEG-30 Hydrogenated Castor Oil Triisostearate	Schinziophyton Rautanenii Kernel Oil PEG-8 Esters
PEG-60 Castor Oil Isostearate	PEG-50 Hydrogenated Castor Oil Triisostearate	Sclerocarya Birrea Seed Oil PEG-8 Esters
PEG-5 Hydrogenated Castor Oil	PEG-60 Hydrogenated Castor Oil Triisostearate	Sesame Seed Oil PEG-8 Esters
PEG-6 Hydrogenated Castor Oil	Adansonia Digitata Seed Oil PEG-8 Esters	Soybean Oil PEG-8 Esters
PEG-8 Hydrogenated Castor Oil	Almond Oil PEG-6 Esters	Soybean Oil PEG-20 Esters
Hydrogenated Castor Oil PEG-8 Esters	Almond Oil PEG-8 Esters	Soybean Oil PEG-36 Esters
PEG-54 Hydrogenated Castor Oil	Apricot Kernel Oil PEG-8 Esters	Sunflower Seed Oil PEG-8 Esters
PEG-55 Hydrogenated Castor Oil	Apricot Kernel Oil PEG-40 Esters	Sunflower Seed Oil PEG-32 Esters
PEG-65 Hydrogenated Castor Oil	Argan Oil PEG-8 Esters	Sweet Almond Oil PEG-8 Esters
PEG-200 Hydrogenated Castor Oil	Avocado Oil PEG-8 Esters	Watermelon Seed Oil PEG-8 Esters
PEG-5 Hydrogenated Castor Oil Isostearate	Bertholletia Excelsa Seed Oil PEG-8 Esters	Wheat Germ Oil PEG-40 Butyloctanol Esters
PEG-10 Hydrogenated Castor Oil Isostearate	Borage Seed Oil PEG-8 Esters	Wheat Germ Oil PEG-8 Esters
	Corn Oil PEG-6 Esters	

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: June 16, 2014

SUBJECT: Specifications PEG-11 Avocado Glycerides and PEG-10 Olive Glycerides

Anonymous. 2013. Specification/certificate of analysis PEG-11 Avocado Glycerides.

Anonymous. 2013. Specification/certificate of analysis PEG-10 Olive Glycerides.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

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11. February 2013

Specification / Certificate of Analysis

Product PEG-11 Avocado Glycerides

Item No.

Description	Specification	Result
Appearance	yellowish to brown liquid	
Odour	characteristic	
pH - value 10% in water 25°C *(SOP 0009)*	5.0 - 7.0	
Saponification value *(SOP 0041)*	60 - 80 mg KOH · g^{-1}	
Iodine value *(SOP 0026)*	25 - 37 g Iodine · $100g^{-1}$	
Water content *(SOP 0025)*	max. 1.0 %	

Further Information:

Shelf Life	24 Months unopened after production date
Results	Measured after production
Storage Conditions	storage temperature (4 - 25 °C) dry, in tightly closed original packaging

The above data represent the results of our quality assessment. They do not free the customer from his own quality check nor do they confirm that the product has certain properties or is suitable for a specific application. This Certificate of Analysis has been produced electronically and is valid without signature.

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11. February 2013

Specification / Certificate of Analysis

Product PEG-10 Olive Glycerides

Item No.

Description	Specification	Result
Appearance	yellowish-brown paste	
Odour	characteristic	
Index of refraction 20°C *(SOP 0008)*	1.465 - 1.475 n^{20} °C	
pH - value 10% in water 25°C *(SOP 0009)*	5.0 - 7.0	
Acid value *(SOP 0028)*	max. 4.00 mg KOH · g^{-1}	
Saponification value *(SOP 0041)*	52 - 72 mg KOH · g^{-1}	
Iodine value *(SOP 0026)*	26 - 36 g Iodine · $100g^{-1}$	
Water content *(SOP 0025)*	max. 1.0	
Solubility 2.5% in water	almost clear to turbid	
Solubility 10% in IPA	clear	

Further Information:

Shelf Life	18 Months unopened after production date
Results	Measured after production
Storage Conditions	storage temperature (4 - 25 °C) dry, in tightly closed original packaging
Reference	mix well before using
	Occasional turbidity may occur and can be eliminated by heating

The above data represent the results of our quality assessment. They do not free the customer from his own quality check nor do they confirm that the product has certain properties or is suitable for a specific application. This Certificate of Analysis has been produced electronically and is valid without signature.

Distributed for Comment Only -- Do Not Cite or Quote

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: June 24, 2014

SUBJECT: Information on PEG-10 Olive Glycerides, PEG-11 Avocado Glycerides and PEG-9 Cocoglycerides

Zschimmer & Schwarz GmbH & Co KG. 2013. Raw material information PEG-10 Olive Glycerides.

Zschimmer & Schwarz GmbH & Co KG. 2012. Raw material information PEG-11 Avocado Glycerides.

Zschimmer & Schwarz GmbH & Co KG. 2013. Raw material information PEG-9 Cocoglycerides.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

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Raw material information

ZSCHIMMER & SCHWARZ
GmbH & Co KG
CHEMISCHE FABRIKEN
D-56112 LAHNSTEIN/RHEIN

Harmonized information on raw material identification according to TEGEWA (Version 2005)

Revision: 4632.008 / 06.2013
Date of printing: 23.07.2013

1.	General information	
1.1	**Trade name**	**OXYPON 288**
1.2	**Manufacturer/Supplier** (address, phone no., fax no., contact person)	ZSCHIMMER & SCHWARZ GmbH & Co KG Max-Schwarz-Str. 3 - 5 56112 LAHNSTEIN
1.3	**Raw material category** (e.g. anionic surfactant)	Emollient and solubilizer for cosmetics
1.4	**Chemical name**	Ethoxylated olive oil
1.5	**INCI (CTFA) name Composition**	PEG-10 Olive Glycerides
1.6	**EC (EINECS/ELINCS) no.**	Polymer
1.7	**CAS no.**	70914-02-2
1.8	**Registration status** (e.g. EU, USA, Japan)	TSCA, EINECS, PICCS, NDSL, ECL, PICCS

2.	Information on production	
2.1	**Origin of starting material** (plant, animal, synthetic)	Vegetable origin
2.2	**Is the starting material derived from genetically modified organisms (GMO)?**	No
2.3	**Information on production process** (general description)	Reaction of olive oil with ethylene oxide

3.	Additives	
3.1	**Preservatives**	Not added
3.2	**Antioxidants**	Not added
3.3	**Solvents**	Not added
3.4	**Bleaching agents**	Not added
3.5	**Others**	Not added

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4.	Microbiological specification	
4.1	Total viable count (colony-forming units/g)	< 1000 colony-forming units/g

5.	By-products The presence of traces of the substances listed in Annex II of Regulation No. 1223/2009 (replaced Directive 76/768/EEC) (incl. cmr cat. I – III substances marked with *) shall be allowed provided that such presence is technically unavoidable in good manufacturing practice and that it conforms with Article 17 of Regulation No. 1223/2009.	
5.1	1,4-Dioxane *	< 5 ppm
5.2	Ethylene oxide *	< 1 ppm
5.3	Residual solvents	Not added
5.4	Residual monomers	< 1 ppm see 5.2
5.5	Amines	Not contained
5.6	Nitrosamines	Not contained
5.7	Heavy metals	Pb < 10 ppm, Ni < 10 ppm, Cd < 1 ppm, As < 1 ppm, Sb < 1 ppm, Hg < 0.2 ppm
5.8	Monochloroacetic acid	Not contained
5.9	Dichloroacetic acid	Not contained
5.10	Allergens according to the 7th Amendment to the Cosmetics Directive (ppm)	Not contained
5.11	Others	

6.	Toxicology	
6.1	Information on acute toxicity	Not determined
6.2	Information on skin irritation	Rabbit (3% active matter): non-irritant (Safepharm 9/82) Guinea pig (50% active matter), 24 h: no irritation observed (Sensitisation-Test, Notox 8/96)
6.3	Information on irritation of the mucous membrane	Rabbit (3% active matter): non-irritant (Safepharm 9/82)
6.4	Information on sensitisation potential	Guinea pig (50% active matter): no sensitisation (Notox 8/96)
6.5	Information on gene toxicity	Mutagenicity (Ames Test): non-mutagenic (Safepharm 1/97)
6.6	Information on percutaneous permeation	Not determined
6.7	Others	Duhring-Chamber-Test (2% active matter): non-irritating to mildly irritating (AMI)

7.	**Ecology**	
7.1	**Degradability/Elimination**	> 60 % after 14 days OECD 301 D
7.2	**Acute aquatic toxicity**	LC50: >100 mg/l after 96 h (Leuciscus idus) OECD 203 EC50: >1000 mg/l after 24 h (Daphnia) OECD 202
7.3	**Others**	

8.	**Additional information** (For details on specification see enclosed instruction sheet; for details on labelling and classification see enclosed safety data sheet.)	
	The toxicology is assumed to be comparable with products having the same or an analogous chemical structure: PEG-15 Glyceryl Isostearate:	 Acute toxicity LD 50: 29,76 ml/kg (rat, oral)
8.1	**Shelf life**	12 months

This Information refers only to the above mentioned product and does not need to be valid if used with other product(s) or in any process. The information is to our best present knowledge correct and complete and is given in good faith but without warranty. It remains the user's own responsibility to make sure that the information is appropriate and complete for his specific use of this product.

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Raw material information

ZSCHIMMER & SCHWARZ
GmbH & Co KG
CHEMISCHE FABRIKEN
D-56112 LAHNSTEIN/RHEIN

Harmonized information on raw material identification according to TEGEWA (Version 2005)

Revision: 1108.004 / 02.2012
Date of printing: 09.02.2012

1.	General information	
1.1	**Trade name**	**OXYPON 365**
1.2	**Manufacturer/Supplier** (address, phone no., fax no., contact person)	ZSCHIMMER & SCHWARZ GmbH & Co KG Max-Schwarz-Str. 3 – 5 56112 LAHNSTEIN
1.3	**Raw material category** (e.g. anionic surfactant)	Solubilizer and emollient
1.4	**Chemical name**	Ethoxylated avocado oil
1.5	**INCI (CTFA) name Composition**	PEG-11 Avocado Glycerides
1.6	**EC (EINECS/ELINCS) no.**	Polymer
1.7	**CAS no.**	70914-02-2
1.8	**Registration status** (e.g. EU, USA, Japan)	EINECS, TSCA, NDSL, PICCS, ECL, IECSC, AICS (103819-44-9)

2.	Information on production	
2.1	**Origin of starting material** (plant, animal, synthetic)	Vegetable origin
2.2	**Is the starting material derived from genetically modified organisms (GMO)?**	No
2.3	**Information on production process** (general description)	Reaction of avocado oil with ethylene oxide

3.	Additives	
3.1	**Preservatives**	Not added
3.2	**Antioxidants**	Not added
3.3	**Solvents**	Not added
3.4	**Bleaching agents**	Not added
3.5	**Others**	Not added

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4.	Microbiological specification	
4.1	Total viable count (colony-forming units/g)	< 1000 colony-forming units/g

5.	By-products The presence of traces of the substances listed in Annex II of Directive 76/768/EEC (incl. cmr cat. I – III substances marked with *) shall be allowed provided that such presence is technically unavoidable in good manufacturing practice and that it conforms with Article 2 of Directive 76/768/EEC.	
5.1	1,4-Dioxane *	< 5 ppm
5.2	Ethylene oxide *	< 1 ppm
5.3	Residual solvents	Not added
5.4	Residual monomers	< 1 ppm
5.5	Amines	Not contained
5.6	Nitrosamines	Not contained
5.7	Heavy metals	Not determined
5.8	Monochloroacetic acid	Not contained
5.9	Dichloroacetic acid	Not contained
5.10	Allergens according to the 7th Amendment to the Cosmetics Directive (ppm)	Not contained
5.11	Others	

6.	Toxicology	
6.1	Information on acute toxicity	see 8.
6.2	Information on skin irritation	see 8.
6.3	Information on irritation of the mucous membrane	see 8.
6.4	Information on sensitisation potential	see 8.
6.5	Information on gene toxicity	see 8.
6.6	Information on percutaneous permeation	Not determined
6.7	Others	

7.	Ecology	
7.1	Degradability/Elimination	> 80 %
7.2	Acute aquatic toxicity	see 8.
7.3	Others	

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8.	**Additional information** (For details on specification see enclosed instruction sheet; for details on labelling and classification see enclosed safety data sheet.)	The toxicology is assumed to be comparable with products having the same or analogous chemical structure.
	PEG-15 Glyceryl Isostearate: acute oral toxicity:	LD 50: 29,76 ml/kg (rat, oral)
	PEG-10 Olive Glycerides: skin irritation:	Rabbit (3% active matter): non-irritant (Safepharm 9/82) Guinea pig, 50% active matter, 24 h application: no irritation observed (Sensitisation-Test, Notox 8/96)
	irritation of the mucous membrane:	Rabbit (3% active matter): non-irritant (Safepharm 9/82)
	sensitisation potential:	Guinea pig (50% active matter): no sensitisation (Notox 8/96)
	mutagenicity (Ames Test):	non-mutagenic (Safepharm 1/97)
	fish toxicity: daphnia toxicity:	LC50: > 100 mg/l after 96h (Leuciscus idus) EC50: >1000 mg/l after 24h
8.1	**Shelf life**	12 months

This information refers only to the above mentioned product and does not need to be valid if used with other product(s) or in any process. The information is to our best present knowledge correct and complete and is given in good faith but without warranty. It remains the user's own responsibility to make sure that the information is appropriate and complete for his specific use of this product.

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Raw material information

ZSCHIMMER & SCHWARZ
GmbH & Co KG
CHEMISCHE FABRIKEN
D-56112 LAHNSTEIN/RHEIN

Harmonized information on raw material identification according to TEGEWA (Version 2005)

Revision: 2815.007 / 07.2013
Date of printing: 23.07.2013

1.	General information	
1.1	**Trade name**	**OXYPON 401**
1.2	**Manufacturer/Supplier** (address, phone no., fax no., contact person)	ZSCHIMMER & SCHWARZ GmbH & Co KG Max-Schwarz-Str. 3 – 5 56112 LAHNSTEIN
1.3	**Raw material category** (e.g. anionic surfactant)	Solubilizer and emollient for cosmetics
1.4	**Chemical name**	Ethoxylated coconut oil
1.5	**INCI (CTFA) name Composition**	PEG-9 Cocoglycerides
1.6	**EC (EINECS/ELINCS) no.**	Polymer
1.7	**CAS no.**	68201-46-7
1.8	**Registration status** (e.g. EU, USA, Japan)	TSCA, EINECS, AICS, DSL, PICCS, ECL, IECSC

2.	Information on production	
2.1	**Origin of starting material** (plant, animal, synthetic)	Vegetable origin
2.2	**Is the starting material derived from genetically modified organisms (GMO)?**	No
2.3	**Information on production process** (general description)	Reaction of coconut oil with ethylene oxide

3.	Additives	
3.1	**Preservatives**	Not added
3.2	**Antioxidants**	Not added
3.3	**Solvents**	Not added
3.4	**Bleaching agents**	Not added
3.5	**Others**	Not added

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4.	Microbiological specification	
4.1	Total viable count (colony-forming units/g)	< 1000 colony-forming units/g

5.	By-products The presence of traces of the substances listed in Annex II of Regulation No. 1223/2009 (replaced Directive 76/768/EEC) (incl. cmr cat. I – III substances marked with *) shall be allowed provided that such presence is technically unavoidable in good manufacturing practice and that it conforms with Article 17 of Regulation No. 1223/2009.	
5.1	1,4-Dioxane *	max. 5 ppm
5.2	Ethylene oxide *	max. 1 ppm
5.3	Residual solvents	Not contained
5.4	Residual monomers	< 1 ppm
5.5	Amines	Not contained
5.6	Nitrosamines	Not contained
5.7	Heavy metals	Corresponds to recommendation of the BGA, Bundesgesundheitsblatt 28, No. 7, July 1985 and No. 4/1996 Pb <20 ppm, Ni <10 ppm, Cd <5 ppm, As <5 ppm, Sb <10 ppm, Hg <1 ppm
5.8	Monochloroacetic acid	Not contained
5.9	Dichloroacetic acid	Not contained
5.10	Allergens according to the 7th Amendment to the Cosmetics Directive (ppm)	Not contained
5.11	Others	

6.	Toxicology	
6.1	Information on acute toxicity	see 8.
6.2	Information on skin irritation	see 8.
6.3	Information on irritation of the mucous membrane	see 8.
6.4	Information on sensitisation potential	see 8.
6.5	Information on gene toxicity	see 8.
6.6	Information on percutaneous permeation	Not determined
6.7	Others	

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7.	Ecology	
7.1	**Degradability/Elimination**	> 90 %
7.2	**Acute aquatic toxicity**	see 8.
7.3	**Others**	

8.	**Additional information** (For details on specification see enclosed instruction sheet; for details on labelling and classification see enclosed safety data sheet.)	The toxicology is assumed to be comparable with products having the same or analogous chemical structure.
	PEG-15 Glyceryl Isostearate: acute oral toxicity:	LD 50: 29,76 ml/kg (rat, oral)
	PEG-10 Olive Glycerides: skin irritation:	Rabbit (3% active matter): non-irritant (Safepharm 9/82) Guinea pig, 50% active matter, 24 h application: no irritation observed (Sensitisation-Test, Notox 8/96)
	irritation of the mucous membrane:	Rabbit (3% active matter): non-irritant (Safepharm 9/82)
	sensitisation potential:	Guinea pig (50% active matter): no sensitisation (Notox 8/96)
	mutagenicity (Ames Test):	non-mutagenic (Safepharm 1/97)
	fish toxicity: daphnia toxicity:	LC50: > 100 mg/l after 96h (Leuciscus idus) EC50: >1000 mg/l after 24h
8.1	**Shelf life**	12 months

This Information refers only to the above mentioned product and does not need to be valid if used with other product(s) or in any process. The information is to our best present knowledge correct and complete and is given in good faith but without warranty. It remains the user's own responsibility to make sure that the information is appropriate and complete for his specific use of this product.

Concentration of Use by FDA Product Category – PEGylated Alkyl Glycerides*

PEG-6 Caprylic/Capric Glycerides
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-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-5 Hydrogenated Corn Glycerides
PEG-8 Hydrogenated Fish Glycerides
PEG-20 Hydrogenated Palm Glycerides
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

Ingredient	Product Category	Maximum Concentration of Use
PEG-6 Caprylic/Capric Glycerides	Bubble baths	0.38-5%
PEG-6 Caprylic/Capric Glycerides	Other bath preparations	0.63%
PEG-6 Caprylic/Capric Glycerides	Eyeliners	0.35%
PEG-6 Caprylic/Capric Glycerides	Mascaras	0.35%
PEG-6 Caprylic/Capric Glycerides	Shampoos (noncoloring)	0.000002-0.6%
PEG-6 Caprylic/Capric Glycerides	Tonics, dressings and other hair grooming aids	0.1-3.5%
PEG-6 Caprylic/Capric Glycerides	Hair rinses (coloring)	1.9%
PEG-6 Caprylic/Capric Glycerides	Bath soaps and detergents	0.3-0.75%
PEG-6 Caprylic/Capric Glycerides	Other personal cleanliness products	0.0002-0.22% (rinse-off)
PEG-6 Caprylic/Capric Glycerides	Aftershave lotions	0.2-0.5%
PEG-6 Caprylic/Capric Glycerides	Skin cleansing	0.24-5%
PEG-6 Caprylic/Capric Glycerides	Face and neck products not spray	0.75%
PEG-6 Caprylic/Capric Glycerides	Body and hand products	

	not spray	0.13%
PEG-6 Caprylic/Capric Glycerides	Other skin care preparations	0.3% (rinse-off)
PEG-20 Almond Glycerides	Tonics, dressings and other hair grooming aids	0.01%
PEG-60 Almond Glycerides	Eye shadow	0.01%
PEG-60 Almond Glycerides	Other eye makeup preparations	0.2% (leave-on)
PEG-60 Almond Glycerides	Hair conditioners	0.05%
PEG-60 Almond Glycerides	Hair sprays aerosol pump spray	 0.5% 0.2%
PEG-60 Almond Glycerides	Hair straighteners	0.1%
PEG-60 Almond Glycerides	Shampoos (noncoloring)	0.1-1%
PEG-60 Almond Glycerides	Tonics, dressings and other hair grooming aids	0.05-1%
PEG-60 Almond Glycerides	Hair dyes and colors	0.25%
PEG-60 Almond Glycerides	Bath soaps and detergents	0.05-1%
PEG-60 Almond Glycerides	Aftershave lotions	0.5%
PEG-60 Almond Glycerides	Skin cleansing	0.001-1.8%
PEG-60 Almond Glycerides	Face and neck products not spray	 0.01-2%
PEG-60 Almond Glycerides	Body and hand products not spray	 0.005-3.2%
PEG-60 Almond Glycerides	Moisturizing products not spray	 0.001-0.3%
PEG-60 Almond Glycerides	Paste masks and mud packs	0.001%
PEG-60 Almond Glycerides	Skin fresheners	0.001%
PEG-60 Almond Glycerides	Other skin care preparations	0.0001-2.8% (leave-on) 6.5% (rinse-off)
PEG-60 Almond Glycerides	Indoor tanning preparations	0.3%
PEG-192 Apricot Glycerides	Moisturizing products not spray	 0.1%
PEG-7 Caprylic/Capric Glycerides	Face and neck products not spray	 2%
PEG-7 Caprylic/Capric Glycerides	Moisturizing products not spray	 2%
PEG-20 Hydrogenated Palm Glycerides	Eyebrow pencil	1.2%
PEG-20 Hydrogenated Palm Glycerides	Eyeliner	0.26%
PEG-20 Hydrogenated Palm Glycerides	Moisturizing products not spray	 0.82%
PEG-20 Hydrogenated Palm Glycerides	Suntan products not spray	 0.23%
PEG-16 Macadamia Glycerides	Bath soaps and detergents	0.05%
PEG-16 Macadamia Glycerides	Skin cleansing products	0.1%

PEG-70 Mango Glycerides	Shampoos (noncoloring)	0.1%
PEG-70 Mango Glycerides	Tonics, dressings and other hair grooming aids	0.05%
PEG-70 Mango Glycerides	Other hair preparations (noncoloring)	0.01%
PEG-10 Olive Glycerides	Shampoos (noncoloring)	0.5%
PEG-10 Olive Glycerides	Tonics, dressings and other hair grooming aids	0.2%
PEG-10 Olive Glycerides	Deodorants not spray	0.02%
PEG-10 Olive Glycerides	Moisturizing products not spray	0.02%
PEG-45 Palm Kernel Glycerides	Other hair preparations (noncoloring)	5%
PEG-45 Palm Kernel Glycerides	Body and hand products Not spray	0.92%
PEG-45 Palm Kernel Glycerides	Paste masks and mud packs	0.5%
PEG-45 Palm Kernel Glycerides	Suntan products pump spray	1.9%
PEG-75 Shea Butter Glycerides	Perfumes	0.005%
PEG-75 Shea Butter Glycerides	Hair conditioners	0.4%
PEG-75 Shea Butter Glycerides	Hair sprays pump spray	0.15%
PEG-75 Shea Butter Glycerides	Shampoos (noncoloring)	0.1-0.3%
PEG-75 Shea Butter Glycerides	Bath soaps and detergents	0.1%
PEG-75 Shea Butter Glycerides	Other personal cleanliness products	0.4%
PEG-75 Shea Butter Glycerides	Skin cleansing	0.5-1%
PEG-75 Shea Butter Glycerides	Face and neck products not spray	1%
PEG-75 Shea Butter Glycerides	Foot products	0.1%
PEG-75 Shea Butter Glycerides	Moisturizing products not spray	0.01%
PEG-10 Sunflower Glycerides	Tonics, dressings and other hair grooming aids	5%
PEG-10 Sunflower Glycerides	Hair shampoos (coloring)	0.8%
PEG-10 Sunflower Glycerides	Skin cleansing	2.5%

*Ingredients included in the title of the table, but not found in the table were included in the concentration of use survey, but no uses were reported.

Informatiopn collected in 2014

Table prepared April 18, 2014

Updated May 12, 2014: PEG-45 Palm Kernel Glycerides deleted 50% Perfume added Body and hand products

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 15, 2014

SUBJECT: Concentration of Use by FDA Product Category: PEG-6 Hydrogenated Palm/Palm Kernel Glyceride

PEG-6 Hydrogenated Palm/Palm Kernel Glyceride was included in a Council concentration of use survey. No uses of this ingredient were reported.

Concentration of Use by FDA Product Category*

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/PPG-6/2 Glyceryl Cocoate
PPG/PEG-2/10 Glyceryl Cocoate

Ingredient	**Product Category**	**Maximum Concentration of Use**
PEG-7 Glyceryl Cocoate	Eye lotion	0.02%
PEG-7 Glyceryl Cocoate	Other fragrance preparations	6%
PEG-7 Glyceryl Cocoate	Shampoos (noncoloring)	0.36-2%
PEG-7 Glyceryl Cocoate	Tonics, dressings and other hair grooming aids	0.18-5.5%
PEG-7 Glyceryl Cocoate	Hair dyes and colors	2.5-4.6%
PEG-7 Glyceryl Cocoate	Other hair coloring preparations	1.8%
PEG-7 Glyceryl Cocoate	Nail polish and enamel removers	0.5%
PEG-7 Glyceryl Cocoate	Bath soaps and detergents	0.5-3%
PEG-7 Glyceryl Cocoate	Deodorants not spray pump spray	 3% 2%
PEG-7 Glyceryl Cocoate	Other personal cleanliness products	1-6.9%
PEG-7 Glyceryl Cocoate	Aftershave lotions	2%
PEG-7 Glyceryl Cocoate	Shaving cream	2%
PEG-7 Glyceryl Cocoate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01-4.8%
PEG-7 Glyceryl Cocoate	Depilatories	5%
PEG-7 Glyceryl Cocoate	Face and neck products not spray	 0.35-3.5%
PEG-7 Glyceryl Cocoate	Body and hand products not spray	 1%
PEG-7 Glyceryl Cocoate	Moisturizing products not spray	 0.02-0.4%
PEG-7 Glyceryl Cocoate	Paste masks and mud packs	1%
PEG-7 Glyceryl Cocoate	Other skin care preparations	1-2%
PEG-30 Glyceryl Cocoate	Hair conditioners	0.72-1%
PEG-30 Glyceryl Cocoate	Shampoos (noncoloring)	1%
PEG-30 Glyceryl Cocoate	Tonics, dressings and other hair grooming aids	0.1%
PEG-30 Glyceryl Cocoate	Other personal cleanliness products	3%
PEG-30 Glyceryl Cocoate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.09-0.85%
PEG-30 Glyceryl Cocoate	Face and neck products not spray	 0.5-2.4%
PEG-30 Glyceryl Cocoate	Moisturizing products not spray	 0.5-2.3%
PEG-30 Glyceryl Cocoate	Paste masks and mud packs	0.5%
PEG-40 Glyceryl Cocoate	Eye makeup remover	0.88%

PEG-40 Glyceryl Cocoate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	3.5-4.8%
PEG-80 Glyceryl Cocoate	Other personal cleanliness products	0.1%
PEG-80 Glyceryl Cocoate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2014

Table prepared August 8, 2014

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: July 9, 2014

SUBJECT: Information on Products Containing PEG Alkyl Glycerides

Peritesco. 2004. Ocular and cutaneous tolerance study of self foaming cleansers containing 1% PEG-75 Shea Butter Glycerides.

Consumer Product Testing Co. 2013. The hen's egg test - utilizing the chorioallantoic membrane (HET-CAM) of a hair stying product containing 11% PEG-7 Glyceryl Cocoate.

TKL Research. 2013. Repeated insult patch test of a hair stying product containing 11% PEG-7 Glyceryl Cocoate.

Harrison Research Laboratories, Inc. 2008. Repeated insult patch test of a hair setting lotion containing 1% PEG-75 Shea Butter Glycerides.

Consumer Product Testing Co. 2005. Safety in use of a female hygiene product containing 0.1% PEG-75 Shea Butter Glycerides.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

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PERITESCO
Centre de Recherche Biomédicale

REPORT

OCULAR AND CUTANEOUS TOLERANCE STUDY OF I ... PRODUCTS "NETTOYANTS MOUSSANTS R ..." (1% PEG-75 Sheabutter glycerides) " PERFORMED IN AT LEAST 10 SUBJECTS DURING 5 DAYS

SPONSOR	INVESTIGATOR
ADDRESS	
[redacted]	PERITESCO 4, rue Villédo 75001 PARIS
STAFF IN CHARGE OF THIS STUDY	
[redacted]	Study director and main investigator: Dr. M. PERICOI Ophthalmologist Co-investigator: Dr. S. LAQUIEZE Dermatologist
REFERENCE	
	2760-43-OD

d

[redacted]

Document consisting of 151 pages

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REPORT DEVELOPMENT

Dr. M. PERICOI:	Main Investigator Ophthalmologist D.E.A of Dermopharmacy Clinical Toxicology and Pharmacology Degree Clinical Expert (Decree of June, 29th 1985)
Dr. S. LAQUIEZE:	Co-investigator Dermatologist Expert in clinical study: Phase I, II et III in Dermatology and Cosmetology Clinical Expert (Decree of the 29th of June, 1985)
Mrs. A. LADURELLE:	Study Director
Mrs. C. GAUTHIER:	Clinical Research Assistant Report Writing Quality Control Manager
Mr. S. LOURDEZ:	Data Control Manager Statistical Analysis Manager

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13-39 not required

49-54 not required

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[redacted]

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CERTIFICATE OF QUALITY POLICY

TITLE: OCULAR AND CUTANEOUS TOLERANCE STUDY OF FOUR PRODUCTS "NETTOYANTS MOUSSANTS (1% PEG-75 Shea butter glycerides in self foaming cleanser) _____ _/' PERFORMED IN AT LEAST 10 SUBJECTS DURING 5 DAYS

REFERENCE: 2760-43-OD

PRODUCTS: NETTOYANTS MOUSSANTS (1% PEG-75 Shea butter glyceridesin self foaming cleanser)

MAIN INVESTIGATOR: Dr M. PERICOI, Ophthalmologist

To my knowledge, the study described in this report was carried out according to the protocol, to PERITESCO Standard Operating Procedures and to the standards of the Good Clinical Practice Guidelines according to the FDA (62 FR 25692 of May 9, 1997), to the EEC (Directive n° 2001/20/CE of April 4, 2001) and to the Ministry of Health of the French Republic (Decree n° 97-888 of October 1, 1997).

Every data observed and event recorded during the study is mentioned in this report.

No event affecting the quality or integrity of the data occurred.

Miss M. Hering
Quality Policy
PERITESCO

04.11.04
date

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CERTIFICATE OF QUALITY CONTROL

TITLE: OCULAR AND CUTANEOUS TOLERANCE STUDY OF FOUR PRODUCTS "NETTOYANTS MOUSSANTS((1% PEG-75 Shea butter glycerides in [redacted] self foaming cleanser) PERFORMED IN AT LEAST 10 SUBJECTS DURING 5 DAYS

REFERENCE: 2760-43-OD

PRODUCTS: NETTOYANTS MOUSSANTS (1% PEG-75 sheabutter glycerides in self foaming cleanser)

MAIN INVESTIGATOR: Dr M. PERICOI, Ophthalmologist

An audit checked that the report presents the raw data of the study.

All the controls on the data veracity and conformity with the protocol were performed at each step of the study:

Control	Date	Controlled by
Protocol Conformity	16/06/2004	AL
Case report form	23/06/2004	SL
Clinical data	20/07/2004	CG
First results	23/07/2004 29/07/2004	SL GC
Report	14/10/2004	SL

Mr. S. LOURDEZ
Quality Control Service
PERITESCO

4/11/04
date

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METHODOLOGY

I. STUDY DESCRIPTION

I.1. Products under study.

The products were supplied by

These products had the following characteristics:

Products denomination	NETTOYANTS MOUSSANTS ((1% PEG-75 Shea butter glycerid[redacted]s)
Presentation	Liquids
Packaging	Pump flask
Supplied quantity	12 samples of each product
Date of receipt	14 June 2004
Storage	Between 15°C and 25°C.

I.2. Clinical methods.

I.2.1. Aim of the study.

The aim of the study was to evaluate and to compare the ocular and cutaneous tolerance of the products under the normal conditions of use, as foreseen by the sponsor, under ophthalmologic and dermatological control.

I.2.2. Study design.

* Location: The study was carried out at the clinical unit of Paris.

* Design: The study was open and randomized.

The randomization table is presented in Appendix III.

I.2.3. Subjects participating in the study.

Ten volunteers completed the whole study. The following table gives information about the participation in the study of all the retained subjects.

	Not included	Included	Stopped during the study
Number of subjects		11	1 (subject n° 4)
Reason			Personal reasons
Day of occurrence			Session 4

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The selected subjects fulfilled the study inclusion criteria (voluntary female subjects, aged over 18 years old, with sensitive skin and eyes).

The average age of the subjects was:

Age: 60.2 ± 6.9 years old (extreme values: 46 - 69 years).

The following table presents the subjects characteristics.

Characteristics		PERCENTAGE OF SUBJECTS
Ocular sensitivity	Sensitive eyes	100%
Cutaneous sensitivity	Sensitive skin	100%
Nature of skin	Combination skin	40%
	Normal	10%
	Dry	50%

The subjects individual characteristics are presented in Appendix IV.

I.3. Protocol amendment.

No protocol amendment was requested.

I.4. Protocol deviation.

The study was conducted according to the protocol specifications.

II. STUDY SCHEDULE.

At each session, the study schedule was the following:

II.1. Initial Time T0.

Before the first application of the product:

- The ophthalmologist practiced:
* a functional signs investigation,
* a biomicroscopic examination of the ocular structures,
* a fluorescein staining of the cornea and the conjunctiva,
* a tear film break-up time measurement.

- The dermatologist practiced:
* a cutaneous functional signs investigation,
* a dermatological examination of the face.

Every observation is reported in the case report form.

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II.2. Initial Time TA+10 min.

Ten minutes after the first application:

- The ophthalmologist practiced:
* a functional signs investigation,
* a biomicroscopic examination of the ocular structures,
* a fluorescein staining of the cornea and the conjunctiva,
* a tear film break-up time measurement.

The dermatologist practiced:
* a cutaneous functional signs investigation,
* a dermatological examination of the face.

Every observation is reported in the case report form.

II.3. Final Time T0

Before the last application:

- The ophthalmologist practiced:
* a functional signs investigation,
* a biomicroscopic examination of the ocular structures,
* a fluorescein staining of the cornea and the conjunctiva.

- The dermatologist practiced:
* a cutaneous functional signs investigation,
* a dermatological examination of the face.

Every observation is reported in the case report form.

II.4. Final Time TA+10 min.

Ten minutes after the last application:

- The ophthalmologist practiced:
* a functional signs investigation,
* a biomicroscopic examination of the ocular structures,
* a fluorescein staining of the cornea and the conjunctiva.

- The dermatologist practiced:
* a cutaneous functional signs investigation,
* a dermatological examination of the face.

Every observation is reported in the case report form.

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III. PRODUCTS APPLICATION.

During each session, the product was used as follows:

Application area	The whole face including the eyes
Applied quantity	Usual and necessary quantity for this kind of product
Frequency	Twice a day
Duration	5 days
Conditions of use	The 4 foaming cleansers were tested by the same voluntary subjects panel: 4 sessions of 5 days. During each session, the product attributed according to the randomization table, was applied on the whole face including the eyes, twice a day during 5 days.
Study constraints	Allowed: - Usual face care products - Light face make-up (powder and blush) except when coming to the clinical unit for the control visits - Lip make-up Not allowed: - Any other face cleansers or make-up removers - Any eye make-up

IV. REGULATORY CONSIDERATIONS.

IV.1. Regulations

The study, without any direct therapeutic aim, was carried out according to the most recent recommendations of the World Medical Association (Helsinki Declaration of 1964, amended in Tokyo in 1975, Venice in 1983, Hong-Kong in 1989, Somerset West in 1996 and Edinburgh in 2000). As this study is not concerned with the French law n° 88-1138 of December 20, 1988 about the protection of subjects involved in biomedical research, modified by the laws n°91-73 of January 18, 1991, n°92-1336 of December 16, 1992, n°93.5 of January 4, 1993, n°94-630 of July 25, 1994 and the edict n°2000-548 of June 15, 2000, the CCPPRB authorization was not required. However, the spirit of the decree n° 97-888 of October 1, 1997 concerned with the enforcement of this law was respected.

The products did not contain and were not derived from material with specific risks as defined by the Commission decision n° 2000/418/CE, modified by the Commission decision n°2001/2/CE.

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* Initial Time TA+10 min:

N°	Code	Dryness (Gr)	Roughness (Gr)
1	IELGI	1	0
2	BIJEL	1	0
5	LEDMA	0	1
6	NEMMA	1	0
9	GOFNI	2	2

* Final Time T0:

N°	Code	Dryness (Gr)	Roughness (Gr)
1	IELGI	1	0
2	BIJEL	1	0
3	CALME	0	1
5	LEDMA	0	1
6	NEMMA	1	0
8	CHACL	1	0
9	GOFNI	1	1
11	BITSA	0	1

* Final Time TA+10 min:

N°	Code	Dryness (Gr)	Roughness (Gr)
6	NEMMA	1	0
11	BITSA	0	1

The results are presented in Appendix VII.

XII.3. Unexpected event.

No unexpected event was reported by the volunteers nor observed by the investigator.

XIII. PRODUCT WEIGHING

The products were weighed before and after 5 days of use.

The average quantity of used product was:

- Quantity of product: 15.77 ± 18.24 (extreme values: 3.7 – 66.7 g), i.e. 3.15 g a day and per subject.

The products weighing table is presented in Appendix VII.

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XIV. OPHTHALMOLOGIC RESULTS.

XIV.1. Clinical results.

XIV.1.1. Functional signs.

The following table presents the functional signs which appeared during the study.

	Nb of occurrences	Nb of subjects	Freq. %	Average intensity	Gr1	Gr2	Gr3	Delay min	Duration min	Irritation freq. %	Total irritation frequency
Ocular stinging	0	0	0.00	0.0	0	0	0	0.00	0.00	0.00	0.00
Ocular burning	0	0	0.00	0.0	0	0	0	0.00	0.00	0.00	
Foreign body feeling	0	0	0.00	0.0	0	0	0	0.00	0.00		
Blur	0	0	0.00	0.0	0	0	0	0.00	0.00		
Palpebral stinging	0	0	0.00	0.0	0	0	0	0.00	0.00		
Other signs	0	0	0.00	0.0	0	0	0	0.00	0.00		

The ocular irritation occurrences regroup the following functional signs: ocular stinging and burning with an intensity and/or duration meaning an irritation.

The objective contact rate noticed by the investigator is 0.00% (of the applications). The subjective contact rate (product entered in the eye reported and felt by the subjects during the applications) is 0.00%.

The results table are presented in Appendix VIII.

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XIV.1.2. Physical signs.

The following tables present the physical signs which appeared during the study.

		INITIAL TIME T0		INITIAL TIME TA+10 min					
		Average grade	Nb of occ.	Average grade	Nb of occ.	Gr 1	Gr 2	Gr 3	Bilateral occ.
Seborrheic hypersecretion	right	1.0	10	1.0	10	10	0	0	10
	left	1.0	10	1.0	10	10	0	0	
Lid margin	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Bulbar redness	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Conjunctival pallor	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Papillae	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Folliculosis	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	

		FINAL TIME T0		FINAL TIME TA+10 min					
		Average grade	Nb of occ.	Average grade	Nb of occ.	Gr 1	Gr 2	Gr 3	Bilateral occ.
Seborrheic hypersecretion	right	1.0	10	1.0	10	10	0	0	10
	left	1.0	10	1.0	10	10	0	0	
Lid margin	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Bulbar redness	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Conjunctival pallor	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Papillae	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Folliculosis	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	

Legend: occ.: occurrence

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The following table presents the number of subjects who showed corneal cells loss.

	Total number of corneal cells loss	Nb	Surface (Grade 0 to 10)	Depth (Grade 0 to 3)
Initial Time T0	0			
Initial Time TA+10 min	0			
Final Time T0	0			
Final Time TA+10 min	0			

The following table presents the physical signs observed at each time of examination.

N°	Code	Seborrheic hypersecretion (Gr)
1	IELGI	1
2	BIJEL	1
3	CALME	1
5	LEDMA	1
6	NEMMA	1
7	BOUYO	1
8	CHACL	1
9	GOFNI	1
10	VETMA	1
11	BITSA	1

The clinical results are presented in Appendix VIII.

XIV.1.3. Unexpected event.

No unexpected event was observed by the investigator nor reported by the volunteers.

XIV.2. Tear film break-up time measurement.

The comparison between individual levels of break-up times before and after application was carried out using a match paired Student test (p = 5%).

The following table regroups the results:

	B.U.T. values (seconds)		Statistics	
	Initial Time T0	Initial Time TA+10 min	Initial Time T0/ Initial Time TA+ 10 min	Difference
Results	5.10 ± 0.88	4.90 ± 1.37	P= 0.555	Not significant

The results of the break-up time measurements are presented in Appendix VIII.

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XIV.3. Fluorescein staining.

The following tables present the colorimetric indexes obtained at different times:

* Initial Time T0:

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate (%)	0%	0%	0%	0%
Conjunctival rate (%)	0%			
Corneal rate (%)			0%	

* Initial Time TA+10 min:

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	1 Grade 1 1 Grade 2
Rate (%)	0%	0%	0%	3%
Conjunctival rate (%)	0%			
Corneal rate (%)			3%	

* Final Time T0:

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate (%)	0%	0%	0%	0%
Conjunctival rate (%)	0%			
Corneal rate (%)			0%	

* Final Time TA+10 min:

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate (%)	0%	0%	0%	0%
Conjunctival rate (%)	0%			
Corneal rate (%)			0%	

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* Results of colorimetric global indexes of the product (difference between the colorimetric index Initial Time TA+10 min and Initial Time T0 and between Final Time TA+10 min and Final Time T0):

	Results
Maximal conjunctival index	0.00%
Maximal corneal index	3.00%

XV. DERMATOLOGICAL RESULTS.

XV.1. Functional signs

The following tables present the functional signs observed during the study at the different times.

* Initial Time T0:

	Nb of occurrences	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous stinging	0	0.0	0.00	0	0	0	0
Pruritus	0	0.0	0.00	0	0	0	0
Burning feeling	0	0.0	0.00	0	0	0	0
Discomfort feeling	1	10.0	1.00	1	0	0	0
Tugging feeling	1	10.0	1.00	1	0	0	0

* Initial Time TA+10 min:

	Nb of occurrences	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4	Duration grade
Cutaneous stinging	0	0.0	0.00	0	0	0	0	0.0
Pruritus	0	0.0	0.00	0	0	0	0	0.0
Burning feeling	0	0.0	0.00	0	0	0	0	0.0
Discomfort feeling	0	0.0	0.00	0	0	0	0	
Tugging feeling	0	0.0	0.00	0	0	0	0	

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*** Final Time T0:**

	Nb of occurrences	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4	Duration grade
Cutaneous stinging	0	0.0	0.00	0	0	0	0	0.0
Pruritus	0	0.0	0.00	0	0	0	0	0.0
Burning feeling	0	0.0	0.00	0	0	0	0	0.0
Discomfort feeling	0	0.0	0.00	0	0	0	0	
Tugging feeling	0	0.0	0.00	0	0	0	0	

*** Final Time TA+10 min:**

	Nb of occurrences	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4	Duration grade
Cutaneous stinging	0	0.0	0.00	0	0	0	0	0.0
Pruritus	0	0.0	0.00	0	0	0	0	0.0
Burning feeling	0	0.0	0.00	0	0	0	0	0.0
Discomfort feeling	0	0.0	0.00	0	0	0	0	
Tugging feeling	0	0.0	0.00	0	0	0	0	

The following tables present the subjects who showed functional signs at Initial Time T0:

N°	CODE	Discomfort feeling (Gr)	Tugging feeling (Gr)
7	BOUYO	1	0
8	CHACL	0	1

The results are presented in Appendix VIII.

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XV.2. Physical signs

The following tables present the physical signs observed during the study at the different times.

*** Initial Time T0:**

	Nb of occurrence	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	0	0.0	0.00	0	0	0	0
Dryness	5	50.0	1.00	5	0	0	0
Roughness	6	60.0	1.00	6	0	0	0
Desquamation	1	10.0	1.00	1	0	0	0

*** Initial Time TA+10 min:**

	Nb of occurrences	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	0	0.0	0.00	0	0	0	0
Dryness	2	20.0	1.00	2	0	0	0
Roughness	0	0.0	0.00	0	0	0	0
Desquamation	1	10.0	1.00	1	0	0	0

*** Final Time T0:**

	Nb of occurrences	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	0	0.0	0.00	0	0	0	0
Dryness	3	30.0	1.00	3	0	0	0
Roughness	4	40.0	1.00	4	0	0	0
Desquamation	1	10.0	1.00	1	0	0	0

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*** Final Time TA+10 min:**

	Nb of occurrences	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	0	0.0	0.00	0	0	0	0
Dryness	2	20.0	1.00	2	0	0	0
Roughness	2	20.0	1.00	2	0	0	0
Desquamation	1	10.0	1.00	1	0	0	0

The following table presents the subjects who showed physical signs:

*** Initial Time T0:**

N°	Code	Dryness (Gr)	Roughness (Gr)	Desquamation (Gr)
1	IELGI	0	1	0
2	BIJEL	1	1	0
3	CALME	1	0	0
5	LEDMA	0	1	0
6	NEMMA	0	1	0
7	BOUYO	1	0	0
8	CHACL	1	0	1
9	GOFNI	1	1	0
10	VETMA	0	1	0

*** Initial Time TA+10 min:**

N°	Code	Dryness (Gr)	Desquamation (Gr)
2	BIJEL	1	0
3	CALME	1	0
11	BITSA	0	1

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* Final Time T0:

N°	Code	Dryness (Gr)	Roughness (Gr)	Desquamation (Gr)
1	IELGI	0	1	0
2	BIJEL	1	0	0
3	CALME	1	0	0
5	LEDMA	0	1	0
6	NEMMA	0	1	0
8	CHACL	1	0	0
10	VETMA	0	1	0
11	BITSA	0	0	1

* Final Time TA+10 min:

N°	Code	Dryness (Gr)	Roughness (Gr)	Desquamation (Gr)
1	IELGI	0	1	0
3	CALME	1	0	0
6	NEMMA	0	1	0
8	CHACL	1	0	0
11	BITSA	0	0	1

The results are presented in Appendix VIII.

XV.3. Unexpected event.

No unexpected event was reported by the volunteers nor observed by the investigator.

XVI. PRODUCT WEIGHING

The products were weighed before and after 5 days of use.

The average quantity of used product was:

- Quantity of product: 17.54 ± 20.74 (extreme values: 4.0 – 68.9 g), i.e. 3.51 g a day and per subject.

The products weighing table is presented in Appendix VIII.

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[redacted]

XVII.4.NETTOYANT MOUSSANT REF. 691100/1.

XVII.4.1.Ophthalmological results.

XVII.4.1.1.Functional signs.

The following table presents the frequency of functional signs.

Functional signs	Frequency
Ocular irritation functional signs	0.00%
Mechanical ocular functional signs	0.00%
Physico-chemical ocular functional signs	0.00%
Palpebral functional signs	0.00%

The product did not induce any ocular or palpebral functional signs.

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The contact rate with eyes is 0.00%, which is very good for this kind of product.

XVII.4.1.2.Physical signs.

The product did not induce any physical signs, which shows the product has **neither a conjunctival nor a corneal irritant potential.**

XVII.4.1.3.Additional investigations.

- **Tear film stability.**

The product did not significantly modify the tear film stability (the B.U.T. value decreases from 5.10 to 4,90). The product therefore **respects the ocular surface defence abilities.**

- **Staining evaluations.**

The staining evaluation revealed a maximal corneal staining index of 3.00% and a maximal conjunctival staining index of 0.00%, which shows an **absence of toxicity of the product to the conjunctiva and a very slight irritant potential to the cornea.**

XVII.4.1.4.Results summary.

The product shows an ocular irritation rate of 3.00/2,000 i.e. 0.15% and an ocular comfort rate of 500.00/500 i.e. 100.00%.

The following table summarizes the results obtained.

Items		Results
Functional signs	Irritant ocular	0.00%
	Mechanical ocular	0.00%
	Physico-chemical ocular	0.00%
	Palpebral	0.00%
Physical signs	Conjunctival redness	No occurrence
	Corneal cells loss	No occurrence
B.U.T.		Initial Time T0: 5.10 seconds Initial Time TA+10 min: 4.90 seconds Not significant modification
Staining evaluation	Maximal conjunctival index	0.00%
	Maximal corneal index	**3.00%**
Ocular irritation rate		0.15%
Ocular comfort rate		100.00%

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The analysis of the impact the product has on the ocular structures shows the followings:

Product kinetics	Practically nil contact
Remanence on tear film	Unknown
Corneal epithelium	Very slightly irritant
Bulbar conjunctiva	Non toxic
Conjunctival epithelium	Non toxic
Lid margin	Non toxic
Contact lens compatibility	Unknown
Functional tolerance	Very good
Product chronic use	No foreseeable risk

The functional and physical signs analysis allows to consider that the product shows a very slight ocular irritant potential, normal for this type of product.

XVII.4.2. Dermatological results.

The following table presents **the new signs** which appeared during the observation period.

	Occurrence number	% of subject	Average intensity	Gr 1	Gr 2	Gr 3	Gr 4
Desquamation	**3**	**10.0**	**1.0**	**3**	0	0	0

The following table presents the **evolution of the signs** already existing on the Initial Time T0.

		% of occurrences		
	Occurrence number	Increase	Decrease	No change
Discomfort feeling	1	0.0	**100.0**	0.0
Tugging feeling	**1**	0.0	**100.0**	0.0
Dryness	**5**	0.0	**40.0**	**60.0**
Roughness	**6**	0.0	**33.3**	**66.7**
Desquamation	**1**	0.0	**100.0**	0.0

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Safety

No significant clinical manifestation of intolerance or allergy induced any premature withdrawal from the study.

* Functional signs

The product did not induce any functional sign of irritation.

* Physical signs

The product did not induce any irritation physical sign.

* Conclusion

Considering these observations, the product presents a very good safety of use and a practically nil cutaneous irritant potential in the conditions of this study.

Comfort

Functional signs

*New signs

The product did not induce any functional sign of discomfort.

*Evolution of the pre-existing signs

100% of the tugging and discomfort feelings present in the beginning of the study decreased during the observation period.

Physical signs

*New signs

The product induced a desquamation (physical sign showing a modification of the cutaneous state) in 1 subject (n° 11) with a very slight intensity.

*Evolution of the pre-existing signs

100% of the physical signs present in the beginning of the study decreased or remain unchanged during the observation period.

Comments

10% of subjects presented physical signs showing a modification of the cutaneous state, which is acceptable for this type of product used twice a day by subjects with sensitive skin.

Conclusion

Considering these observations, the product is regarded as comfortable under the conditions of this study.

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Globally, none of the products present any risk of use in the conditions of this study. They present a good ocular and cutaneous safety and a good ocular and cutaneous comfort.

IX CONCLUSION.

[redacted]

In the conditions of the study, the product "GEL NETTOYANT (1% PEG-75 Sheabutter glycerides)

- Presents a **very good ocular comfort**, a **good ocular safety** and a **very good global ocular tolerance** in subjects with sensitive eyes,
- Presents a **good cutaneous tolerance** in subjects with sensitive skin.

XVIII. SIGNATURES.

IN AGREEMENT WITH THIS REPORT.

Dr. M. PERICOI
Main investigator
PERITESCO

04.11.04
date

Dr. S. LAQUIEZE
Co-investigator
PERITESCO

04.11.04
date

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Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT: [redacted]

ATTENTION: [redacted] I.D.

TEST: The Hen's Egg Test - Utilizing the Chorioallantoic Membrane (HET-CAM)

TEST ARTICLE: Hair styling Product (11% PEG-7 Glyceryl cocoate)

EXPERIMENT REFERENCE NO.: V13-0280-1

2/6/13

Steven Nitka
Vice President
Laboratory Director

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Consumer Product Testing Co.
EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: V13-0280-1

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed in accordance with standard operating procedures and applicable standard protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study. The findings of this inspection may have been reported to management and the Study Director.

Quality Assurance:

Christine Hendricks 2/6/13
Signature/Date

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

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Objective:

To evaluate the test article for irritancy potential utilizing the HET-CAM test. The test is a modification of that described by Kemper and Luepke.[1]

Introduction:

The chick embryo has been used extensively in toxicology. "The chorioallantoic membrane (CAM) of the chick embryo is a complete tissue with organoid elements from all germ cell layers. The chorionic epithelium is ectodermal and the allantoic epithelium is endodermal. The mesoderm located between these epithelia is a complete connective tissue including arteries, capillaries, veins and lymphatic vessels. The CAM responds to injury with a complete inflammatory reaction, comparable to that induced in the rabbit eye test. It is technically easy to study, and is without nerves to sense pain."[2]

Test Article: Hair styling product (11% PEG-7 Glyceryl cocoate)

Reference Articles: . Alcohol-Free Spray-On Gel
: Alcohol-Free Sculpting Gel

Assay Date: January 18, 2013

[1]Kemper, F.H. & Luepke, N.P., (1986). The HET-CAM Test: An Alternative to the Draize Test. *FD Chem. Toxic.* 24, p. 495 - 496.

[2]Leighton, J., Tchao, R., Verdone, J. & Nassauer, J. Macroscopic Assay of Focal Injury in the Chorioallantoic Membrane. In: *Alternative Methods in Toxicology*, Vol. 3, *In Vitro* Toxicology E2, pp. 357 - 369, Alan M. Goldberg, (ed.), Mary Ann Liebert Publishers, Inc., New York, 1985.

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Method:

White Leghorn eggs were obtained from Moyer's Chicks, Inc., in Quakertown, Pennsylvania. For incubation at this facility, the eggs were placed in a Kuhl, humidified incubator. The incubator is such that the eggs are automatically rotated once every hour. The temperature was controlled at 37° C (± 2° C). On day eight (8) the eggs were turned so that the acutely angled end faced down.

On day ten (10) each egg was removed from the incubator and placed in a Plexiglas work enclosure. This enclosure had been preheated and humidified so that its environment approached that of the incubator. A cut was made in the larger end of each egg, where the air sack is located. A Dremel® Moto-Flex Tool (model 232-5) equipped with a Dremel® Cut-Off Wheel (No. 409) was used to make each cut. Forceps were then used to remove the shell down to the shell-membrane junction. The inner egg membrane was then hydrated with a warm, physiological saline solution. The saline was removed after a two (2) to five (5) minute exposure. Utilizing pointed forceps, the inner egg membrane was then carefully removed to reveal the CAM.

The test or reference article, at a dosage of three-tenths of one milliliter (0.3 ml) of a liquid or three-tenths of one gram (0.3 g) of a solid, was then administered to each of four (4) CAM's. Twenty seconds later, the test or reference article was rinsed from each CAM with five (5) milliliters of physiological saline. All CAM's were observed immediately prior to test article administration and at 30 seconds, two (2) and five (5) minutes after exposure to the test article. The reactions of the CAM, the blood vessels, including the capillaries, and the albumin were examined and scored for irritant effects as detailed below:

		Score		
Effect	**Time (min.)**	**0.5**	**2**	**5**
Hyperemia		5	3	1
Minimal Hemorrhage ("Feathering")		7	5	3
Hemorrhage (Obvious Leakage)		9	7	5
Coagulation and/or Thrombosis		11	9	7

The numerical, time dependent scores were totaled for each CAM. Each reaction type can be recorded only once for each CAM, therefore the maximum score per CAM is 32. The mean score was determined for all CAM's similarly tested.

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Results:

Test Article (%)	CAM #	Scores @ 0.5 min.	2 min.	5 min.	Total
DT051832 42940 SS10 (50%)	1	0	0	0	0
	2	0	0	1	1
	3	0	3	0	3
	4	0	0	1	1
				Average:	**1.25**

Reference Article (%)	CAM #	Scores @ 0.5 min.	2 min.	5 min.	Total
Alcohol-Free Spray-On Gel (50%)	1	0	0	1	1
	2	0	3	0	3
	3	0	0	1	1
	4	0	3	0	3
				Average:	**2.00**

Reference Article (%)	CAM #	Scores @ 0.5 min.	2 min.	5 min.	Total
Alcohol-Free Sculpting Gel (50%)	1	0	3	0	3
	2	0	0	1	1
	3	0	0	1	1
	4	0	0	1	1
				Average:	**1.50**

Each article was then classified as indicated in the following:

Mean Score	Irritation Potential
0.0 - 4.9	Practically none
5.0 - 9.9	Slight
10.0 - 14.9	Moderate
15.0 - 32.0	Severe

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Discussion:

Previous studies have shown that the CAM of the hen's egg is more sensitive to liquid irritants than is the rabbit eye. Therefore, 50% dilutions of the liquid test and reference articles were used to determine the 100% irritation potential.

Historical *In Vivo* Results:

The reference products have historically been categorized as being practically non-irritating, eliciting scores approaching 0, at 24 hours, when dosed at 100% and tested using the Draize ocular irritation methodologies (Draize Scale: 0 – 110).

Conclusion:

Under the conditions of this test, the results indicate that " Hair styling product (11% PEG-7 Glyceryl cocoate) ", at 100%, would have practically no ocular irritation potential, *in vivo*.

Record Retention:

All records and documents pertaining to the conduct of this study shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QA Department to obtain custody of study records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, study-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

Professional personnel involved:

Steven Nitka, B.S.	-	Vice President Laboratory Director (Study Director)
Lillian Vazquez, B.S.	-	Laboratory Supervisor
Christine Hendricks	-	Quality Assurance Group Leader

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TKL RESEARCH

REPEATED INSULT PATCH TEST

TKL STUDY NO. DS104013/104313-4

Hair Styling Product (11% PEG-7 Glyceryl cocoate)

[redacted]

DATE OF ISSUE:

July 19, 2013

201.587.0500 • www.tklresearch.com

TKL Research, Inc. 365 West Passaic Street, Rochelle Park, NJ 07662

Version 1.0

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SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

Jonathan S. Dosik, MD
Dermatologist
Principal Investigator

07/19/13
Date

c/o K.G.

Kathleen Georgeian
Director, Dermatologic Safety Testing

7/19/13
Date

Michelle Medina
Manager, Dermatologic Safety Testing

7/19/13
Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

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TITLE OF STUDY
Repeated Insult Patch Test

STUDY MATERIAL
Hair Styling

DATE STUDY INITIATED
May 13, 2013

DATE STUDY COMPLETED
June 28, 2013

DATE OF ISSUE
July 19, 2013

INVESTIGATIVE PERSONNEL
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Principal Investigator

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Michelle Medina
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SUMMARY

One study material, hair styling product , was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using a semi-occlusive repeated insult patch study. Two hundred four (204) subjects completed the study.

One subject on DS104313 showed evidence of possible presensitization (definite erythema, definite edema, ++). Patching of the product on this subject was discontinued for the remainder of the study.

Under the conditions employed in this study, there was no evidence of sensitization being induced by hair styling product (11% PEG-7 glyceryl cocoate)

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1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 200 completed subjects. In the absence of any sensitization reactions in this sample size (200 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 to 70 years of age, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

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2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding;
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated; and/or
6. Were participating in another study or had been recruited to participate in another study concurrently.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2]

Following the 9th evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the 6th week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

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24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1[3]	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

DAY	ACTIVITIES
1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

DAY	ACTIVITIES
1-6	Same as Week 2

WEEK 4

DAY	ACTIVITIES
1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU patches
3	Staff graded MU induction sites at MU visit
2-7	Rest Period

WEEK 5

DAY	ACTIVITIES
1-7	Rest Period

[3] Study flow starting with Week 1, Day 1, was altered when enrollment occurred on Wednesday or Friday. Study flow could be altered if a holiday occurred during the study.

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WEEK 6

DAY	ACTIVITIES
1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

SYMBOL		REACTION
-	=	No reaction
?	=	Minimal or doubtful response, slightly different from surrounding normal skin
+	=	Definite erythema, no edema
++	=	Definite erythema, definite edema
+++	=	Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E	=	Marked/severe erythema
S	=	Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p	=	Papular response > 50%
pv	=	Papulovesicular response > 50%
D	=	Damage to epidermis: oozing, crusting and/or superficial erosions
I	=	Itching
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Not applied
NP	=	Not patched (due to reaction achieved)
N9G	=	No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

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4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : [redacted] Hair Styling
Amount Applied : 0.2 g

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material was kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patches are secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pads are affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours.

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Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of TKL.

7.0 RESULTS AND DISCUSSION

Two hundred thirty-one (231) subjects between the ages of 18 and 70 were enrolled and 204 subjects completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition.

Number enrolled:		231
Number discontinued:		27
Lost to follow-up:	21	
Voluntary withdrawal:	4	
Other: (Poor personal hygiene)	1	
Adverse events:	1	
Number completed:		204

Source: Table 1, Appendix I

Subject No. 099 on DS104313 showed evidence of possible presensitization (definite erythema, definite edema, ++) at the 2nd Induction reading. Patching of the product on this subject was discontinued for the remainder of the study.

There was one non-product related adverse event (AE) reported during these studies (DS104013). Subject No. 055 took an exclusionary medication for a sinus infection.

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A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

Adverse events are presented in Data Listing 4, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization being induced by hair styling product (11% PEG-7 Glyceryl cocoate)

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APPENDIX I

SUMMARY TABLES

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Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	117
Subjects completed induction phase	105 (89.7)
Subjects completed all phases	103 (88.0)
Total subjects discontinued	14 (12.0)
Lost to follow-up	9 (7.7)
Voluntary withdrawal	4 (3.4)
Adverse events	1 (0.9)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	50 (42.7)
N (%) 45 to 65	59 (50.4)
N (%) 66 and up	8 (6.8)
Mean (SD)	46.2 (14.3)
Median	46.8
Range	18.5 to 70.4
Gender	
N (%) Male	34 (29.1)
N (%) Female	83 (70.9)
Race	
Amer Ind	1 (0.9)
Asian	2 (1.7)
Black	20 (17.1)
Caucasian	71 (60.7)
Hispanic	21 (17.9)
Other	2 (1.7)

See data listing 2 for further detail.

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Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	109	105	106	108	106	107	106	103	101	6	104	103	
?	0	1	0	0	0	0	0	0	0	0	0	0	
Total evaluable	109	106	106	108	106	107	106	103	101	6	104	103	
Number absent	4	3	3	1	2	1	0	2	4		0	0	
Number discontinued	4	8	8	8	9	9	11	12	12		13	14	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=105)

Response	n(%) Subjects
-	104 (99.0%)
?	1 (1.0%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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TKL Study No. DS104013

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

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Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	114
Subjects completed induction phase	104 (91.2)
Subjects completed all phases	101 (88.6)
Total subjects discontinued	13 (11.4)
Lost to follow-up	12 (10.5)
Other reasons	1 (0.9)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	39 (34.2)
N (%) 45 to 65	70 (61.4)
N (%) 66 and up	5 (4.4)
Mean (SD)	48.6 (12.7)
Median	51.7
Range	18.5 to 70.7
Gender	
N (%) Male	36 (31.6)
N (%) Female	78 (68.4)
Race	
Amer Ind	1 (0.9)
Black	17 (14.9)
Caucasian	74 (64.9)
Hispanic	22 (19.3)

See data listing 2 for further detail.

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Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	109	99	101	105	100	105	103	100	101	27	101	100	
?	0	0	0	1	1	0	0	0	0	0	0	0	
+	1	0	0	0	0	0	0	0	0	0	0	0	
++	0	1	0	0	0	0	0	0	0	0	0	0	
Total evaluable	110	100	101	106	101	105	103	100	101	27	101	100	
Number absent	1	11	8	3	6	0	0	3	2		0	0	
Number discontinued	3	3	4	4	6	8	10	10	10		12	13	
Patch not applied	0	0	1	1	1	1	1	1	1		1	1	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=104)

Response	n(%) Subjects
-	102 (98.1%)
?	1 (1.0%)
++	1 (1.0%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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TKL Study No. DS104313

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

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HARRISON RESEARCH LABORATORIES, INC.

2497 Vauxhall Road · Union, NJ 07083 · Phone (908) 688-7600
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PURPOSE:	To evaluate the potential of the Test Material, as a result of repeated applications, to induce dermal sensitization in human subjects.
IRB APPROVAL:	Both the HRL Standard Protocol #100 and the Informed Consent were approved by the New England Institutional Review Board (NEIRB) on 1/24/08.
AUTHORIZATION:	Sponsor authorization dated February 19, 2008
PRINCIPAL INVESTIGATOR: DERMATOLOGISTS:	Lynne B Harrison, PhD Deborah R Spey, MD, FAAD Kimberly K Ruhl, MD, PhD, FAAD
TEST FACILITY:	Harrison Research Laboratories, Inc. (HRL) 2497 Vauxhall Road Union, New Jersey 07083
TEST MATERIAL:	**SETTING LOTION (1% PEG-75 SHEA BUTTER GLYCERIDES)** , was received on February 20, 2008, with the following instructions: Test as received; patch semi-occlusively.
SUBJECTS:	240 subjects were inducted; 219 subjects completed the test. Twenty-one subjects discontinued. No subject discontinued due to test material reaction.
METHOD:	This test was conducted according to HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations). See pages 3 – 4.

-CONTINUED-

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Fax (908) 688-7601

TEST DATES:	March 25, 2008 through April 4, 2008
SCORING SYSTEM:	See Tables I .
RESULTS:	See Tables I . During the Induction Phase, two subjects exhibited low-level, transient (±) reactions. At the Challenge, five subjects exhibited low-level (±/1) reactions.
CONCLUSION:	In this Repeated Insult Patch Test, test material **Setting lotion (1% PEG-75 Shea butter glycerides)**, did not induce dermal sensitization in human subjects.

Kimberly K Ruhl, MD, PhD, FAAD
Medical (Dermatological) Investigator

4/9/08
Date

Lynne B Harrison, PhD
Principal Investigator

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SUBJECTS: Each potential subject completed an HRL Subject History Form (HRL Form:SHF), including relevant medical history. (An updated Subject History Form is secured approximately every two years.) Each accepted subject was assigned a permanent HRL Identification Number. No subject was used if he or she exhibited any dermatological or other medical or physical condition that would preclude topical application of the Test Material. No known pregnant nor nursing women were used on this RIPT.

An appropriate clearance period had elapsed since a subject was patched on a Repeated Insult Patch Test (RIPT) or a Photoallergy Test (PA) before being used in this RIPT.

Legally valid written informed consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

METHOD: Induction Phase: A webril/adhesive patch (Kendall Healthcare Products Company Patch #4022) was used semi-occlusively. Approximately 0.2 gm of Test Material was applied to each patch. The test site was wiped with a dry Kimwipe® prior to each patching. As per HRL Standard Operating Procedures (SOP) (HRL Form:SOP/RIPT), the left side of the back was usually the test area for the Induction Phase. The subject's skin was marked with gentian violet surgical marker at the left side of the test site. The test site was recorded on the anatomical diagram of each subject's individual Data Form, HRL Form: Data RIPT. In addition, at this time, the prospective placement of the Challenge test site was also recorded on the anatomical diagram.

Each subject was instructed that the patch was to remain in place and kept dry for approximately 24 hours, at which time the patch was to be removed by the subject. A 24 hour period, during which no test material was applied, followed the weekday patch removals; a 48 hour period followed the weekend patch removal.

Each subject returned to HRL on the appropriate day. The test site was observed by the HRL technician, and the reaction scored and recorded (see **SCORING SYSTEM**, below). The identical test site was then repatched until the nine Induction patchings were completed.

If a subject was unable to make up a missed patching during the same week, the subject was either patched four days the following week or was repatched at the end of the Induction Phase (tenth test day). Any absences and repatchings are noted by the dates on the individual Data Form.

A series of nine (9) Induction patchings was completed over a period of approximately three weeks.

Rest Period: A Rest Period of approximately two weeks followed the last Induction patching; no test material was applied during the Rest Period.

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METHOD: (continued)

Challenge Phase: At the Challenge Phase, the original Induction test site was observed and each subject queried as to whether any reaction was experienced during the Rest Period. A webril/adhesive patch (Kendall Healthcare Products Company Patch #4022) was used semi-occlusively. Approximately 0.2 gm of Test Material was applied to each patch. As per HRL RIPT SOP, the right side of the back was usually the virgin test site for the Challenge Phase.

As per HRL RIPT SOP, the Challenge patch was applied to the virgin site only. Each subject was again instructed to keep the patch on and dry.

Each subject reported to HRL approximately 24 hours later (C1 visit), at which time the patch was removed and the Challenge site scored and recorded by the HRL technician. The original test site was also observed. (See **RESULTS**, below.)

Subject #224 (HRL #26477) missed the C1 visit; the subject was instructed to keep his patch on until he returned to HRL for the C2 visit.

Each subject reported to HRL at approximately 48 hours (C2 visit), 72 hours (C3 visit) and 96 hours (C4 visit) post-patching for additional observations; reactions were scored and recorded.

Subjects #044 (HRL #18634), #077 (HRL #22201), #128 (HRL #31199), #133 (HRL #25223), #157 (HRL #17593) and #227 (HRL #23969) missed the C4 visit. All of the subjects returned to HRL on April 7, 2008 and their test sites were negative. A verbal report from each of these subjects stated 'no reaction present' at what would have been his or her C4 visit.

SCORING SYSTEM: See Tables I-II, pages 5-16. The test sites were scored using the modified scoring scale of the International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 1986: p 26.

RESULTS: See Tables I-II. This test was conducted under the supervision of a Board-Certified Dermatologist, the Co-Investigator. A total of 219 subjects completed the test; 66 male and 153 female. The subjects range in age from 19 to 70.

RETENTION: All original Data Forms will be retained at HRL for a period of three years, or such other time as may be required by law. A laboratory retainer bottle of the Test Material shall be retained for at least two years, or as required by law. Return or disposal of unused Test Material shall be as per the Sponsor's instructions—to be communicated within 30 days of receipt of this Final Report. HRL shall appropriately dispose of any test material after six months if no Sponsor instructions have been communicated.

HRL Form:FR/RIPT(4)-08/07

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TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS INDUCTED: 240

Reaction	Induction Reading									Challenge Reading			
Grade	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**C1**	**C2**	**C3**	**C4**
0	233	232	230	229	228	224	223	223	222	215	212	214	211
±	1						1			2	2	1	1
1										2	2	1	1
1E													
2													
2E													
3													
4													
-										1	4	3	6
N9R													
Total	**234**	**232**	**230**	**229**	**228**	**224**	**224**	**223**	**222**	**220**	**220**	**219**	**219**

SCORING SYSTEM:

0	No visible reaction
±	Faint, minimal erythema
1	Erythema
2	Intense erythema, induration
3	Intense erythema, induration, vesicles
4	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	Edema
-	No reading
N9R	No 9th reading

SCORING SYSTEM:

0	No visible reaction
±	Faint, minimal erythema
1	Erythema
2	Intense erythema, induration
3	Intense erythema, induration, vesicles
4	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	Edema
DR	Dryness
^	Hyperpigmentation
ST	Staining
P	Peeling
C	Change of test site
-	No reading
N9R	No 9th reading
X	Discontinued

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QUALITY ASSURANCE MEMORANDUM

This Final Report was reviewed for accuracy and conformity with both HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations).

Inspections were accomplished as determined by a random sampling approach and reported to the Project Manager and the Principal Investigator immediately following their completion.

The raw data for this study are retained at Harrison Research Laboratories, Inc.

HARRISON RESEARCH LABORATORIES, INC.

Susan Lauck

SUSAN LAUCK
Quality Assurance Manager

INTERNAL QUALITY ASSURANCE UNIT

Dated: 4/9/08

This report is only submitted for the use of the party to whom it is addressed, and neither it nor the name of our company or any member of our staff may be used in connection with any advertising or sale without our written authorization

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Consumer Product Testing Co.

EST. 1076

FINAL REPORT

[redacted]

[redacted]

TEST: Safety In-Use of a Bath or Feminine Hygiene Product
Protocol No.: LRLA-033

TEST MATERIAL: FEMALE HYGEINE PRODUCT (0.1% PEG-75 SHEA BUTTER GLYCERIDES)

EXPERIMENT REFERENCE NUMBER: C05-0357.01

Michael Kane, M.D.
Board Certified Gynecologist

Michael Traudt, Ph.D
Director, Clinical Evaluations

Joy Frank, R.N.
Executive Vice President, Clinical Evaluations

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report nor the name of these Laboratories nor any member of its staff, may be used in connection with the advertising or sale of any product or process without written authorization.

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

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Consumer Product Testing Co.

Est. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: C05-0357.01

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of clinical laboratory studies. These studies have been performed with adherence to the applicable ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 CFR parts 50 and 56 and in accordance to standard operating procedures and applicable protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study. All data pertinent to this study will be stored in the Consumer Product Testing Company archive, unless specified otherwise, in writing by the Sponsor.

Quality Assurance personnel involved:

Scott 5·18·05

Quality Assurance Date

The representative signature of the Quality Assurance Unit signifies that this study has been performed in accordance with standard operating procedures and study protocol as well as government regulations regarding such procedures and protocols.

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Clinical • Toxicology • Analytical Chemistry • Microbiology

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Objective: To evaluate the potential of a bath product to induce vaginovulvar irritation under normal use conditions.

Participants: Twenty-one (21) qualified female subjects, ranging in age from 23 to 59 years, were selected for this study. All twenty-one (21) subjects completed the study.

Inclusion Criteria:

1. Healthy females, 18 to 60 years of age.
2. Absence of previous history or visible evidence of chronic skin disease or regional infection which might be confused with a reaction to the test material.
3. No history of sensitivity to similar formulations.
4. Dependability and intelligence in following directions.
5. Willingness to cooperate.
6. Completion of a Medical History form, understanding and signing of an Informed Consent form.

Exclusion Criteria:

1. Subjects who are pregnant or lactating.
2. Subjects who have any disease or condition which, in the opinion of the investigator, could affect or influence the test results.
3. Subjects who have a history of genital herpes, recurrent vaginal infections, or urinary bladder infections.
4. Subjects who are using concomitant medication which might affect or influence the test results.
5. Subjects with a history of allergy or hypersensitivity to any bath or feminine hygiene product.
6. Subjects with a menstrual schedule that coincides with the scheduled speculum examination.
7. Subject should not be participating in any other studies at this or any other facility.

Test Material: FEMALE HYGEINE PRODUCT (0.1% PEG-75 SHEA BUTTER GLYCERIDES)

Study Schedule:

Initiation Date	Completion Date
May 3, 2005	May 10, 2005

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Study Design: A one (1) week Monadic, In-Use Evaluation.

Methodology: Prior to the initiation of this study, all subjects received a complete gynecological examination, conducted by a Board Certified Gynecologist. Examinations were performed to detect signs of erythema, edema, and any vaginal or perineal inflammation or irritation, including the use of a plastic speculum, which was rotated through 180° to insure visualization of the entire vaginal wall and cervix.

All observations were recorded on individual Case Record forms. Observations of erythema, edema, etc., were graded for intensity and significance. Additional noteworthy comments were also recorded.

For qualification, the initial findings of the vaginal/perineal examination were required to be within the normal range (less than grade 2) in order for the subject to enter into the study.

Key for Gynecological Observations:

0 = None
1 = Minimal
2 = Moderate
3 = Marked

Observations for evidence of unusual dryness, pustules, fissures, etc. were also recorded.

After completion of the gynecological examination, acceptable candidates received the test product and were instructed to use the test product daily for one (1) week, according to the following directions:

Use only the test product for the study period.
Discontinue the use of your current bath/shower products. Do not introduce any new feminine hygiene products to your body during the study. Keep out of reach of children. Do not let anyone else use this product. This is an exclusive study. You may not be involved in any other clinical test while participating in this study.

Squeeze a quarter size amount under tap to create a bubble bath. Bathe 10 – 20 minutes, once (1) a day.
Avoid contact with eyes. For external use only.

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Methodology: (continued)

In addition, all subjects were instructed to maintain a daily diary of each use to document compliance.

After one week of daily product usage, all subjects received a final gynecological examination, as previously described.

Daily diaries were reviewed for completeness before dismissal of the subjects.

Adverse Events:

There were no adverse events reported during the test interval.

Results:

The results of all gynecological examinations remained within normal limits throughout the test interval.

Initial and Final Examinations Records and completed daily diaries are provided under separate cover.

Subject Demographics are presented in Table 1.

A review of all completed daily diaries revealed the following significant comments:

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Results (continued):

Positive

No. of Subjects	Comments
8	Nice smelling/pleasant smelling/great smell/smells good
3	Left skin feeling clean
2	It made skin softer
1	It's very good
1	I loved it
1	Liked product very much
1	Left skin feeling smooth
1	Gave a fresh feeling
1	Nice scent on skin

Negative

No. of Subjects	Comments
2	Bubbles were wimpy/bubbles hardly there at all/bubbles disappeared quickly
1	I don't think I would buy it
1	Smell was sort of masculine
1	Left skin a little dry
1	No smell hardly at all

Summary: Under the conditions of the study, test material, 'female hygeine product did not induce evidence of vaginovulvar irritation, when subjected to normal use conditions.

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Table 1

Subject Demographics

Subject Number	Initials	Age
1	RS	56
2	AO	44
3	RC	47
4	CB	38
5	BT	45
6	BP	45
7	AL	47
8	DG	43
9	TG	24
10	AQ	43
11	VB	51
12	KJ	47
13	JM	27
14	QO	27
15	DS	29
16	LP	45
17	MR	32
18	DV	59
19	JA	30
20	MQ	54
21	LR	23

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 24, 2014

SUBJECT: Information on PEG Alkyl Glycerides

Anonymous. 2005. Assessment of the eye irritation potential of PEG-7 Glyceryl Cocoate in the hen's egg test on the chorioallantoic membrane (HET-CAM).

Anonymous. 2005. Assessment of the eye irritation potential of PEG-7 Glyceryl Cocoate by cytotoxicity measurement in the neutral red uptake assay (NRU) on human keratinocytes (HaCaT).

Hazleton Laboratories America, Inc. 1989. Summary of 28-day subchronic oral toxicity study in rats with a material containing 0.8% PEG-7 Glyceryl Cocoate.

Research Toxicology Centre S.p.A. 1995. Delayed dermal sensitisation study in the guinea pig (PEG-7 Glyceryl Cocoate).

TKL Research, Inc. 2004. Repeated insult patch test of a styling pomade (BCS578-094) containing PEG-7 Glyceryl Cocoate.

TKL Research, Inc. 2004. Repeated insult patch test of a styling pomade (BCS578-098) containing PEG-7 Glyceryl Cocoate.

Pharmaco UK Ltd. 1994. Human repeat insult patch test of PEG-20 Almond Glycerides.

Leberco-Celsis Testing. 1997. Ocular irritation screen of PEG-10 Sunflower Glycerides using the chorioallanotic membrane vascular assay (CAMVA).

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Raltech Scientific Services. 1981. Skin corrosivity (perfume containing 4% PEG-6 Caprylic/Capric Glycerides).

Springborn Institute for Bioresearch, Inc. 1981. Rabbit eye irritation (perfume containing 4% PEG-6 Caprylic/Capric Glycerides).

Anonymous. 1981. Human sensitization test of a perfume containing 4% PEG-6 Caprylic/Capric Glycerides.

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[redacted]

Study number: [redacted]
Test item code: **22129**

Marly, 07 March 2005 [redacted]

[redacted]

ASSESSMENT OF THE EYE IRRITATION POTENTIAL OF
PEG-7 Glyceryl Cocoate
RAW MATERIAL NO. 22129

IN THE HEN's EGG TEST ON THE CHORIOALLANTOIC MEMBRANE (HET-CAM)

FINAL REPORT

Sponsor: [redacted]

Test Facility: [redacted]

Head of Test Facility: [redacted] Biologist

Study Director: [redacted] Cert. Biologist

Quality Assurance: [redacted] Biochemist

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HET-CAM
Study number: [redacted]
Test item code: **22129**

The Swiss GLP Monitoring Authorities

Swiss Federal Office of Public Health

Swiss Agency for the Environment, Forests and Landscape

swissmedic Swissmedic Swiss Agency for Therapeutic Products

Statement of GLP Compliance

It is hereby confirmed that

during the period of November 27-28, 2003

the following Test Facility of [redacted]

was inspected by the Federal Office of Public Health with respect to the compliance with the Swiss legislation on Good Laboratory Practice.

Test Facility	**areas of expertise***
[redacted]	TOX (in vitro)

the inspection was performed in agreement with the OECD Guidelines for National GLP Inspections and Audits. It was found that the aforementioned test facility was operating in compliance with the Swiss Ordinance relating to Good Laboratory Practice [RS 813.016.5] at the time it was inspected.

Federal Office of Public Health
The Director

Bern, March 2004

Prof. Th. Zeltner

* TOX = Toxicology

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HET-CAM
Study number: [redacted]
Test item code: **22129**

STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE (GLP)

This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted February 2nd, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final].

[redacted]
Study Director
[redacted]

07.03.2007
date

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HET-CAM
Study number: [redacted]
Test item code: **22129**

STATEMENT OF QUALITY ASSURANCE UNIT (QAU)

This study has been inspected in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted February 2nd, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final].

This final report accurately reflects the raw data obtained during the experiments.

Date:	Type and phase of inspection:	Information to Study Director:	Information to the Head of Test Facility:
06.12.04	Study plan / valid SOPs	13.12.04	13.12.04
02.12.04	Process based: Incubation of the eggs (SOP HET 3.1), Study HC 289	13.12.04	13.12.04
10.12.04	Facility based	13.12.04	13.12.04
02.03.05	Draft Final Report	04.03.05	04.03.05
07.03.05	Final report	07.03.05	07.03.05

[redacted]
Head of Quality Assurance Unit
[redacted]

7.3.2005
(date)

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GUIDELINES

As no official guidelines exist, the Hen's Egg Test on the Chorioallantoic Membrane (HET-CAM) is performed according to the SOP HET 5.1 of [redacted] which is based on the Standard Operating Procedure developed by Dr. W. Steiling, HENKEL KGaA, D-40191 Düsseldorf, Germany, 2nd Edition, revised and completed in December 1994, for the COLIPA (the European Cosmetic, Toiletry and Perfumery Association) International Validation Study on Alternatives to the Draize Rabbit Eye Irritation Test (Brantom et al. 1997).

TIME SCHEDULE

Order:	26.11.2004
Study plan:	06.12.2004
Experimental starting date:	10.12.2004
Experiment completion date:	23.12.2004
Final report:	07.03.2005

ARCHIVING

All raw data and notes as described in SOP HET 6.1, the samples of the test and reference items as well as the originals of the study plan and of the final report are stored in the archives of [redacted] for at least 30 years (or up to the expiry date).

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SUMMARY

The aim of this study was to assess the acute eye irritation potential of the test item using the Hen's Egg Test on the Chorioallantoic Membrane (HET-CAM). The test item was applied onto the CAM of fertilized chicken eggs at day 9 of incubation and irritation parameters such as haemorrhage, lysis of blood vessels and protein coagulation were evaluated.

In this study, the test item was tested twice according to the reaction-time method (RTM) for transparent test items, at three concentrations: undiluted and at 50 and 10% (w/w) in water. The test item was applied onto the CAM for 5 minutes and the times of first appearance of haemorrhage, lysis and coagulation were registered. These time points were used to calculate an irritation index which was then divided by the irritation index of a reference item (= quotient Q).

In this HET-CAM study, the test item caused haemorrhage, lysis of blood vessels and coagulation on the CAM resulting in median Q-values which were decreasing in a dose-dependent manner: **Q = 0.5** when applied undiluted, **Q = 0.2** at 50% and **Q = 0.1** at 10%. Coagulation was the reaction appearing first at all doses.

In conclusion, according to the COLIPA classification model for eye irritation (a), comprising 5 irritation categories (non-irritant, slight, moderate, irritant, severe), the test item is classified as **slight irritant** when tested undiluted and at 50 and 10% (w/w) in water.
Furthermore, according to our internal HET-CAM classification system (b), comprising 3 classes for the reaction-time method (non-irritant, irritant, severe) and where the HET-CAM is performed as part of an in vitro test battery, the test item is classified as **non-irritant** at all doses tested.

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INTRODUCTION

The Hen's Egg Test on the Chorioallantoic Membrane (HET-CAM) is an alternative method to the Draize rabbit eye irritation test, used to assess the ocular irritation potential of both finished products and raw materials (Luepke, 1985). The assay protocol is based on the reaction-time method described by Sterzel et al. (1990) for transparent test items, which was then adapted for testing different types of chemicals for the EC/HO (European Commission / British Home Office) Validation Study performed in 1992-1994 (Balls et al. 1995) as well as for the COLIPA Validation Study (1994–1997, Brantom et al. 1997, Steiling 1994 and Steiling et al., 1999).
The test protocol assesses three endpoints, haemorrhage, blood vessel lysis and protein coagulation, which are macroscopic changes occurring in the vascularized chorioallantoic membrane (CAM) of fertilized chicken eggs after contact with the test item at day 9 of incubation, and which are measured as indicators of potential damage to mucous membranes. In the protocol for transparent test items, the first appearance of the three endpoints over a 5-minute exposure period is registered and these reaction times are used to calculate an irritation index which is then divided by the irritation index of the reference item Texapon® ASV, containing 5% active substance, determined on the same day (= quotient Q). In the protocol for non-transparent test items, the test item is rinsed off 30 seconds after application and the three endpoints are visually scored 30 seconds after rinsing (= score S) according to the intensity of the effects observed on the CAM.

MATERIAL AND METHODS

1. Test item

Code: 22129

Batch: Lot R 0006028

Trade name:

Supplier:

Other name: PEG-7 GLYCERYL COCOATE 100%

CAS number: 68553-02-6

Raw material number: 22129

Appearance: clear, light yellow, viscous liquid oil

Date of receipt: 26.11.2004 [redacted]

Stability: expiry date: 22.09.2005

Storage conditions: at room temperature, in the dark

Diluting agent: water

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2. Reference item

V-70: sodium magnesium lauryl–myristyl-6-ethoxy-sulfate, provided by Fa. [redacted] batch CS 23360023; active substance content: 67.6 %; expiry date: 12/2004

3. Test system

3.1 Incubation of the eggs

Freshly fertilized chicken eggs (JA; approximately 50 g weight) were delivered by a local breeding farm (OPTIGAL SA, 1523 Granges-près-Marnand) less than one week after laying and stored before incubation at room temperature (approx. 20 ± 5°C) for up to five days. The eggs were then placed horizontally onto incubator trays (with the ends close to each other) and incubated at 37.5 ± 1.5°C and 55 ± 10% relative humidity for 9 days in a special incubator which automatically rotates the eggs once every 4 hours.

3.2 Selection of the eggs

At the end of the incubation, the eggs were illuminated with a lamp and the air cell at the blunt end was marked with pencil. The eggs were then kept in an incubator (37 ± 1.5°C) until use for testing. Eggs which were not fertilized or did not undergo normal embryogenesis were eliminated.

3.3 Preparation of the CAM

The egg shell around the air cell was removed with forceps and the white egg membrane was moistened with a few ml of a 0.9 % NaCl solution (pre-warmed at 37 ± 1°C). If not used immediately, the opened eggs were placed again into an incubator (37 ± 1.5°C) until use (but not more than 20 min.). Before application of the test item, the NaCl solution was poured off and the egg membrane carefully removed with pointed tweezers.
During preparation of the CAM, any damage to the fine blood vessels (e.g. bleeding) had to be avoided and only eggs with intact and clearly delineated vascular system were considered suitable for testing.

4. Experimental procedure

The assay was carried out according to the SOP HET 5.1 of [redacted] which is based on the Standard Operating Procedure developed by Dr. W. Steiling for the COLIPA International Validation Study on Alternatives to the Draize Rabbit Eye Irritation Test (Steiling et al., 1999). The test procedure comprises two protocols: the reaction-time method (RTM) for transparent and the endpoint assessment (EPA) for non-transparent test items.
In this study, two independent tests were performed with the RTM (see 4.2).

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4.1 Definition of the HET-CAM parameters

Haemorrhage:	bleeding out from the blood vessels of the vascularized CAM
Lysis:	disappearance of small blood vessels on the CAM due to dystonia or real blood vessel disintegration
Coagulation:	intra- and extravascular protein denaturation, including opacity of the CAM

4.2 Preliminary test

A preliminary test was carried out to decide on the test protocol for the main study: endpoint assessment or reaction-time method. For that purpose, 300 µl of undiluted and 10-x diluted (10%) test item were applied onto three prepared membranes (CAM). As the test item was transparent when applied undiluted and at 10%, i.e. as it did not hinder the continuous observation of the whole CAM during 5 minutes, the RTM protocol was chosen for the main study.

4.3 Test item concentrations

The test item, which is a raw material, was tested at 3 concentrations ranging from 10 to 100% (= undiluted). It was applied first at 10% (w/w in water) and then, according to the intensity of the effects, the dose was increased with the aim of demonstrating, if possible, a dose-effect relationship and determining an irritation threshold, which is defined as the highest dose with the classification "slight" or "non-irritant".

4.4 Reaction-time method (RTM)

Three hundred µl of the test item were applied onto the chorioallantoic membrane (CAM) of 6 eggs for 5 minutes. The times of first occurrence of the three parameters, haemorrhage, lysis and coagulation, were recorded and then used to calculate an irritation index (RI) by means of the computer program "HetCam.exe" generated in-house on the basis of the model of the "BRUTEI©" and "HET4.exe©" programs provided by HENKEL (Steiling, 1994). The reference item, Texapon® ASV with 5% active substance (AS) content, was additionally tested on the same day in order to calculate the final test result of the reaction-time method, defined as the Q-value obtained by dividing the RI of the test item by that of Texapon® ASV 5% AS.

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5. Test evaluation

5.1 Evaluation of the reaction-time method (RTM)

The reaction times obtained according to the RTM were used to calculate an irritation index (RI) by means of the computer program "HetCam.exe" (see description of the mathematical model in Appendix 1).
On each testing day, the irritation index (RI) of Texapon® ASV 5% AS was determined on 6 eggs as a reference. According to our experience and on the basis of historical RI values obtained in our laboratory, results of RI between 550 and 820 are considered acceptable for Texapon® ASV 5% AS (see Appendix 2).
The final irritation value of the reaction-time method, represented as the [Q]-value, is the quotient obtained by dividing the RI of the test item by that of Texapon® ASV 5% AS. The Q-values obtained in repeated experiments are averaged and the median is used for the HET-CAM evaluation according to the eye irritation classification models reported below (see 5.2).

5.2 *HET-CAM classification systems for eye irritation*

a) On the basis of the results obtained in the HET-CAM, the test item is classified according to the following eye irritation prediction scheme using the [Q]-value from the reaction-time method for transparent test items (Steiling et al. 1999, COLIPA Validation Study):

Quotient [Q] (5-min. contact)	Predicted irritation category
0.0	non-irritant
≤ 0.8	slight
> 0.8, < 1.2	moderate
≥ 1.2, < 2.0	irritant
≥ 2.0	severe

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b) According to our in-house experience and based on data obtained with cosmetic formulations [redacted], the following internal classification system for the HET-CAM assay performed as part of an in vitro test battery, comprising also e.g. Red Blood Cell (RBC) test, Neutral Red Uptake (NRU), Neutral Red Release (NRR), can be used for the assessment of eye irritation:

Quotient [Q]	Classification
≤ 1.0	non-irritant
> 1, < 2.5	irritant
≥ 2.5	severe

If the results obtained in the different assays of the in vitro test battery are contradictory, the ultimate decision may be made on a "worst case" basis.

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RESULTS AND DISCUSSION

In this study, the acute eye irritation potential of the test item was assessed in the Hen's Egg Test on the Chorioallantoic Membrane (HET-CAM). Based on the results of the preliminary test (see Experimental procedure, Chapter 4.2), the test item was tested twice according to the reaction-time method (RTM) for transparent test items, at three concentrations ranging from 10 (w/w) in water to 100% (= undiluted), with the aim to cover the range of effective concentrations and to determine an irritation threshold.
The detailed experimental data of the HET-CAM experiments (the individual and mean values of the times of first appearance of the reactions, the calculated irritation indices (RI) and Q-values) are presented in the Tables 1 and 2.

In all experiments, the mean irritation indices (RI) of the reference item Texapon® ASV 5% (active substance) were within the historical range established in our laboratory (see Material and Methods, Chapter 5.1 and Appendix 2).

The results of the HET-CAM with the test item are summarized in the following table:

Test item	Dose % (w/w)	Test results Quotient [Q]	Prediction of eye irritation a) COLIPA *(non-irritant, slight, moderate, irritant, severe)*	b) internal classification system* *(non-irritant, irritant, severe)*
22129	100 (undiluted)	0.5	slight	non-irritant
		0.6	slight	non-irritant
	Median	**0.5**	**slight**	**non-irritant**
	50 (2-x diluted)	0.2	slight	non-irritant
		0.2	slight	non-irritant
	Median	**0.2**	**slight**	**non-irritant**
	10 (10-x diluted)	0.1	slight	non-irritant
		0.2	slight	non-irritant
	Median	**0.1**	**slight**	**non-irritant**

[Q] = RI of test item devided by RI of reference item * to be used in the context of an in vitro test battery

In this HET-CAM study, the test item caused haemorrhage, lysis of blood vessels and coagulation on the CAM resulting in median Q-values which were decreasing in a dose-dependent manner from Q = 0.5 when applied undiluted to Q = 0.1 at 10% (see below dose-response curves). Coagulation was the reaction appearing first at all doses.
Furthermore, as the effects were slight at all the doses tested, no irritation threshold (= highest test item concentration with the classification "slight" or "non-irritant") could be defined.

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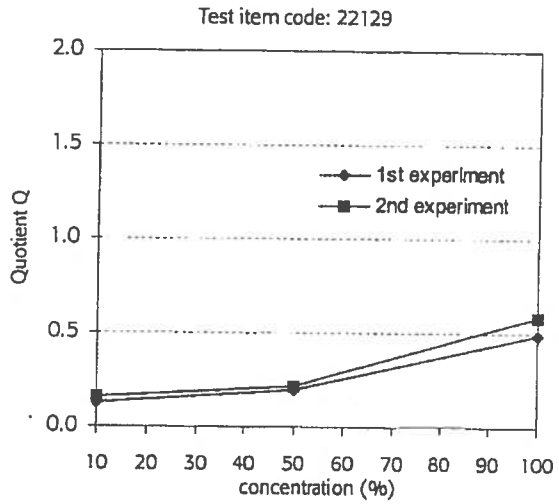

Dose-response curves (Q-value vs. concentration)

CONCLUSION

From the results obtained in this HET-CAM study and under the experimental conditions reported, it is concluded that the test item is classified as **slight irritant** when tested at three doses ranging from 10% (w/w) in water to 100% (= undiluted), according to the COLIPA classification model for eye irritation (a), comprising 5 irritation categories (non-irritant, slight, moderate, irritant, severe).
Furthermore, according to our internal HET-CAM classification system (b), comprising 3 classes for the reaction-time method (non-irritant, irritant, severe) and where the HET-CAM is performed as part of an in vitro test battery, the test item is classified as **non-irritant**.

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Table 1: Results of the HET-CAM performed according to the reaction-time method *(continuous observation during the 5-minute application)*

1st experiment (16.12.2004)

Treatment	Conc. [% w/w]	Egg no.	Reaction times* [sec.]			Evaluation ("HetCam.exe")	
			Haem.	Lysis	Coag.	RI	[Q]
Texapon® ASV (reference item)	5 (AS)	1	20	30	301	645.6	
		2	17	26	301	763.1	
		3	19	25	301	723.1	
		4	16	24	301	820.9	
		5	18	25	301	748.0	
		6	18	29	301	702.4	
		mean	**18**	**27**	**301**	**733.8**	**1.00**
22129 (test item)	10	1	254	275	55	106.8	
		2	270	289	61	93.9	
		3	262	281	51	117.0	
		4	296	301	67	83.2	
		5	296	300	72	75.7	
		6	301	301	72	75.7	
		mean	**280**	**291**	**63**	**92.0**	**0.13**
	50	1	142	164	47	163.5	
		2	115	121	60	150.1	
		3	106	123	63	147.7	
		4	132	146	58	141.1	
		5	110	123	68	137.4	
		6	119	131	73	124.0	
		mean	**121**	**135**	**62**	**144.0**	**0.20**
	100 (= undiluted)	1	53	62	35	402.4	
		2	55	61	40	371.0	
		3	60	70	37	361.3	
		4	76	83	34	339.1	
		5	53	66	39	372.4	
		6	60	70	43	331.5	
		mean	**60**	**69**	**38**	**363.0**	**0.49**

AS = active substance Haem. = haemorrhage Coag. = coagulation RI = irritation index [Q] = quotient
*Time of first appearance of the reaction; if this time is greater than 5 min. (i.e. no reaction within 5 min.), it is reported as 301

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Table 2: Results of the HET-CAM performed according to the reaction-time method *(continuous observation during the 5-minute application)*

2nd experiment (23.12.2004)

Treatment	Conc. [% w/w]	Egg no.	Reaction times* [sec.]			Evaluation ("HetCam.exe")	
			Haem.	Lysis	Coag.	RI	[Q]
Texapon® ASV (reference item)	5 (AS)	1	19	29	301	674.5	
		2	18	28	301	709.5	
		3	17	29	301	727.2	
		4	19	28	301	684.6	
		5	18	31	301	681.2	
		6	19	30	301	665.1	
		mean	**18**	**29**	**301**	**690.3**	**1.00**
22129 (test item)	10	1	246	263	60	99.8	
		2	236	257	49	127.7	
		3	222	250	59	102.9	
		4	257	275	65	89.9	
		5	247	272	61	97.7	
		6	233	263	49	127.7	
		mean	**240**	**263**	**57**	**107.6**	**0.16**
	50	1	140	165	44	175.1	
		2	145	153	53	147.2	
		3	146	160	60	129.3	
		4	136	154	46	170.6	
		5	145	157	57	136.6	
		6	143	149	57	138.5	
		mean	**143**	**156**	**53**	**149.5**	**0.22**
	100 (= undiluted)	1	67	73	47	304.0	
		2	43	51	38	448.5	
		3	53	64	30	443.2	
		4	54	60	31	439.5	
		5	50	54	34	441.2	
		6	60	68	37	370.0	
		mean	**55**	**62**	**36**	**407.7**	**0.59**

AS = active substance Haem. = haemorrhage Coag. = coagulation RI = irritation index [Q] = quotient
*Time of first appearance of the reaction; if this time is greater than 5 min. (i.e. no reaction within 5 min.), it is reported as 301

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- Appendix 1 -

Reaction-Time Method: Mathematical model (originally developed by HENKEL)

The aim of the model is to describe the local compatibility of a test substance by exactly one number. The basis of all considerations is that the "reaction time" largely determines this quantity. In this context "reaction time" is understood to be the time in seconds that elapses between application of the test substance and the occurrence of the relevant reaction. The assessment of the egg membrane is terminated at the latest after 5 minutes. Any reaction not observed within this period is described by the term "301 seconds".

In the context of evaluating a test substance it appears logical to give greater weight to reactions that occur very quickly after application of the test substance than to reactions that appear relatively late.

In order to develop a generally valid model, recourse must be made to a formal representation. The measurement of local compatibility is described below.

The test substance is usually applied to the chorioallantoic membrane of the incubated egg with the help of a pipette and the evaluator/tester measures the time that elapses before a specific reaction occurs. In general, "K" different reaction types are assessed on "M" eggs. Reaction times $X_{k,j}$ (measured in seconds) are therefore obtained, where k varies between 1 and K and j between 1 and M.

It also seems plausible that more strongly irritant substances should be characterized by higher values than less irritant substances. Because, however, reaction to strongly irritant substances occurs very quickly, a sort of 5-minute complement must be formulated.

(1) $$Y_{k,j} = \frac{301 - X_{k,j}}{X_{k,j}} \qquad \text{for all } k,j$$

As a result of this quotient formulation the smaller values, i.e. the rapidly occurring reactions, are given greater weighting.

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- Appendix 1 – (continued)

In order to evaluate the reaction types a weighting factor g_k^1 is formulated for each reaction:

(2) $$g_k^1 = \frac{301 - \frac{1}{M} \cdot \sum_{j=1}^{M} X_{k,j}}{10}$$

The subtrahend in the numerator is the mean value of all times for all eggs; it is obviously less than or equal to 301, so that g_k^1 is always positive; g_k^1 is later referred to as "factor 1".

Another weighting is introduced to take account of cases where a specific reaction is not observed on at least one egg. The following definition applies:

(3) $$d_{k,j} = \begin{cases} \mathbf{1}, \text{ if } X_{k,j} \neq 301 \text{ (reaction)} \\ \mathbf{0}, \text{ if } X_{k,j} = 301 \text{ (no reaction)} \end{cases}$$

If the arithmetic mean of this quantity is calculated in accordance with

(4) $$g_k^2 = \frac{1}{M} \cdot \sum_{j=1}^{M} \cdot d_{k,j} \qquad \text{for all k}$$

the sum in (4) represents exactly the number of times that the reaction k is observed on the various eggs; g_k^2 therefore lies between 0 and 1 and is later referred to as "factor 2".

These two weighting factors:

$$g_k^1 \text{ and } g_k^2$$

enable us to define the contribution of reaction k on egg j to the local compatibility potential of the substance.

(5) $$R_{k,j} = g_k^1 \cdot Y_{k,j} \cdot g_k^2 \qquad \text{for all k and j}$$

The last step is to calculate the sum of the contributions of the egg j with regard to all reactions K.

(6) $$S_j = \sum_{k=1}^{K} \cdot R_{k,j} \qquad \text{for all j}$$

In accordance with (6), M (normally 6) measured values are thus obtained for a specific substance. The irritation index (RI) is the mean value of the 6 S_j values.

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- Appendix 2 -

Historical range of the irritation index (RI) obtained with the reaction-time method (5-minute exposure) for the reference item Texapon® ASV 5% active substance (AS)

Reaction-time method: RI of Texapon® ASV 5% AS						
Test period	Median (Q2)	n	Min.	Max.	Quartile 1 (Q1)	Quartile 3 (Q3)
01.01.1996 – 31.12.1996	723.0	15	592.2	777.7	634.2	740.8
01.01.1997 – 31.12.1997	682.3	34	610.0	743.7	662.4	708.0
01.01.1998 - 31.12.1998	695.8	9	642.6	745.3	668.5	710.1
01.01.1999 - 31.12.1999	652.9	20	557.5	756.3	626.4	674.4
01.01.2000 - 31.12.2000	703.1	10	623.2	800.6	695.5	748.4
01.01.2001 – 31.12.2001	653.7	20	559.9	740.1	619.8	682.6
01.01.2002 – 31.12.2002	688.4	39	580.0	770.4	657.7	699.6
01.01.2003 – 31.12.2003	687.0	28	624.9	755.3	666.2	705.6
01.01.2004 – 31.12.2004	690.3	21	651.4	733.8	670.8	695.6

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[redacted]

Study number: [redacted]
Test item code: **22129**

Marly, 17 January 2005 [redacted]

[redacted]

ASSESSMENT OF THE EYE IRRITATION POTENTIAL OF
PEG-7 Glyceryl Cocoate
RAW MATERIAL NO. 22129

BY CYTOTOXICITY MEASUREMENT

IN THE NEUTRAL RED UPTAKE ASSAY (NRU) ON HUMAN KERATINOCYTES (HaCaT)

FINAL REPORT

Sponsor: [redacted]

Testing Facility: [redacted]

Head of Testing Facility: [redacted] Biologist

Study Director: [redacted] Cert. Biologist

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DECLARATION

The experiments reported here were performed in accordance with the Principles of Good Laboratory Practice (GLP), although the procedures were **not inspected** by a Quality Assurance Unit (QAU). There were no significant deviations from the GLP Regulations which could have affected the quality or the integrity of the study and this final report accurately reflects the raw data obtained during the experiments.

[redacted]

Study Director

[redacted]

17.01.2005

Date

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GUIDELINES

As no official guidelines exist, the Neutral Red Uptake (NRU) assay was essentially performed according to the Standard Operating Procedure developed for the COLIPA (the European Cosmetic, Toiletry and Perfumery Association) International Validation Study on Alternatives to the Draize Rabbit Eye Irritation Test (Brantom et al. 1997), with the following modifications:

- human keratinocytes from the cell line HaCaT were used instead of the Balb/c 3T3 mouse fibroblasts
- the treatment was performed in serum-free culture medium
- an in-house classification system was used instead of the COLIPA prediction model.

TIME SCHEDULE

Order:	26.11.2004
Experimental starting date:	01.12.2004
Experimental completion date:	22.12.2004
Final report:	17.01.2005

ARCHIVING

All raw data, samples and the original of the final report are stored in the archives of [redacted] for at least 30 years (or up to the expiry date).

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SUMMARY

The aim of this study was to assess the eye irritation potential of the test item by measuring its cytotoxicity in the Neutral Red Uptake assay. Monolayers of human keratinocytes (HaCaT) were exposed in 96-well microtiter plates to various concentrations of the test item, for 24 hours. Cell viability was measured by neutral red uptake, and the concentration causing 50% reduction in neutral red uptake in treated cells compared to untreated control cells (NRU-50) was determined.

In this Neutral Red Uptake study comprising two definitive independent assays, the test item caused cytotoxicity to the HaCaT cells, resulting in a median NRU-50 value of **427** µg/ml.

According to our in-house NRU classification system for the assessment of eye irritation potential, based on NRU-50 and comprising 3 classes (non-irritant, not classified, severe), and where the NRU assay is performed as part of an in vitro test battery, the test item is considered as **not classified**.

INTRODUCTION

The Neutral Red Uptake (NRU) assay is an in vitro cytotoxicity test proposed as an alternative method to the Draize rabbit eye irritation test. The NRU assay protocol is essentially based on the method originally described by Borenfreund et al. (1984 & 1985) with Balb/c 3T3 mouse fibroblasts, which was first modified for the EC/HO (European Commission / British Home Office) Validation Study performed in 1992-1994 (Balls et al. 1995; ECVAM INVITTOX protocol number 100) and then for the COLIPA Validation Study (1994–1997, Brantom et al. 1997, Jones et al. 1999). Finally, HaCaT cells, a spontaneously immortalized human keratinocyte line (Boukamp et al. 1988), are used instead of the Balb/c 3T3 mouse fibroblasts.

The Neutral Red Uptake assay is an in vitro short-term test measuring basic cytotoxic effects on cells in culture. Neutral red (= 3-amino-7-dimethylamino-2-methyl-phenazine hydrochloride), a weakly cationic vital dye, has been shown to be selectively retained in the lysosomes of living cells by electrostatic bounds to anionic sites in the lysosomal matrix, and the amount of neutral red taken up by the cells is directly proportional to the number of viable cells in culture. Dead cells or cells with damaged membranes are unable to take up and bind neutral red.
The neutral red absorbed by the cells after exposure to the test item is extracted and measured spectrophotometrically at 540 nm. Toxic effects induce a reduction in the neutral red uptake, and the cytotoxicity endpoint is determined as the concentration of test item causing a 50% reduction compared to negative control cells.

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MATERIAL AND METHODS

1. Test item

Code: 22129

Batch: Lot R 0006028

Trade name:

Supplier:

Other name: PEG-7 GLYCERYL COCOATE 100%

CAS number: 68553-02-6

Raw material number: 22129

Appearance: clear, light yellow, viscous liquid oil

Date of receipt: 26.11.2004 [redacted]

Stability: expiry date: 22.09.2005

Storage conditions: at room temperature, in the dark

Archives number: TOX 581

Vehicle: KGM® (serum-free keratinocyte growth medium), Clonetics CC-3101 (KBM®, keratinocyte basal medium) supplemented with CC-4131 (KGM® SingleQuots®, premeasured, single-use aliquots of growth factors and antimicrobials)

2. Reference item

Sodium dodecyl sulfate (= Sodium Lauryl Sulfate, SLS); Sigma L-4509; CAS 151-21-3; $C_{12}H_{25}O_4SNa$; FW 288.38; minimum 98.5% GC; batch 074K0041; expiry date: 16.11.2007

3. Test system

The Neutral Red Uptake assay in this study is performed with HaCaT cells, a spontaneously immortalized human keratinocyte line (Boukamp et al. 1988), kindly provided by Prof. Dr. N. E. Fusenig (Deutsches Krebsforschungszentrum DKFZ, Heidelberg, Germany). HaCaT cells are maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 2 mM L-glutamine, 10% (v/v) foetal calf serum (FCS), 100 IU/ml penicillin and 100 µg/ml streptomycin, at 37 ± 1°C in a humidified atmosphere of 95% air and 5% CO2. A stock of cells is stored frozen (at -196°C in liquid nitrogen) in aliquots of 1-2 x 10^6 cells/ml in DMEM containing 20% FCS and 10% dimethylsulfoxide (DMSO).
For the NRU assay, the HaCaT cells are first grown for 24 hours in the maintenance medium described above, and then exposed to the test item in serum-free biochemically defined keratinocyte growth medium (KGM), which is a modified MCDB 153 formulation (from the laboratory of Dr. Richard Ham, University of Colorado, Department of Molecular and Cellular Developmental Biology) supplemented by the supplier (Clonetics) with 0.1 ng/ml epidermal growth factor, 5 µg/ml insulin, 0.5 µg/ml hydrocortisone, 0.15 mM Ca^{++}, 0.4 % v/v bovine pituitary extract (7.5 mg/ml), and antibiotics.

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4. Experimental procedure

4.1 Principle of the assay

The NRU assay is based on the inability of dead or damaged cells to take up the vital dye neutral red. The amount of neutral red which is taken up by the cells after exposure to the test item is proportional to the number of viable cells in culture. After extraction of the neutral red retained in the lysosomes of living cells the absorbances are measured spectrophotometrically and compared with negative control (untreated) cells. The NRU-50 endpoint, which is the test item concentration causing 50% reduction in neutral red uptake relative to negative control, is determined directly from the graph of "percentage relative cell viability" versus "test item concentration".

4.2 Experimental design

An initial dose-range-finding experiment is carried out using 8 concentrations, with half-log dilution factor, up to 10'000 µg/ml KGM to establish the appropriate test item dose range for the definitive neutral red uptake assays. If the test item is not readily soluble in KGM, dimethylsulfoxide (DMSO) or ethanol can be used as a solvent at the maximal test concentration of 1% in KGM. In this case, the test item is first dissolved in the solvent at 100'000 µg/ml and then diluted 100-fold in KGM (highest working concentration = 1000 µg/ml). Based on the range-finding assay results, a series of 8 appropriate concentrations, with 1/6th log dilution factor, covering the range of doses where the NRU-50 value will occur, are selected for the definitive Neutral Red Uptake assay. A second independent assay is carried out with the same doses. In all of these NRU assays, both the pH and the osmolality of the highest test item concentration are measured, and Sodium Lauryl Sulfate (SLS) is included as a reference item at 50, 25, 10 and 1 µg/ml in the same 96-well microplate as the test item.

4.3 Neutral Red Uptake assay procedure

The Neutral Red Uptake assay is carried out according to the standard operating procedure developed for the COLIPA International Validation Study on Alternatives to the Draize Rabbit Eye Irritation Test (Brantom et al. 1997), with the following modifications: human keratinocytes from the cell line HaCaT are used instead of the Balb/c 3T3 mouse fibroblasts and the treatment is performed in serum-free culture medium.
HaCaT cells are seeded in the 60 central wells of 96-well microtiter plates (approximately 2 x 10^4 cells per well in 250 µl maintenance medium), whereas the edge wells, used as blank controls, receive the maintenance medium only. The plates are incubated for 24 hours at 37°C in a humidified atmosphere of 5% CO2/95% air. The culture medium is then removed and replaced by treatment medium only or by treatment medium containing various concentrations of the test or of the reference item. The blank wells (= edge wells), along with 2 vertical columns of six wells at either side of the plate which are to be used as (negative) cell controls, are filled with 250 µl of treatment medium KGM (serum-free keratinocyte growth medium), with or without solvent as appropriate, but no test item. The remainder of the plate (i.e. the central wells) consists of 12 horizontal groups of four wells enabling the dosing of 8 concentrations of the test item (in KGM) and 4 concentrations of SLS (in KGM) in quadruplicate, on the same plate.

NRU assay
Study number: [redacted]
Test item code: **22129**

96-well plate layout:

	1	2	3	4	5	6	7	8	9	10	11	12
A	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC
B	BC	CC	TI1	TI1	TI1	TI1	TI2	TI2	TI2	TI2	CC	BC
C	BC	CC	TI3	TI3	TI3	TI3	TI4	TI4	TI4	TI4	CC	BC
D	BC	CC	TI5	TI5	TI5	TI5	TI6	TI6	TI6	TI6	CC	BC
E	BC	CC	TI7	TI7	TI7	TI7	TI8	TI8	TI8	TI8	CC	BC
F	BC	CC	SLS1	SLS1	SLS1	SLS1	SLS2	SLS2	SLS2	SLS2	CC	BC
G	BC	CC	SLS3	SLS3	SLS3	SLS3	SLS4	SLS4	SLS4	SLS4	CC	BC
H	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC

BC = blank controls; CC = cell controls (= negative controls)
TI1 – TI 8 = eight test item doses; SLS1 –SLS4 = four SLS doses (reference item)

After 24 hours of exposure, the treatment medium is replaced by maintenance medium containing 50 µg/ml neutral red. The plates are returned to the incubator for 3 hours. Thereafter, the medium is removed, the cells are quickly washed with a fixative (1% formaldehyde /1% calcium chloride solution) and then 100 µl of extraction solution (1% glacial acetic acid in 50% ethanol) are added to each well to extract the dye. After 20 minutes incubation at room temperature, the absorbance of neutral red at 540 nm is measured with a microplate reader.

5. Test evaluation

5.1 Test data calculation

Cytotoxicity dose-response curves are drawn for the test and reference items using the median of the blank-corrected absorbances of replicate wells, expressed as a percentage viability of negative control, versus test concentrations. Then, the NRU-50 value, which is the test item concentration required to reduce the neutral red uptake to 50% of negative control, is determined from the graph by interpolation. The NRU-50 values generated in the definitive valid assays are averaged and the median NRU-50 value is reported as the cytotoxicity endpoint of the study and used for the classification.

5.2 Acceptability of the NRU assay

The acceptability of the test item NRU-50 value is assessed using the result of a reference item obtained on the same plate. For that purpose, SLS is included as a positive cytotoxic control on each 96-well microtiter plate at 50, 25, 10 and 1 µg/ml. According to our experience and on the basis of all the historical NRU-50 values obtained in our laboratory with the reference item SLS (see Appendix 1), an NRU assay 96-well plate with an NRU-50 value of SLS between 10 and 30 µg/ml will be considered acceptable.

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5.3 Evaluation of the test results

According to the conclusions of the COLIPA International Validation Study (Jones P. et al. 1999), the Neutral Red Uptake assay, using Balb/c 3T3 mouse fibroblasts, appeared to have limited value as a replacement of the Draize rabbit eye irritation test. On the basis of in-house data on cosmetic products, the overall linear in vivo/in vitro correlation obtained by comparing the in vivo MMAS (Modified Maximum Average Score) with the NRU-50 values was demonstrated to be better for HaCaT cells (= human keratinocytes) than for the 3T3 mouse fibroblasts ([redacted], but not yet sufficient to be used to develop a prediction model relating NRU-50 directly to in vivo MMAS.

Because of the limitations mentioned above, we use the NRU-50 values as a relative cytotoxicity parameter enabling us to rank different formulations of similar composition or different chemicals with similar structure, or to assess the irritation potential of a new test item by comparison with benchmarks.

Furthermore, based on the literature (Jones P. et al. 1999) and according to our in-house experience with cosmetic formulations [redacted] the following internal classification system for the NRU assay performed as part of an in vitro test battery, comprising also e.g. Red Blood Cell (RBC), Neutral Red Release (NRR), Hen's Egg Test (HET-CAM), for the assessment of eye irritation, can be used to identify products of low and high irritation potential:

NRU-50 [µg/ml]	**Classification**
≥750	non-irritant
110 - 749	not classified
< 110	severe

If the results obtained in the different assays of the in vitro test battery are contradictory, the ultimate decision is then normally taken on a "worst case" basis.

According to our experience, it is not recommended to apply this classification system to:
- products containing more than 50% alcohol (risk of false negatives)
- products containing more than 20% surfactant (risk of false positives).

Furthermore, according to the literature, inorganic acids or bases represent also known limitations to the use of the NRU assay (risk of false negatives).

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RESULTS

In this study, the eye irritation potential of the test item was assessed by measuring its cytotoxicity in the Neutral Red Uptake assay. One dose-range-finding assay and two independent definitive NRU assays with identical test item doses were performed. The detailed experimental data (individual and median values of absorbance at 540 nm; calculated percentages of relative viability of treated compared to negative control cells; NRU-50 values of both test and reference items, determined from the graph of percentage viability versus concentration) are presented in the Tables 1 to 3.
In the three NRU assays of this study, the NRU-50 values of the reference item SLS were within the historical range established in our laboratory (see Appendix 1 and acceptability criteria in chapter 5.2 of Material and Methods).
In the initial dose-range-finding assay, the NRU-50 value of the test item was identified between 1000 and 316.2 µg/ml (Table 1). On the basis of this result, eight doses ranging from 1468 to 100 µg/ml were tested in the two definitive NRU assays.
The results of the two definitive NRU assays are summarized in the following table:

	NRU-50 [µg/ml]			Classification*
Test item code	1st definitive assay	2nd definitive assay	median	(non-irritant, not classified, severe)
22129	419	435	**427**	not classified

* to be used in the context of an in vitro test battery

CONCLUSION

From the results obtained in the NRU assays of this study and under the experimental conditions reported, it is concluded that the test item caused cytotoxicity to the HaCaT cells, resulting in a median NRU-50 value of **427 µg/ml**.

According to our in-house NRU classification system for the assessment of eye irritation potential, based on NRU-50 and comprising 3 classes (non-irritant, not classified, severe), and where the NRU assay is performed as part of an in vitro test battery, the test item is considered as **not classified**.

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Jones P. A., Bracher M., Marenus K. and Kojima H. (1999) Performance of the neutral red uptake assay in the COLIPA international validation study on alternatives to the rabbit eye irritation test. *Toxicology in Vitro* **13**, 325-333.

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NRU assay
Study number: [redacted]
Test item code: **22129**

Table 1: Results of the NRU dose-range-finding assay

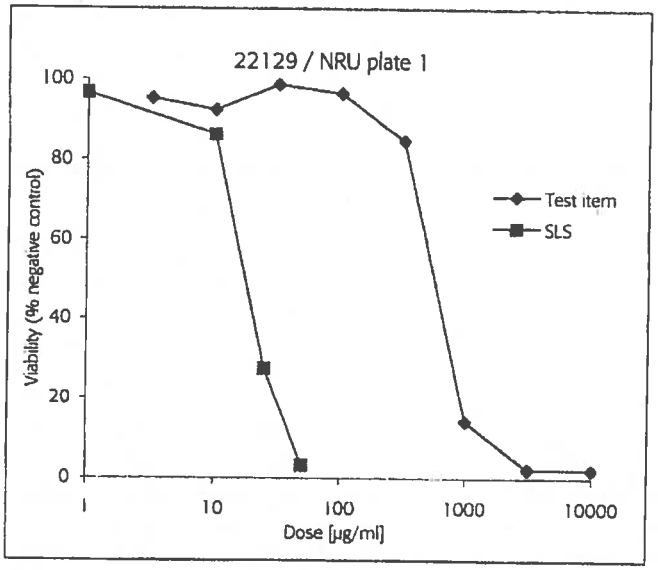
Absorbances at 540 nm (A540) measured in the 96-well microtiter plate — Date: 03.12.2004

	1	2	3	4	5	6	7	8	9	10	11	12
A	0.051	0.051	0.050	0.050	0.050	0.050	0.056	0.051	0.053	0.053	0.052	0.054
B	0.050	1.146	0.072	0.074	0.070	0.074	0.075	0.075	0.074	0.078	1.154	0.051
C	0.047	1.148	0.185	0.215	0.234	0.195	1.002	0.914	0.991	0.962	1.188	0.050
D	0.044	1.141	1.104	1.089	1.123	1.106	1.123	1.130	1.129	1.150	1.171	0.049
E	0.047	1.114	1.059	1.080	1.038	1.063	1.052	1.075	1.110	1.131	1.170	0.047
F	0.050	1.127	0.086	0.091	0.084	0.079	0.416	0.355	0.343	0.297	1.132	0.053
G	0.050	1.115	1.041	0.988	1.002	0.939	1.108	1.113	1.106	1.079	1.124	0.049
H	0.050	0.051	0.050	0.051	0.048	0.051	0.051	0.048	0.049	0.048	0.048	0.050

Median of blanks = 0.050

	Wells	*Dose [µg/ml]*	*pH*	*Osmol.* [Osm/kg]*	*A540 (- median of blanks) median*	*Viability (% neg. contr.)*
Test item	B3:B6	10'000	7.4	0.372	0.023	2.1
	B7:B10	3162	-	-	0.025	2.3
	C3:C6	1000	-	-	0.155	14.2
	C7:C10	316.2	-	-	0.927	84.7
	D3:D6	100	-	-	1.055	96.5
	D7:D10	31.62	-	-	1.080	98.7
	E3:E6	10	-	-	1.011	92.5
	E7:E10	3.162	-	-	1.043	95.3
Negative control	B2:G2;B11:G11	0	-	-	1.094	100
SLS	F3:F6	50	-	-	0.035	3.2
(Reference item)	F7:F10	25	-	-	0.299	27.3
	G3:G6	10	-	-	0.945	86.4
	G7:G10	1	-	-	1.057	96.7

**Osmol. = osmolality*



Final results:	*NRU-50 [µg/ml]*
Test item:	**652.8**
SLS:	19.2

NRU assay
Study number: [redacted]
Test item code: **22129**

Table 2: Results of the first definitive NRU assay

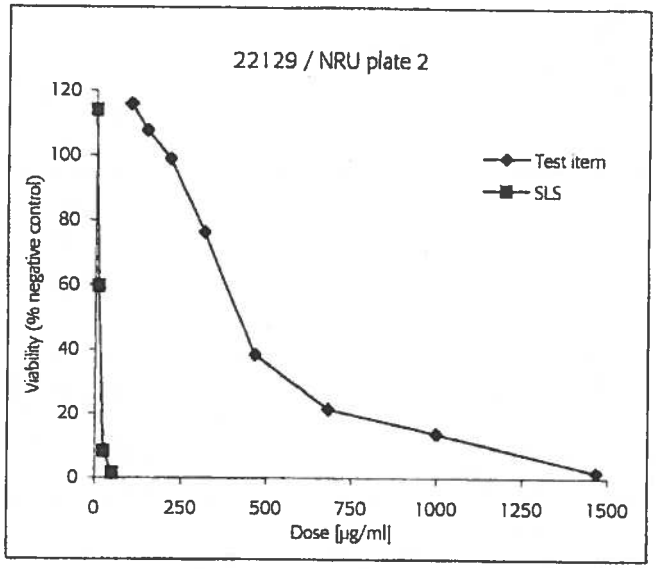
Absorbances at 540 nm (A540) measured in the 96-well microtiter plate — Date: 15.12.2004

	1	2	3	4	5	6	7	8	9	10	11	12
A	0.057	0.060	0.058	0.058	0.061	0.055	0.059	0.058	0.059	0.058	0.057	0.059
B	0.060	0.918	0.075	0.072	0.070	0.085	0.176	0.173	0.158	0.225	0.932	0.060
C	0.059	0.929	0.330	0.242	0.236	0.221	0.361	0.409	0.298	0.418	0.856	0.060
D	0.052	0.895	0.709	0.729	0.705	0.642	0.994	0.839	0.859	0.938	1.017	0.053
E	0.058	0.900	0.884	1.019	0.980	0.966	1.047	1.039	0.924	1.080	0.846	0.086
F	0.059	0.890	0.067	0.068	0.072	0.073	0.131	0.123	0.126	0.149	0.915	0.058
G	0.057	0.849	0.531	0.523	0.721	0.597	0.942	1.011	1.043	1.091	1.011	0.060
H	0.052	0.055	0.055	0.055	0.054	0.053	0.056	0.055	0.054	0.066	0.058	0.063

Median of blanks = 0.058

	Wells	*Dose [µg/ml]*	*pH*	*Osmol.* [Osm/kg]*	*A540 (- median of blanks) median*	*Viability (% neg. contr.)*
Test item	B3:B6	1468	7.4	0.360	0.016	1.8
	B7:B10	1000	-	-	0.117	13.7
	C3:C6	681.3	-	-	0.181	21.3
	C7:C10	464.2	-	-	0.327	38.5
	D3:D6	316.2	-	-	0.649	76.4
	D7:D10	215.4	-	-	0.841	98.9
	E3:E6	146.8	-	-	0.915	107.7
	E7:E10	100	-	-	0.985	116.0
Negative control	B2:G2;B11:G11	0	-	-	0.850	100
SLS (Reference item)	F3:F6	50	-	-	0.012	1.4
	F7:F10	25	-	-	0.071	8.3
	G3:G6	10	-	-	0.506	59.6
	G7:G10	1	-	-	0.969	114.1

**Osmol. = osmolality*



Final results:	*NRU-50 [µg/ml]*
Test item:	**419.3**
SLS:	12.8

NRU assay
Study number: [redacted]
Test item code: **22129**

Table 3: Results of the second definitive NRU assay

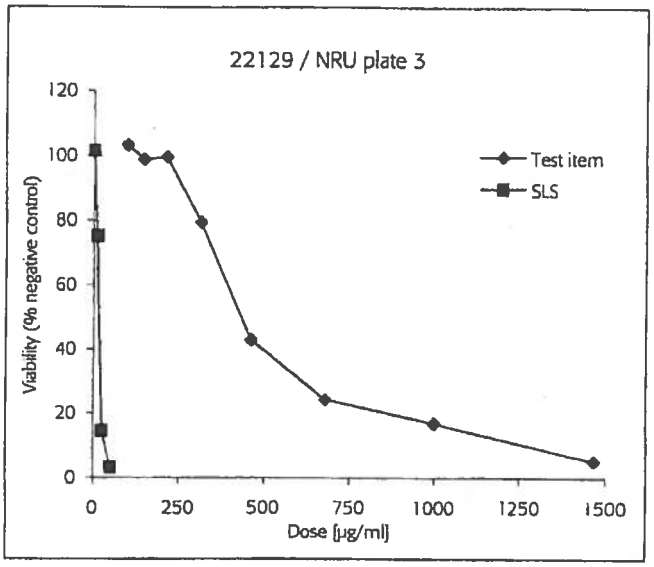
Absorbances at 540 nm (A540) measured in the 96-well microtiter plate — Date: 22.12.2004

	1	2	3	4	5	6	7	8	9	10	11	12
A	0.053	0.057	0.053	0.053	0.053	0.052	0.053	0.052	0.054	0.055	0.054	0.053
B	0.054	1.108	0.106	0.109	0.119	0.103	0.243	0.183	0.225	0.239	1.169	0.054
C	0.055	1.109	0.266	0.307	0.356	0.315	0.545	0.479	0.520	0.503	1.147	0.059
D	0.045	1.084	0.942	0.804	0.868	0.935	1.159	1.038	1.156	1.080	1.140	0.048
E	0.051	1.105	1.106	1.114	1.076	1.125	1.142	1.082	1.258	1.173	1.201	0.051
F	0.054	1.093	0.079	0.086	0.086	0.085	0.217	0.196	0.211	0.206	1.154	0.051
G	0.054	1.067	0.825	0.855	0.888	0.860	1.131	1.136	1.184	1.142	1.164	0.050
H	0.050	0.055	0.057	0.053	0.051	0.054	0.057	0.053	0.067	0.053	0.056	0.053

Median of blanks = 0.053

	Wells	*Dose [µg/ml]*	*pH*	*Osmol.* [Osm/kg]*	*A540 (- median of blanks) median*	*Viability (% neg. contr.)*
Test item	B3:B6	1468	7.4	0.360	0.055	5.1
	B7:B10	1000	-	-	0.179	16.7
	C3:C6	681.3	-	-	0.258	24.1
	C7:C10	464.2	-	-	0.459	42.8
	D3:D6	316.2	-	-	0.849	79.2
	D7:D10	215.4	-	-	1.065	99.4
	E3:E6	146.8	-	-	1.057	98.6
	E7:E10	100	-	-	1.105	103.1
Negative control	B2:G2;B11:G11	0	-	-	1.072	100
SLS	F3:F6	50	-	-	0.033	3.0
(Reference item)	F7:F10	25	-	-	0.156	14.5
	G3:G6	10	-	-	0.805	75.1
	G7:G10	1	-	-	1.086	101.4

**Osmol. = osmolality*



Final results:	*NRU-50 [µg/ml]*
Test item:	**434.9**
SLS:	16.2

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- Appendix 1 -

Historical NRU-50 values for the reference item Sodium Lauryl Sulfate (SLS; Sigma L-4509) used at the concentrations of 1, 10, 25 and 50 µg/ml in the Neutral Red Uptake assay with HaCaT cells:

NRU-50 of SLS controls [µg/ml]						
Test period	mean	s.d.	s.e.m.	n	min.	max.
01.01.1997 – 31.12.1997	17.0	2.8	0.2	144	11.3	23.8
01.01.1998 – 31.12.1998	18.0	3.1	0.2	168	9.7	26.6
01.01.1999 – 31.12.1999	22.1	5.1	0.5	92	12.9	30.4
01.01.2000 – 31.12.2000	16.2	2.4	0.3	64	13.1	24.0
01.01.2001 – 31.12.2001	15.3	3.1	0.3	148	10.4	28.0
01.01.2002 – 31.12.2002	15.8	3.1	0.2	164	10.2	26.8
01.01.2003 – 31.12.2003	16.2	2.3	0.2	147	11.8	24.6
01.01.2004 – 31.12.2004	16.0	2.9	0.2	195	10.6	27.7

s.d. = standard deviation s.e.m. = standard error of the mean

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HAZLETON
LABORATORIES AMERICA, INC.
1330-B PICCARD DRIVE, ROCKVILLE, MARYLAND 20850

Sponsor:

[redacted]

FINAL REPORT

Study Title:

28-Day Subchronic Oral Toxicity Study in Rats with
S1202.01 [redacted]

contains 0.8% PEG-7 Glyceryl Cocoate

Author:

Merrill R. Usheroff, Ph.D., D.A.B.T.

Study Completion Date:

July 7, 1989

Performing Laboratory:

Hazleton Laboratories America, Inc.
1330-B Piccard Drive
Rockville, Maryland 20850

[redacted]

Laboratory Project Identification:

HLA Study No. [redacted]

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HAZLETON
LABORATORIES AMERICA, INC.
1290-B PICCARD DRIVE, ROCKVILLE, MARYLAND 20850

[redacted]

COMPLIANCE STATEMENT
28-Day Subchronic Oral Toxicity Study in Rats with
S1202.03 [redacted]

This study was conducted in compliance with the Good Laboratory Practice Regulations as set forth in Title 21 of the U.S. Code of Federal Regulations Part 58. There were no deviations from the aforementioned regulations which affected the quality or integrity of the study or the interpretation of the results in the report.

Study Director:

Merrill R. Osheroff 7/7/89

MERRILL R. OSHEROFF, Ph.D., D.A.B.T. /Date
Life Sciences Division

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HAZLETON
LABORATORIES AMERICA, INC.
[redacted]

QUALITY ASSURANCE UNIT

Project Title: 28-Day Subchronic Oral Toxicity Study in Rats with S1202.01 [redacted]

Project No.: [redacted]

Quality Assurance inspections of the study and review of the final report of the above referenced project were conducted according to the procedures described in the standard operating procedures of the Quality Assurance Unit and according to the general requirements of the Good Laboratory Practice Regulations, 21 CFR Part 58 as issued by the Food and Drug Administration. Findings from the inspections and the final report review were reported to management on the following dates:

Inspections/Review	Findings Reported	Inspector/Reviewer
Protocol 8/1/88	8/5/88	R. Fuller
Inspection 8/3-5/88	8/5/88	R. Fuller
Final Report 11/9-11,14-18,20/88 12/5/88	12/9/88	R. Fuller

Final Report Reviewer
Quality Assurance Unit

6/15/89
Date Released

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HAZLETON
LABORATORIES AMERICA, INC.
1500-E PICCARD DRIVE, ROCKVILLE, MARYLAND 20850

[redacted]

STUDY IDENTIFICATION
28-Day Subchronic Oral Toxicity Study in Rats with
S1202.01 [redacted]

HLA Study Number	[redacted]
Test Material	S1202.01 [redacted]
Sponsor/Study Monitor	[redacted]
Study Director	Merrill R. Osheroff, Ph.D., D.A.B.T. Hazleton Laboratories America, Inc. 9200 Leesburg Turnpike Vienna, Virginia 22180 (703) 893-5400

Study Timetable

Study Initiation (Protocol Signature)	June 22, 1988
Initiation of Dosing	July 7, 1988
Completion of Terminal Necropsy	August 5, 1988

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HAZLETON
LABORATORIES AMERICA, INC
1930-B PICCARD DRIVE, ROCKVILLE, MARYLAND 20850

[redacted]

STUDY PERSONNEL
28-Day Subchronic Oral Toxicity Study in Rats with
51202.01 [redacted]

Study Director:	Merrill R. Osheroff, Ph.D., D.A.B.T.
Study Coordinator:	Ellen T. Czeh, B.S.
Clinical Pathologist:	Richard D. Alsaker, D.V.M., M.S., D.A.B.T. Diplomate, American College of Veterinary Pathologists
Histopathologist:	George A. Parker, D.V.M. Diplomate, American College of Veterinary Pathologists
Veterinarian:	Joseph A. Manda, III, D.V.M., M.S.
Statistician:	Ajit K. Thakur, Ph.D.
Laboratory Supervisor:	Howard D. Thornett, B.S.

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7530-B RICCARD DRIVE ROCKVILLE, MARYLAND 20850

[redacted]

SUMMARY

This study was designed to assess the toxicity of a test material when administered to rats in the diet for at least 28 days. The test material, 51202.01 [redacted], was administered to three groups of male rats (10/group) at levels of 2.5 (Group 3), 5.0 (Group 4), or 7.5% (Group 5). In addition, 10 male rats were administered basal diet only (Group 1) and 10 additional male rats were administered 7.5% celluflour in basal diet (Group 2) and served as the concurrent control groups. Rats were observed twice daily for mortality and/or moribundity and for obvious signs of toxic effects. Body weights, food consumption, physical examinations, and detailed clinical observations were recorded/performed weekly. Ophthalmoscopic examinations were performed prior to initiation of dosing and during the week prior to the terminal sacrifice. Clinical pathology evaluations (hematology and clinical chemistry) were performed on all animals prior to termination. After at least 28 days of treatment, all animals were sacrificed in the presence of a veterinary pathologist and subjected to a complete gross necropsy. Organ weight evaluations (brain, liver, kidneys, testes, spleen, and heart) were performed on each animal, and a histomorphologic examination of protocol-specified tissues was performed on all animals in Groups 1 and 5 and on all gross lesions.

There was no mortality during the course of the study. In addition, there were no ophthalmic lesions, and the only apparent compound-related clinical observation noted was that of soft feces in a number of the Group 4 and 5 males. Statistical evaluation of weekly mean body weight values and mean body weight gains (Weeks 0-4) failed to reveal any evidence of a compound-related effect. Mean food consumption values indicate a significantly greater intake (Weeks 3 and 4) for the Group 5 rats in comparison to the Group 1 controls, although this difference was not reflected in an increased mean body weight for the Group 5 rats.

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[redacted]

Statistical evaluation of clinical pathology data demonstrated comparability of results for those parameters assayed. Organ weight evaluations revealed a significant decrease (and significant linear trend for a dose-related decrease) in the Group 5 absolute and relative mean spleen weight values when compared to both the Group 1 and Group 2 controls. Although no histologic evidence of altered spleen morphology was noted, the significant depression in spleen weight may be associated with compound administration.

At necropsy, gross examination of tissues revealed a distended cecum and/or material in the lumen of the cecum, as well as enlarged mesenteric lymph nodes in a number of the Group 4 and 5 rats. Microscopic examination of protocol-specified tissues failed to reveal any histomorphologic evidence of a compound-related effect.

Based on the data generated from this study, it may be concluded that the administration of S1202.01 to male Sprague-Dawley rats at dose levels of 5.0% or greater results in soft feces, grossly observable distended cecum and/or material in the lumen of the cecum, grossly enlarged mesenteric lymph nodes, and significantly reduced spleen weight values. Due to the lack of any corroborating histomorphological information as well as the absence of any apparent toxic manifestations, the toxicological significance of these aforementioned signs is questionable. However, a no-observable-effect level of S1202.01 in the diet of male Sprague-Dawley rats is identified as 2.5%.

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RESEARCH TOXICOLOGY CENTRE S.p.A.

= PEG-7 Glyceryl Cocoate

DELAYED DERMAL SENSITISATION STUDY IN THE GUINEA PIG

FINAL REPORT

RTC Study Number: [redacted]

Seen and approved by:

A. Nunziata
Responsible for Toxicological
Experimentation as authorized
by the Italian Ministry of Health

A. Marzoli
President

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[redacted]

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COMPLIANCE STATEMENT

We, the undersigned, hereby declare that this report is a true and faithful account of the procedures adopted and the results obtained in the performance of this study. The aspects of this study conducted by Research Toxicology Centre S.p.A. were performed in accordance with:

A. "Good Laboratory Practice Standards" of the U.S. Environmental Protection Agency, Code of Federal Regulations, 40, Part 792, U.S. Federal Register, Vol. 54, No. 158, 17th August 1989.

B. Decreto Legislativo 27 gennaio 1992 n.120 published in the Gazzetta Ufficiale della Repubblica Italiana 18 febbraio 1992.

(Adoption of the Commission Directive of 18th December 1989 adapting to technical progress the Annex to Council Directive 88/320/EEC on the inspection and verification of Good Laboratory Practice (90/18/EEC)).

(G. Haynes, B.Sc., C.Biol., M.I.Biol.)
Study Director:

Date: 27 APRIL 1995

(J. Brightwell, Ph.D.)
Scientific Director:

Date: 27.04.95

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[redacted]

QUALITY ASSURANCE STATEMENT

Study phases monitored by RTC's QAU according to current relevant Standard Operating Procedures	Quality Assurance Inspections (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
STUDY PROTOCOL AND AMENDMENT	04-08-94 25-10-94	04-08-94 25-10-94	04-08-94 25-10-94
PROCEDURES, DATA AND FACILITIES RELEVANT TO THIS TYPE OF STUDY	27-10-94 14-11-94 07-12-94 13-12-94 14-12-94 14-12-94 16-12-94 16-01-95 26-01-95 30-01-95 10-02-95 14-02-95 24-02-95		10-11-94 02-12-94 13-12-94 21-12-94 21-12-94 21-12-94 23-12-94 13-02-95 01-02-95 01-03-95 01-03-95 17-02-95 01-03-95
FINAL REPORT Review of this report by RTC's QAU found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.		Review completed 26 April, 1995	

Valent Sforza

V. Sforza, B.S.
(Head of Quality Assurance)

26/04/95
Date

[redacted]

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1. SUMMARY

The potential of the test substance, [redacted] to induce and elicit delayed dermal sensitisation was assessed by a guinea pig model using the maximisation test of Magnusson and Kligman.

The concentrations of the test substance used in the main study were determined by the results of preliminary screening tests.

The main sensitisation test was undertaken using a test group of ten animals and a control group of ten animals. In an attempt to induce sensitisation test animals were intradermally injected with an emulsion of Freund's complete adjuvant and the test substance at 1% concentration in both the vehicle and an emulsion of Freund's complete adjuvant. One week later this was boosted by the topical application of the test substance at 100% concentration over the injection sites. Control group animals were treated in the same manner but the selected vehicle (sterile water) was used in place of the test substance. Two weeks after the second induction stage, all animals were challenged by topical application of both the vehicle and the undiluted test substance.

One animal from the control group died during the study.

No response to either the test substance or the vehicle was observed in any animal of either the test or control group.

Changes in body weight during the period of the study were similar in animals from both test and control groups.

These results indicate that the test substance does not elicit a sensitisation response in the guinea pig. Classification based on these results would indicate the following:-

Classification: Not required
Symbol: None indicated
R phrase: None indicated

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[redacted]

2. INTRODUCTION

The purpose of the study was to assess the ability of the test substance to induce and elicit delayed dermal hypersensitivity (skin sensitisation) by use of a guinea pig model. This allowed an indication of hazard classification required by the Classification, Packaging and Labelling of Dangerous Substances regulations.

The procedures used were those of the maximisation test developed by B. Magnusson and A. M. Kligman (J. Invest. Dermatol., 52, 268, 1969 and Allergic Contact Dermatitis in the Guinea Pig, publ. Thomas, Springfield, Illinois, 1970). These meet the requirements of the test for skin sensitisation described by the Organisation for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals, Number 406, adopted on 17th July 1992. These methods are recognised by Commission Directive 92/69/EEC of 31st July 1992 (adapting to technical progress for the seventeenth time, Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances).

The species and route of administration were those stated in the guidelines, giving a valid model for the assessment of sensitisation.

The test was designed to assess the potential for delayed dermal sensitisation to occur on exposure to the test substance during manufacturing, handling or use.

The study was carried out at: Research Toxicology Centre S.p.A.
Via Tito Speri, 12
00040 Pomezia (Roma)
Italy

The study started on 26th July 1994 with Study Director signature of the protocol. It was completed on the date shown against the Study Director signature at the front of this report. The in-life phase of the study commenced on 30th November 1994 with allocation to treatment of animals for the preliminary dose-ranging screen and was completed on 2nd February 1995.

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3. TEST SUBSTANCE

Details of the test substance received at the testing facility were as follows:

Name	:
Raw Material Number	: 22129
Lot or Batch Number	: 01774125
Expiry date	: -
Received from	: [redacted]
Date received	: 8th September 1994
Amount shipped	: 203.49 grams gross
Description	: Pale yellow liquid
Container	: Dark glass bottle
Storage at RTC	: Approximately +4°C, in a dessicator
RTC reference number	: 1631

Detailed characterisation of the test substance was not undertaken at the testing facility. The determination of the identity, strength, purity, composition, stability and method of derivation and/or synthesis of the test substance was the responsibility of the Sponsor. An aliquot of the test substance was taken and will be retained within the RTC archives for a minimum period of five years.

The test substance was prepared for dosing by mixing with sterile water. A range of concentrations was selected for the preliminary tolerance phase of the study and the results of this indicated that the test substance at 1% concentration would be suitable for use in the intradermal injection phase of the induction procedure, being physically injectable and tolerated by the test system. The undiluted test substance was used at both the topical induction and challenge stages.

Freund's complete adjuvant (FCA), a mixture of paraffin oil, an emulsifier and killed mycobacteria, was used to enhance the potential of the test substance to cause a delayed contact hypersensitivity reaction. It was used as a 50% v/v emulsion of FCA in sterile water. The test substance was mixed with sterile water prior to emulsification with the adjuvant.

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[redacted]

4. METHODS

Any deviations from the study protocol are detailed within the text of the report. No deviations occurred that were considered to have compromised the purpose or conduct of the study.

Dated and signed records of all activities relating to the day by day conduct and maintenance of the study were made.

4.1 Animal management

4.1.1 Animal supply

Young adult female guinea pigs of the Dunkin-Hartley strain were ordered from Charles River Italia S.p.A., Calco (Como), Italy. Animals were ordered nulliparous and non-pregnant, within the weight range of 300 to 350 grams and 5 to 6 weeks of age.

The animals were delivered to the testing facility on 27th October and 22nd December 1994 for the different phases of the study. Animals appeared to be in an acceptable condition when they arrived and an acclimatisation period of at least thirteen days was permitted before undertaking any dosing procedure.

4.1.2 Animal husbandry

Animals used in the preliminary intradermal tolerance screen were housed, in groups of two animals, in stainless steel cages measuring 68 x 32 x 67 cm, with a grid floor (Techniplast Gazzada S.a.r.l., Buguggiate, Varese, Italy). Other animals were housed, in groups of up to five animals, in stainless steel cages, measuring 69 x 45 x 51 cm, with a grid floor (Techniplast Gazzada S.a.r.l., Buguggiate, Varese, Italy). Cages were suspended over metal trays which held an absorbent material. This was inspected daily and changed as necessary. Throughout the study, each cage was identified by a label, colour-coded according to group, recording the study number, animal numbers and details of treatment.

Controls for the animal room were set to maintain temperature within the range of 17 to 23°C and relative humidity within the range of 30 to 70%. Actual conditions achieved were recorded daily.

The room was lit by fluorescent light to give an artificial cycle of twelve hours light/twelve hours dark.

4.1.3 Water and diet

Animals were offered drinking water supplied to each cage via a water bottle and a commercially available laboratory diet (Altromin MSK, A. Rieper S.p.A., Bolzano, Italy) ad libitum throughout the study.

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There was no information to indicate that any component was present in either diet or drinking water at a level likely to interfere with the purpose or conduct of the study.

4.1.4 Allocation to groups

Animals were selected from available stock and randomly allocated to treatment groups prior to each phase of the study. Animals were then identified by tattoo in the ear with an individual number.

4.2 Experimental Procedure

The study was divided into two distinct phases. The first of these was a dose-ranging screen which was used to determine suitable dose levels for use in the second phase. This second phase formed the main study, a determination of the sensitisation potential of the test substance.

4.2.1 Intradermal injection tolerance test

Two animals were selected from those available and the hair over the scapulae was removed using an electric clipper with suitable blade. Six sites were selected on each animal and these injected intradermally with 0.1 ml of the test substance. Each site was injected with a single concentration of the test substance. The two animals of the group were treated with the substance at concentrations of 100%, 50%, 20%, 10%, 5% and 1% in sterile water.

The treated sites of all animals were then examined after five days for any signs of reaction to treatment. Observed irritation was recorded using the Draize scoring scale (below) and any response not covered by the scoring scale was separately described.

Erythema and eschar formation	Value
No response	0
Very slight erythema	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema to slight eschar formation	4

4.2.2 Topical application tolerance test

Five animals were selected from those available and the hair over the scapulae was removed using an electric clipper with suitable blade. Each animal was then injected intradermally at the prepared site with two injections, each of 0.1 ml, of emulsified Freund's complete adjuvant.

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[redacted]

At least seven days later the flanks of each animal were clipped free of hair. Each animal was dosed with two concentrations of the test substance, one on either flank. A gauze patch measuring at least 20 x 20 mm was soaked with 0.2 ml of the selected concentration of the test substance. This was then placed onto the selected treatment site and secured in position using a patch of adhesive strapping.

When both sites of the animal had been treated, they were covered with a strip of aluminium foil to act as an occlusive barrier and the trunk of the animal was wrapped with an elastic adhesive bandage to keep the test substance in contact with the skin.

All animals were treated in this manner such that a total of five concentrations (100%, 50%, 20%, 10% and 5% in sterile water) of the test substance were each dosed in duplicate. The adhesive dressings and gauze patches were removed after twenty four hours contact with the skin.

Twenty four and forty eight hours after removal of the dressings, the treated sites were examined for signs of reaction to treatment. Each site was assessed and scored on the following scale:-

Score	Reaction observed
0	No visible change
1	Discrete or patchy erythema
2	Moderate and confluent erythema
3	Intense erythema and swelling

4.2.3 Main study - Induction - Intradermal injection

Animals were allocated to treatment to give a test group of ten animals and a control group of ten animals. On the day of dosing (Day 1) the hair was clipped from the scapular region of each animal over an area approximately 20 x 40 mm. Three pairs of intradermal injections were made at the prepared skin site of each animal. All injections were made at the edge of the prepared site and the anterior and median injections were positioned close together and distant from the posterior injections. A volume of 0.1 ml was injected at each point.

Animals of the test group were treated as follows:-

Injection site	Treatment
Anterior	Emulsified Freund's complete adjuvant
Median	1% test substance in the vehicle
Posterior	1% test substance in emulsified Freund's complete adjuvant

[redacted]

Animals of the control group were treated in the same manner except that the test substance was replaced by the vehicle alone. The treatment plan was:-

Injection site	Treatment
Anterior	Emulsified Freund's complete adjuvant
Median	Vehicle (sterile water)
Posterior	Vehicle mixed with emulsified Freund's complete adjuvant

Skin reaction at the injection sites was assessed approximately twenty four hours after injection.

4.2.4 Main study - Induction - Topical application

Six days after injection, the area surrounding the injection sites on each animal was clipped free of hair and 0.5 ml of sodium lauryl sulphate (10% in petrolatum) was spread evenly over the sites. This was intended to provoke irritation of the skin and enhance potential absorption of the test substance.

The next day (Day 8 of the study), animals of the test group were treated with the undiluted test substance. A gauze patch was covered with 0.4 ml of the test substance and placed over the injection sites. This was covered with a strip of aluminium foil to serve as an occlusive barrier and the animal was then wrapped with a length of elastic adhesive bandage to keep the gauze patch in contact with the skin. All animals of the test group were treated in this manner and animals of the control group were similarly treated with sterile water (the vehicle alone).

After a contact period of forty eight hours the dressings were removed and the treated sites gently cleaned by washing with warm water. Reaction to treatment was assessed at the treated sites approximately twenty four hours after removal of the dressings using the following scoring system:-

Score	Reaction to treatment
0	No visible change
1	Discrete or patchy erythema
2	Moderate and confluent erythema
3	Intense erythema and swelling

[redacted]

4.2.5 Main study - Challenge

On Day 22, three weeks after preparing the animals for the first induction phase of the main study, all animals were prepared for challenge by clipping the flanks free of hair to expose areas approximately 50 mm x 50 mm on each flank. Patches of gauze measuring 20 mm x 20 mm were soaked with 0.2 ml aliquots of the undiluted test substance. These were placed on the right flank of each animal, of both test and control groups, in the centre of the prepared skin site. The left flank of each animal was similarly treated with patches soaked with 0.2 ml of sterile water (the vehicle) alone.

The treated sites were covered with a strip of aluminium foil to act as an occlusive barrier and each animal then wrapped with a length of elastic adhesive bandage to keep the test substance and vehicle in contact with the skin. After a contact period of twenty four hours the dressings and patches were removed.

Approximately twenty one hours after removal of the dressings and patches, the treated sites were closely clipped to remove any hair that may have grown.

Approximately three hours later, twenty four hours after removal of the dressings, the treated sites were examined for any signs of reaction to treatment.

The following scoring scale was used to describe any observed reaction:-

Score	Reaction to treatment
0	No visible change
1	Discrete or patchy erythema
2	Moderate and confluent erythema
3	Intense erythema and swelling

This examination was repeated twenty four hours later, forty eight hours after removal of the dressings.

4.2.6 Body weight

Animals of the main study phase were weighed at the start of the treatment phase and on termination of the study.

4.2.7 Termination and necropsy

The animal found dead during the study, underwent a necropsy examination to establish, where possible, the cause of death or ill health.

Other animals were killed by carbon dioxide narcosis following the end of the experimental procedure but were not subjected to any necropsy procedure.

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[redacted]

4.3 Classification

The results obtained on testing were used to classify the test substance according to the requirements of the classification, packaging and labelling of dangerous substances regulations (Commission Directive 83/467/EEC of 29th July 1983, updated by Commission Directive 91/325/EEC of 1st March 1991).

The test would be considered positive if 30% or more of animals in the test group exhibit erythema or dermal swelling following challenge with a non-irritant concentration of the test substance. The non-irritant nature of the test substance at the concentration used at challenge would be demonstrated by the lack of dermal responses in the control group.

Should the test have been considered positive, the test substance would require labelling with the risk phrase (R 43) "May cause sensitisation by skin contact" and symbol "Xi".

In addition, the incidence of positive responses was used to classify the test substance using a scheme based on that described by A. M. Kligman (J. Invest. Dermatol., 47, 393-409, 1966).

Sensitisation incidence	Grade	Classification
0% - 8%	I	Weak
9% - 28%	II	Mild
29% - 64%	III	Moderate
65% - 80%	IV	Strong
81% - 100%	V	Extreme

4.4 Archives

The raw data and documentation generated during the course of this study will be retained at RTC for five years after which the Sponsor will be contacted regarding despatch or disposal of the material.

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[redacted]

5. RESULTS

5.1 Preliminary tolerance tests (Tables 1 and 2)

The preliminary tolerance test to establish a suitable concentration for injection in the main sensitisation test indicated that the test substance at 1% concentration was reasonably tolerated by the test system.

The topical application test demonstrated that the undiluted test substance was suitable for use at the topical induction and challenge stages of the study, being tolerated by the test system and exhibiting no irritant response.

5.2 Induction (Tables 3 and 4)

Significant reaction was apparent at the sites of intradermal injection following administration of Freund's complete adjuvant (test and control groups), the vehicle mixed with Freund's complete adjuvant (control group) and the test substance mixed with Freund's complete adjuvant (test group). Those sites treated with the test substance in the vehicle (test group) exhibited a slightly reduced response to treatment. Sites treated with the vehicle alone (control group) exhibited minor response.

No reaction was noted around the injection sites following forty eight hours topical exposure to either the test substance (test group) or the vehicle (control group).

5.3 Challenge (Table 5)

No response to either test substance or the vehicle was observed in any animal of either test or control groups after the end of the challenge dosing procedure.

5.4 Body weight (Table 6)

Changes in body weight during the period of the study were similar in animals from both test and control groups.

5.5 Necropsy (Table 7)

Examination of the animal that died during the study revealed no significant abnormalities. There was nothing to indicate that death was caused as a result of administration of the test substance.

[redacted]

6. CONCLUSION

The results of this study indicate that the test substance, , does not act as a sensitiser in the guinea pig, there being no response to challenge following an induction procedure with the substance.

This result would classify the substance as a weak (Grade I) sensitiser when using the classification scale of Kligman. Evaluation of sensitisation required by regulations on the classification, packaging and labelling of dangerous substances indicated the following :-

Classification: Not required
Symbol: None indicated
R phrase: None indicated

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[redacted]

TABLE 1 - INTRADERMAL INJECTION TOLERANCE TEST - INDIVIDUAL RESULTS

This table details the results of examination of injection sites five days after injection of a range of concentrations of the test substance in the selected vehicle (sterile water).

Animal number	Test substance concentration	Erythema	Additional comments
563	100%		Necrosis
	50%		Necrosis
	20%		Necrosis
	10%		Necrosis
	5%	4	None
	1%	2	None
565	100%		Necrosis
	50%		Necrosis
	20%		Necrosis
	10%	4	None
	5%	4	None
	1%	0	None

KEY

0 = No response
1 = Very slight erythema
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema to slight eschar formation

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[redacted]

TABLE 2 - TOPICAL APPLICATION TOLERANCE TEST - INDIVIDUAL RESULTS

This table details the results of examination of treated sites following topical application of a range of concentrations of the test substance [redacted] in the selected vehicle (sterile water).

Animal number	Observation time	Test substance concentration 100%	50%	20%	10%	5%
65	24 hours	0	0			
	48 hours	0	0			
67	24 hours		0	0		
	48 hours		0	0		
69	24 hours			0	0	
	48 hours			0	0	
71	24 hours				0	0
	48 hours				0	0
73	24 hours	0				0
	48 hours	0				0

KEY

0 = No visible change
1 = Discrete or patchy erythema
2 = Moderate and confluent erythema
3 = Intense erythema and swelling

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[redacted]

TABLE 3 - MAIN STUDY - INJECTION INDUCTION - INDIVIDUAL RESULTS

This table details the responses observed twenty four hours after injection of animals either with the test substance [redacted], at 1% concentration or the vehicle alone (sterile water) in the initial phase of induction.

Group function	Animal number	Dermal response					
		Anterior (FCA emulsion)		Median (Vehicle)		Posterior (Vehicle/FCA)	
		Left	Right	Left	Right	Left	Right
	225	3	3	1	1	3	3
	227	3	3	0	0	3	3
C	229	3	3	1	1	3	3
O	231	3	3	0	0	3	3
N	233	3	3	0	0	3	3
T	235	3	3	0	0	3	3
R	237	3	3	1	1	3	3
O	239	3	3	0	0	3	3
L	241	3	3	0	0	3	3
	243	3	3	0	0	3	3
		Anterior (FCA emulsion)		Median (Substance)		Posterior (Substance/FCA)	
		Left	Right	Left	Right	Left	Right
	245	3	3	2	2	3	3
	247	3	3	2	2	3	3
	249	3	3	2	2	3	3
T	251	3	3	2	2	3	3
E	253	3	3	2	2	3	3
S	255	3	3	3	3	3	3
T	257	3	3	2	2	3	3
	259	3	3	3	3	3	3
	261	3	3	3	3	3	3
	263	3	3	3	3	3	3

KEY: 0 = No response
1 = Very slight erythema
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema to slight eschar formation

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[redacted]

TABLE 4 - MAIN STUDY - TOPICAL INDUCTION - INDIVIDUAL RESULTS

This table details the findings at the injection sites of each animal following topical application of the test substance at 100% concentration or vehicle alone (sterile water) during the second stage of the induction procedure.

Group function	Animal number	Dermal response
CONTROL	225	0
	227	0
	229	0
	231	0
	233	0
	235	0
	237	0
	239	0
	241	0
	243	0
TEST	245	0
	247	0
	249	0
	251	0
	253	0
	255	0
	257	0
	259	0
	261	0
	263	0

KEY: 0 = No visible change
1 = Discrete or patchy erythema
2 = Moderate and confluent erythema
3 = Intense erythema and swelling

[redacted]

TABLE 5 - MAIN STUDY - CHALLENGE - INDIVIDUAL RESULTS

This table details the responses observed following challenge by topical application of the test substance at 100% concentration and the vehicle alone (sterile water).

Group function	Animal number	Dermal response			
		Vehicle		Test substance	
		24 hours	48 hours	24 hours	48 hours
	225	0	0	0	0
	227	0	0	0	0
C	229	-	-	-	-
O	231	0	0	0	0
N	233	0	0	0	0
T	235	0	0	0	0
R	237	0	0	0	0
O	239	0	0	0	0
L	241	0	0	0	0
	243	0	0	0	0
	245	0	0	0	0
	247	0	0	0	0
	249	0	0	0	0
T	251	0	0	0	0
E	253	0	0	0	0
S	255	0	0	0	0
T	257	0	0	0	0
	259	0	0	0	0
	261	0	0	0	0
	263	0	0	0	0

KEY: 0 = No visible change
1 = Discrete or patchy erythema
2 = Moderate and confluent erythema
3 = Intense erythema and swelling
- = Decedent

[redacted]

TABLE 6 - MAIN STUDY - BODY WEIGHTS - INDIVIDUAL VALUES

This table details the body weights of animals used in the study.

Group function	Animal number	Body weight (g) on Day:- 1	25	Change in body weight (g) Day 1 to Day 25
	225	451	528	77
	227	552	662	110
	229	476	-	-
C	231	448	533	85
O	233	504	585	81
N	235	492	636	144
T	237	481	617	136
R	239	436	489	53
O	241	461	627	166
L	243	470	566	96
	Mean	477.1	582.6	105.3
	S.Dev.	33.5	57.9	36.7
	245	527	594	67
	247	468	530	62
	249	471	561	90
	251	450	523	73
T	253	445	516	71
E	255	456	612	156
S	257	480	581	101
T	259	503	603	100
	261	452	520	68
	263	468	573	105
	Mean	472.0	561.3	89.3
	S.Dev.	25.7	36.7	28.4

KEY

- = Decedent

[redacted]

TABLE 7 - MAIN STUDY - NECROPSY - INDIVIDUAL FINDINGS

This table details the necropsy findings on examination of those animals that died during the study.

Group	Animal number	Tissue/ organ	Finding
Control	229	Injection site	Right eye, fore-limbs and hind-limbs cannibalised. Subcutis of skin dark and thickened.

[redacted]

TABLE 8 - RELIABILITY CHECK - SUMMARY

This table summarises the results obtained in the most recent reliability checks.

REFERENCE SUBSTANCE:	Mercaptobenzothiazole	
CONCENTRATION:	INDUCTION (INJECTION)	- 2% in Alembicol D
	(TOPICAL)	- 50% in acetone
	CHALLENGE	- 25% in acetone
CRITICAL DATES:	INDUCTION (INJECTION)	- 11th January 1995
	(TOPICAL)	- 18th January 1995
	CHALLENGE	- 1st February 1995
RESULTS:	100% response in test group at challenge 0% response in control group at challenge	
INTERPRETATION:	Incidence at challenge acceptable Test system regarded as valid	

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REPEATED INSULT PATCH STUDY

TKL STUDY NO. [redacted]

[redacted]

Styling Pomade containing 8% PEG-7 Glyceryl Cocoate

CONDUCTED FOR:

[redacted]

DATE OF REPORT:

January 21, 2004

TKL Research, Inc., 4 Forest Avenue, Paramus, NJ 07652 Tel (201) 587-0500 Fax (201) 587-0878 Email: info@tklresearch.com

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SIGNATURES

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Kathleen Georgeian, Clinical Research Coordinator and Manager, Dermatologic Safety Testing — Date

1/20/04

Jonathan S. Dosik, MD
Principal Investigator — Date

STATEMENT OF QUALITY ASSURANCE

This report has been reviewed by the TKL Research, Inc. (TKL) Corporate Quality Assurance Department and the report accurately reflects the raw data for this study.

Clinical research studies are performed by TKL in accordance with all applicable federal regulations and proposed guidelines for Good Clinical Practices, which include:

21 CFR Part 312,	Investigational New Drug Application
21 CFR Part 50,	Protection of Human Subjects
21 CFR Part 56,	Institutional Review Boards

Henry Brisco 1/21/04

Quality Assurance — Date

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TITLE OF STUDY

Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIAL

TSIN: BCS578-094 Styling Pomade ← 8% PEG-7 Glyceryl Cocoate in styling pomade

DATE STUDY INITIATED

September 3, 2003

DATE STUDY COMPLETED

October 10, 2003

DATE OF REPORT

January 21, 2004

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INVESTIGATIVE PERSONNEL

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SUMMARY

One study material, TSIN: BCS578-094, was evaluated neat to determine its ability to sensitize the skin of normal volunteer subjects using a semi-occlusive repeated insult patch study. One hundred three subjects completed the study. The dermatologist was in attendance for the 48-hour challenge evaluation.

Under the conditions employed in this study, there was no evidence of sensitization to TSIN: BCS578-094.

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1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 100 completed subjects.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. were males or females, 18 years of age or older, in general good health;

2. were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;

3. were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;

4. had completed a medical screening procedure; and

5. had read, understood, and signed an informed consent agreement.

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3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;

3. had psoriasis and/or active atopic dermatitis/eczema;

4. were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or

5. had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed informed consent document in compliance with FDA regulations (21 CFR Part 50) was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix IV).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 consecutive applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application*.

* A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

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Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days.

Subjects who were absent once during the induction phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization.

3.2.2 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

- = No reaction
? = Minimal or doubtful response, slightly different from surrounding normal skin
\+ = Definite erythema, no edema
++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema
S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p = Papular response > 50%
pv = Papulovesicular response > 50%
D = Damage to epidermis: oozing, crusting and/or superficial erosions
I = Itching
X = Subject absent
PD = Patch dislodged
NA = Not applied
NP = Not patched (due to reaction achieved)
N9G = No ninth grading

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3.2.3 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 Study Material Specifications

Identification	:	TSIN: BCS578-094 Styling Pomade
Amount Applied	:	0.1g ± 0.03g
Special Instructions	:	Applied to patch no longer than 30 minutes prior to patch application.

4.2 Storage, Handling, and Documentation of Study Material

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. At the conclusion of the clinical study, the remaining study material was discarded or returned to the sponsor and the disposition documented in the logbook. All information regarding the receipt, storage, and disposition of the study material was also recorded on a Clinical Material Record form (see Appendix III), which is incorporated in this study report. All study material is kept in a locked product storage room accessible to clinical staff members only.

4.3 Application of Study Material

Study material was applied to the patch as instructed. The patch was applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 Description of Patch Conditions

Material evaluated under occlusive patch conditions was applied to a 2-cm x 2-cm Webril pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch was secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions was applied to a 2-cm x 2-cm Webril pad. The pad was affixed to the skin with hypoallergenic tape (Micropore).

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5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred rechallenge procedure involves the application of the product to naïve sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 PROTOCOL

See Protocol - Appendix V.

7.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) are designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, and end of study status. Originals or copies of all CRFs, source documents, IRB documents (if required), correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage is maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provides a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the sponsor's review on the premises of TKL.

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8.0 RESULTS AND DISCUSSION

One hundred eight subjects between the ages of 20 and 69 were enrolled and 103 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).

The following table summarizes subject enrollment and disposition.

Number enrolled:		108
Number discontinued:		5
Lost to follow-up:	3	
Voluntary withdrawal:	2	
Number completed:		103

Source: Table 1, Appendix I

There were no adverse events.

The dermatologist was present at the 48-hour challenge evaluation, a deviation from the protocol-specified 72-hour evaluation.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

9.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to TSIN: BCS578-094.

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APPENDIX I

SUMMARY TABLES

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TKL STUDY NO. [redacted]

TABLE 1: SUMMARY OF SUBJECT ENROLLMENT AND DISPOSITION

	N	(%)
SUBJECTS ENROLLED	108	
SUBJECTS COMPLETED ALL PHASES	103	(95.4)
TOTAL SUBJECTS DISCONTINUED	5	(4.6)
LOST TO FOLLOW-UP	3	(2.8)
VOLUNTARY WITHDRAWAL	2	(1.9)

NOTE: ALL PERCENTAGES ARE RELATIVE TO TOTAL SUBJECTS ENROLLED

SEE DATA LISTING 1 FOR FURTHER DETAIL

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TKL STUDY NO. [redacted]
TABLE 2: SUMMARY OF SUBJECT DEMOGRAPHICS
ALL ENROLLED SUBJECTS

AGE	
N (%) 18 TO 44	42 (38.9)
N (%) 45 TO 64	56 (51.9)
N (%) 65 AND UP	10 (9.3)
MEAN (SD)	48.1 (12.0)
MEDIAN	49.8
RANGE	20.0 TO 69.9
GENDER	
N (%) MALE	21 (19.4)
N (%) FEMALE	87 (80.6)
RACE	
N (%) CAUCASIAN	4 (3.7)
N (%) HISPANIC	104 (96.3)

SEE DATA LISTING 2 FOR FURTHER DETAIL

PROGRAM: DEMOSMY.SAS/USES: DEMOGS/21OCT03:09:20:40

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[redacted]
TKL STUDY NO. [redacted]

TABLE 3: SUMMARY OF DERMATOLOGIC RESPONSE GRADES
NUMBER OF SUBJECTS BY PRODUCT

PRODUCT= TSIN: BCS578-094

	INDUCTION READING									MAKE-	CHALLENGE PHASE		
RESPONSE	1	2	3	4	5	6	7	8	9	UP	48HR	72HR	96HR(*)
-	106	101	104	104	103	101	102	102	103	14	103	103	
TOTAL EVALUABLE	106	101	104	104	103	101	102	102	103	14	103	103	
NUMBER ABSENT	1	5	2	1	2	2	1	1	0		0	0	
NUMBER DISCONTINUED	1	2	2	3	3	5	5	5	5		5	5	

MAXIMUM ELICITED RESPONSE DURING INDUCTION
ALL SUBJECTS COMPLETING INDUCTION (N=103)

RESPONSE	N(%) SUBJECTS
-	103 (100.0%)

(*) WHEN REQUIRED

KEY TO SYMBOLS:
- = NO REACTION
? = MINIMAL OR DOUBTFUL RESPONSE, SLIGHTLY DIFFERENT FROM SURROUNDING NORMAL SKIN
+ = DEFINITE ERYTHEMA, NO EDEMA
++ = DEFINITE ERYTHEMA, DEFINITE EDEMA
+++ = DEFINITE ERYTHEMA, DEFINITE EDEMA AND VESICULATION
D = DAMAGE TO EPIDERMIS: OOZING, CRUSTING AND/OR SUPERFICIAL EROSIONS
P = PAPULAR RESPONSE >50%

PROGRAM: SUMMARY.SAS/USES: RESPONSE, PRODLIST, FINAL/21OCT03:09:20:46

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APPENDIX II

DATA LISTINGS

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TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
1	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
2	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
3	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
4	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
5	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
6	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
7	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
8	09/03/03	09/03/03		09/10/03	I1	L	8
9	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
10	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
11	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
12	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
13	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
14	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
15	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
16	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
17	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
18	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
19	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
20	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
21	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
22	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
23	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
24	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
25	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
26	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
27	09/03/03	09/03/03		09/19/03	I5	L	17
28	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
29	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
30	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
31	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
32	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
33	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
34	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
35	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
36	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
37	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
38	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
39	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38

KEY: LAST READING # (I=INDUCTION PHASE, C=CHALLENGE PHASE)
COMPLETION STATUS (C=COMPLETED, L=LOST TO FOLLOW-UP, S=VOLUNTARY WITHDRAWAL
V=PROTOCOL VIOLATION, AE=ADVERSE EVENT, O=OTHER)

PROGRAM: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
40	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
41	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
42	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
43	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
44	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
45	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
46	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
47	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
48	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
49	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
50	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
51	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
52	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
53	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
54	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
55	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
56	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
57	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
58	09/03/03	09/03/03		09/12/03	I3	S	10
59	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
60	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
61	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
62	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
63	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
64	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
65	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
66	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
67	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
68	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
69	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
70	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
71	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
72	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
73	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
74	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
75	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
76	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
77	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
78	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38

KEY: LAST READING # (I=INDUCTION PHASE, C=CHALLENGE PHASE)
COMPLETION STATUS (C=COMPLETED, L=LOST TO FOLLOW-UP, S=VOLUNTARY WITHDRAWAL
V=PROTOCOL VIOLATION, AE=ADVERSE EVENT, O=OTHER)

PROGRAM: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
79	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
80	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
81	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
82	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
83	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
84	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
85	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
86	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
87	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
88	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
89	09/03/03	09/03/03		09/05/03	I0	S	3
90	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
91	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
92	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
93	09/03/03	09/03/03		09/19/03	I5	L	17
94	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
95	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
96	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
97	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
98	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
99	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
100	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
101	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
102	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
103	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
104	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
105	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
106	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
107	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
108	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38

KEY: LAST READING # (I=INDUCTION PHASE, C=CHALLENGE PHASE)
COMPLETION STATUS (C=COMPLETED, L=LOST TO FOLLOW-UP, S=VOLUNTARY WITHDRAWAL
V=PROTOCOL VIOLATION, AE=ADVERSE EVENT, O=OTHER)

PROGRAM: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 2: SUBJECT DEMOGRAPHICS

SUBJECT NO.	AGE	GENDER	RACE
1	59.0	MALE	HISPANIC
2	45.1	FEMALE	HISPANIC
3	56.4	FEMALE	HISPANIC
4	53.6	FEMALE	CAUCASIAN
5	59.4	MALE	HISPANIC
6	44.1	FEMALE	HISPANIC
7	37.0	FEMALE	HISPANIC
8	37.2	FEMALE	HISPANIC
9	62.0	MALE	HISPANIC
10	58.2	MALE	HISPANIC
11	31.8	FEMALE	HISPANIC
12	56.3	MALE	HISPANIC
13	57.8	FEMALE	HISPANIC
14	55.8	FEMALE	HISPANIC
15	65.3	FEMALE	HISPANIC
16	61.4	FEMALE	HISPANIC
17	35.0	FEMALE	HISPANIC
18	66.0	FEMALE	HISPANIC
19	36.1	FEMALE	HISPANIC
20	39.0	MALE	HISPANIC
21	34.5	FEMALE	HISPANIC
22	63.3	FEMALE	HISPANIC
23	58.2	FEMALE	HISPANIC
24	28.3	FEMALE	HISPANIC
25	63.3	FEMALE	HISPANIC
26	56.3	FEMALE	HISPANIC
27	58.9	FEMALE	HISPANIC
28	42.8	MALE	HISPANIC
29	49.1	FEMALE	HISPANIC
30	56.3	MALE	HISPANIC
31	55.7	FEMALE	HISPANIC
32	50.1	FEMALE	HISPANIC
33	38.1	FEMALE	HISPANIC
34	44.7	FEMALE	HISPANIC
35	26.0	FEMALE	HISPANIC
36	35.4	FEMALE	HISPANIC
37	51.0	FEMALE	HISPANIC
38	48.8	FEMALE	HISPANIC
39	54.7	FEMALE	HISPANIC
40	47.7	MALE	HISPANIC

PROGRAM: DEMOLIST.SAS/USES: DEMOGS/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 2: SUBJECT DEMOGRAPHICS

SUBJECT NO.	AGE	GENDER	RACE
41	45.2	MALE	HISPANIC
42	53.1	FEMALE	HISPANIC
43	38.5	FEMALE	HISPANIC
44	29.5	FEMALE	HISPANIC
45	32.3	FEMALE	HISPANIC
46	37.6	FEMALE	HISPANIC
47	43.8	FEMALE	HISPANIC
48	54.6	MALE	HISPANIC
49	48.8	FEMALE	HISPANIC
50	53.6	FEMALE	HISPANIC
51	47.4	FEMALE	HISPANIC
52	23.7	FEMALE	HISPANIC
53	41.2	FEMALE	HISPANIC
54	35.9	FEMALE	HISPANIC
55	27.6	FEMALE	HISPANIC
56	25.6	FEMALE	HISPANIC
57	50.2	FEMALE	HISPANIC
58	20.0	MALE	HISPANIC
59	34.3	FEMALE	HISPANIC
60	53.8	FEMALE	HISPANIC
61	69.8	FEMALE	HISPANIC
62	56.3	FEMALE	CAUCASIAN
63	37.3	FEMALE	HISPANIC
64	34.7	FEMALE	HISPANIC
65	54.6	FEMALE	HISPANIC
66	50.6	FEMALE	HISPANIC
67	28.6	FEMALE	HISPANIC
68	41.1	FEMALE	HISPANIC
69	55.8	FEMALE	HISPANIC
70	46.5	FEMALE	CAUCASIAN
71	45.5	FEMALE	HISPANIC
72	69.2	FEMALE	HISPANIC
73	38.1	MALE	HISPANIC
74	64.1	FEMALE	HISPANIC
75	41.6	FEMALE	HISPANIC
76	66.9	FEMALE	HISPANIC
77	54.3	FEMALE	HISPANIC
78	41.6	FEMALE	HISPANIC
79	50.3	FEMALE	HISPANIC
80	65.1	FEMALE	HISPANIC

PROGRAM: DEMOLIST.SAS/USES: DEMOGS/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 2: SUBJECT DEMOGRAPHICS

SUBJECT NO.	AGE	GENDER	RACE
81	66.7	FEMALE	HISPANIC
82	46.9	FEMALE	HISPANIC
83	53.9	FEMALE	HISPANIC
84	36.3	FEMALE	HISPANIC
85	58.3	FEMALE	HISPANIC
86	38.2	FEMALE	HISPANIC
87	69.9	FEMALE	HISPANIC
88	69.0	FEMALE	HISPANIC
89	44.5	MALE	HISPANIC
90	56.5	FEMALE	HISPANIC
91	38.8	MALE	HISPANIC
92	61.2	FEMALE	HISPANIC
93	23.0	MALE	HISPANIC
94	53.2	FEMALE	HISPANIC
95	55.8	MALE	CAUCASIAN
96	55.1	MALE	HISPANIC
97	39.5	FEMALE	HISPANIC
98	60.2	FEMALE	HISPANIC
99	68.5	FEMALE	HISPANIC
100	37.2	MALE	HISPANIC
101	49.8	FEMALE	HISPANIC
102	49.7	MALE	HISPANIC
103	48.9	FEMALE	HISPANIC
104	30.2	FEMALE	HISPANIC
105	52.5	FEMALE	HISPANIC
106	41.4	FEMALE	HISPANIC
107	49.9	MALE	HISPANIC
108	56.7	FEMALE	HISPANIC

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[redacted]
TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= TSIN: BCS578-094

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
1	-	-	-	-	-	-	-	-	-		-	-	
2	-	-	-	-	-	-	-	-	-		-	-	
3	-	-	-	-	-	-	-	-	-		-	-	
4	-	-	-	-	-	-	-	-	-		-	-	
5	-	-	-	-	-	-	-	-	-		-	-	
6	-	-	-	-	-	-	-	-	-		-	-	
7	-	-	-	-	-	-	-	-	-		-	-	
8	-	X	X	X	X	X	X	X	X		X	X	
9	-	-	-	-	-	-	-	-	-		-	-	
10	-	-	-	-	-	-	-	-	-		-	-	
11	-	-	-	-	-	-	-	-	-		-	-	
12	-	-	-	-	-	-	-	-	-		-	-	
13	-	-	-	-	-	-	-	-	-		-	-	
14	-	-	-	-	-	-	-	-	-		-	-	
15	-	-	-	-	-	-	-	-	-		-	-	
16	-	-	-	-	-	-	-	-	-		-	-	
17	-	-	-	-	-	-	-	-	-		-	-	
18	-	-	-	-	-	-	-	-	-		-	-	
19	-	-	-	-	-	-	-	-	-		-	-	
20	-	-	-	-	-	-	-	-	-		-	-	

KEY TO SYMBOLS:

- = NO REACTION
? = MINIMAL OR DOUBTFUL RESPONSE, SLIGHTLY DIFFERENT FROM SURROUNDING NORMAL SKIN

+ = DEFINITE ERYTHEMA, NO EDEMA
++ = DEFINITE ERYTHEMA, DEFINITE EDEMA

+++ = DEFINITE ERYTHEMA, DEFINITE EDEMA AND VESICULATION

N9G = NO NINTH GRADING
NA=NOT APPLIED
NP=NOT PATCHED DUE TO REACTION ACHIEVED
X = READING NOT PERFORMED DUE TO MISSED VISIT OR SUBJECT DISCONTINUATION
D = DAMAGE TO EPIDERMIS: OOZING, CRUSTING AND/OR SUPERFICIAL EROSIONS
P = PAPULAR RESPONSE >50%
NR=DATA NOT RECORDED
MU = MAKE-UP READING FOR MISSED INDUCTION VISIT

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/21OCT03:09:20:27

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TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= TSIN: BCS578-094

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
21	-	-	-	-	-	-	-	-	-		-	-	
22	-	-	-	-	-	-	-	-	-		-	-	
23	-	-	-	-	-	-	-	-	-		-	-	
24	-	-	-	-	-	-	-	-	-		-	-	
25	-	-	-	-	-	-	-	-	-		-	-	
26	-	-	-	-	-	X	-	-	-	-	-	-	
27	-	-	-	-	-	X	X	X	X		X	X	
28	-	-	-	-	-	-	-	-	-		-	-	
29	-	-	-	-	-	-	-	-	-		-	-	
30	-	-	-	-	-	-	-	-	-		-	-	
31	-	-	-	-	-	-	-	-	-		-	-	
32	-	-	-	-	-	-	-	-	-		-	-	
33	-	-	-	-	-	-	-	-	-		-	-	
34	-	-	-	-	-	-	-	-	-		-	-	
35	-	-	-	-	-	-	-	-	-		-	-	
36	-	-	-	-	-	-	-	-	-		-	-	
37	-	-	-	-	-	-	-	-	-		-	-	
38	-	X	-	-	-	-	-	-	-	-	-	-	
39	-	-	-	-	-	-	-	-	-		-	-	
40	-	-	-	-	-	-	-	-	-		-	-	
41	-	-	-	-	-	-	-	-	-		-	-	
42	-	-	-	-	-	-	-	X	-	-	-	-	
43	-	-	-	-	-	-	-	-	-		-	-	
44	-	X	-	-	-	-	-	-	-	-	-	-	
45	-	-	-	-	-	-	-	-	-		-	-	
46	-	-	-	-	-	-	-	-	-		-	-	
47	-	-	-	-	-	-	-	-	-		-	-	
48	-	-	-	-	-	-	-	-	-		-	-	
49	-	-	-	-	-	-	-	-	-		-	-	
50	-	-	-	-	-	-	-	-	-		-	-	
51	-	-	-	-	-	-	-	-	-		-	-	
52	-	-	-	-	-	-	-	-	-		-	-	

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/21OCT03:09:20:27

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TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= TSIN: BCS578-094

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
53	-	-	-	-	-	-	-	-	-		-	-	
54	-	-	-	-	-	-	-	-	-		-	-	
55	-	-	-	-	X	-	-	-	-	-	-	-	
56	-	-	-	-	-	-	-	-	-		-	-	
57	-	-	-	-	-	-	-	-	-		-	-	
58	X	-	-	X	X	X	X	X	X		X	X	
59	-	-	-	-	-	-	-	-	-		-	-	
60	-	-	-	-	-	-	-	-	-		-	-	
61	-	-	-	-	-	-	-	-	-		-	-	
62	-	-	-	-	-	-	-	-	-		-	-	
63	-	-	-	-	-	-	-	-	-		-	-	
64	-	-	-	-	-	-	-	-	-		-	-	
65	-	-	-	-	-	-	-	-	-		-	-	
66	-	-	-	-	-	-	-	-	-		-	-	
67	-	-	-	-	-	-	-	-	-		-	-	
68	-	-	-	-	-	-	-	-	-		-	-	
69	-	-	-	-	-	-	-	-	-		-	-	
70	-	-	-	-	-	-	-	-	-		-	-	
71	-	-	-	-	-	-	-	-	-		-	-	
72	-	-	-	-	-	-	-	-	-		-	-	
73	-	-	-	-	-	-	-	-	-		-	-	
74	-	-	-	-	-	-	-	-	-		-	-	
75	-	-	-	-	-	-	-	-	-		-	-	
76	-	X	-	-	-	-	-	-	-	-	-	-	
77	-	-	-	-	-	-	-	-	-		-	-	
78	-	-	-	-	-	-	-	-	-		-	-	
79	-	-	-	-	-	-	-	-	-		-	-	
80	-	-	-	-	-	-	-	-	-		-	-	
81	-	-	-	-	-	-	-	-	-		-	-	
82	-	-	-	-	-	-	-	-	-		-	-	
83	-	-	-	-	-	-	-	-	-		-	-	
84	-	-	-	-	-	-	-	-	-		-	-	

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/21OCT03:09:20:27

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TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= TSIN: BCS578-094

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
85	-	-	-	-	-	-	-	-	-		-	-	
86	-	-	-	-	-	-	-	-	-		-	-	
87	-	-	-	-	-	-	X	-	-	-	-	-	
88	-	-	-	-	-	-	-	-	-		-	-	
89	X	X	X	X	X	X	X	X	X		X	X	
90	-	-	-	-	-	-	-	-	-		-	-	
91	-	-	-	-	-	-	-	-	-		-	-	
92	-	-	X	-	-	-	-	-	-	-	-	-	
93	-	-	-	-	-	X	X	X	X		X	X	
94	-	-	-	-	-	-	-	-	-		-	-	
95	-	-	-	-	-	-	-	-	-		-	-	
96	-	-	-	-	-	-	-	-	-		-	-	
97	-	-	-	-	-	-	-	-	-		-	-	
98	-	-	-	-	-	-	-	-	-		-	-	
99	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	X	-	-	-	-	-	-	-	-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	X	-	-	-	-	-	-	-	-	
103	-	-	-	-	X	-	-	-	-	-	-	-	
104	-	-	-	-	-	X	-	-	-	-	-	-	
105	-	-	-	-	-	-	-	-	-		-	-	
106	-	-	-	-	-	-	-	-	-		-	-	
107	-	X	-	-	-	-	-	-	-	-	-	-	
108	-	X	-	-	-	-	-	-	-	-	-	-	

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/21OCT03:09:20:27

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REPEATED INSULT PATCH STUDY

TKL STUDY NO [redacted]

[redacted]

styling pomade containing 8% PEG-7 Glyceryl Cocoate

CONDUCTED FOR:

[redacted]

DATE OF REPORT:

January 21, 2004

TKL Research, Inc., 4 Forest Avenue, Paramus, NJ 07652 Tel (201) 587-0500 Fax (201) 587-0878 Email: info@tklresearch.com

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SIGNATURES

Kathleen Georgeian
Kathleen Georgeian, Clinical Research Coordinator and Manager, Dermatologic Safety Testing

1/21/04
Date

Jonathan S. Dosik, MD
Principal Investigator

1/20/04
Date

STATEMENT OF QUALITY ASSURANCE

This report has been reviewed by the TKL Research, Inc. (TKL) Corporate Quality Assurance Department and the report accurately reflects the raw data for this study.

Clinical research studies are performed by TKL in accordance with all applicable federal regulations and proposed guidelines for Good Clinical Practices, which include:

21 CFR Part 312,	Investigational New Drug Application
21 CFR Part 50,	Protection of Human Subjects
21 CFR Part 56,	Institutional Review Boards

Henry Bruce
Quality Assurance

1/21/04
Date

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TITLE OF STUDY

Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIAL

TSIN: BCS578-098 Styling Pomade ← 8% PEG-7 Glyceryl Cocoate in styling pomade

DATE STUDY INITIATED

September 3, 2003

DATE STUDY COMPLETED

October 10, 2003

DATE OF REPORT

January 21, 2004

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INVESTIGATIVE PERSONNEL

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Principal Investigator

Hilary Baldwin, MD
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and Manager, Dermatologic Safety Testing

Tina Kelly
Assistant Manager, Dermatologic Safety Testing

Silvia Guadalupe
Assistant Clinical Research Coordinator

Joanne Mruczek, RN
Senior Clinical Assistant

CLINICAL SITE

TKL RESEARCH, INC.
578 Driggs Avenue
Brooklyn, NY 11211

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SUMMARY

One study material, TSIN: BCS578-098, was evaluated neat to determine its ability to sensitize the skin of normal volunteer subjects using a semi-occlusive repeated insult patch study. One hundred three subjects completed the study. The dermatologist was in attendance for the 48-hour challenge evaluation.

Under the conditions employed in this study, there was no evidence of sensitization to TSIN: BCS578-098.

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1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 100 completed subjects.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. were males or females, 18 years of age or older, in general good health;

2. were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;

3. were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;

4. had completed a medical screening procedure; and

5. had read, understood, and signed an informed consent agreement.

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3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;

3. had psoriasis and/or active atopic dermatitis/eczema;

4. were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or

5. had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed informed consent document in compliance with FDA regulations (21 CFR Part 50) was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix IV).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 consecutive applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application*.

* A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

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Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days.

Subjects who were absent once during the induction phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization.

3.2.2 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

- = No reaction
? = Minimal or doubtful response, slightly different from surrounding normal skin
\+ = Definite erythema, no edema
++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema
S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p = Papular response > 50%
pv = Papulovesicular response > 50%
D = Damage to epidermis: oozing, crusting and/or superficial erosions
I = Itching
X = Subject absent
PD = Patch dislodged
NA = Not applied
NP = Not patched (due to reaction achieved)
N9G = No ninth grading

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3.2.3 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 Study Material Specifications

Identification	:	TSIN: BCS578-098 Styling Pomade
Amount Applied	:	0.1g ± 0.03g
Special Instructions	:	Applied to patch no longer than 30 minutes prior to patch application.

4.2 Storage, Handling, and Documentation of Study Material

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. At the conclusion of the clinical study, the remaining study material was discarded or returned to the sponsor and the disposition documented in the logbook. All information regarding the receipt, storage, and disposition of the study material was also recorded on a Clinical Material Record form (see Appendix III), which is incorporated in this study report. All study material is kept in a locked product storage room accessible to clinical staff members only.

4.3 Application of Study Material

Study material was applied to the patch as instructed. The patch was applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 Description of Patch Conditions

Material evaluated under occlusive patch conditions was applied to a 2-cm x 2-cm Webril pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch was secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions was applied to a 2-cm x 2-cm Webril pad. The pad was affixed to the skin with hypoallergenic tape (Micropore).

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5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred rechallenge procedure involves the application of the product to naïve sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 PROTOCOL

See Protocol - Appendix V.

7.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) are designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, and end of study status. Originals or copies of all CRFs, source documents, IRB documents (if required), correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage is maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provides a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the sponsor's review on the premises of TKL.

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8.0 RESULTS AND DISCUSSION

One hundred eight subjects between the ages of 20 and 69 were enrolled and 103 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).

The following table summarizes subject enrollment and disposition.

Number enrolled:		108
Number discontinued:		5
Lost to follow-up:	3	
Voluntary withdrawal:	2	
Number completed:		103

Source: Table 1, Appendix I

There were no adverse events.

The dermatologist was present at the 48-hour challenge evaluation, a deviation from the protocol-specified 72-hour evaluation.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

9.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to TSIN: BCS578-098.

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10.0 REFERENCES

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APPENDIX I

SUMMARY TABLES

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TKL STUDY NO. [redacted]

TABLE 1: SUMMARY OF SUBJECT ENROLLMENT AND DISPOSITION

	N	(%)
SUBJECTS ENROLLED	108	
SUBJECTS COMPLETED ALL PHASES	103	(95.4)
TOTAL SUBJECTS DISCONTINUED	5	(4.6)
LOST TO FOLLOW-UP	3	(2.8)
VOLUNTARY WITHDRAWAL	2	(1.9)

NOTE: ALL PERCENTAGES ARE RELATIVE TO TOTAL SUBJECTS ENROLLED

SEE DATA LISTING 1 FOR FURTHER DETAIL

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TKL STUDY NO. [redacted]
TABLE 2: SUMMARY OF SUBJECT DEMOGRAPHICS
ALL ENROLLED SUBJECTS

AGE	
N (%) 18 TO 44	42 (38.9)
N (%) 45 TO 64	56 (51.9)
N (%) 65 AND UP	10 (9.3)
MEAN (SD)	48.1 (12.0)
MEDIAN	49.8
RANGE	20.0 TO 69.9
GENDER	
N (%) MALE	21 (19.4)
N (%) FEMALE	87 (80.6)
RACE	
N (%) CAUCASIAN	4 (3.7)
N (%) HISPANIC	104 (96.3)

SEE DATA LISTING 2 FOR FURTHER DETAIL

PROGRAM: DEMOSMY.SAS/USES: DEMOGS/21OCT03:09:20:40

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[redacted]

TKL STUDY NO. [redacted]

TABLE 3: SUMMARY OF DERMATOLOGIC RESPONSE GRADES
NUMBER OF SUBJECTS BY PRODUCT

PRODUCT= TSIN: BCS578-098

	INDUCTION READING									MAKE-	CHALLENGE PHASE		
RESPONSE	1	2	3	4	5	6	7	8	9	UP	48HR	72HR	96HR(*)
-	105	101	104	104	103	101	102	102	103	14	103	103	
?	1	0	0	0	0	0	0	0	0	0	0	0	
TOTAL EVALUABLE	106	101	104	104	103	101	102	102	103	14	103	103	
NUMBER ABSENT	1	5	2	1	2	2	1	1	0		0	0	
NUMBER DISCONTINUED	1	2	2	3	3	5	5	5	5		5	5	

MAXIMUM ELICITED RESPONSE DURING INDUCTION
ALL SUBJECTS COMPLETING INDUCTION (N=103)

RESPONSE	N(%) SUBJECTS
-	102 (99.0%)
?	1 (1.0%)

(*) WHEN REQUIRED

KEY TO SYMBOLS:
- = NO REACTION
? = MINIMAL OR DOUBTFUL RESPONSE, SLIGHTLY DIFFERENT FROM SURROUNDING NORMAL SKIN
+ = DEFINITE ERYTHEMA, NO EDEMA
++ = DEFINITE ERYTHEMA, DEFINITE EDEMA
+++ = DEFINITE ERYTHEMA, DEFINITE EDEMA AND VESICULATION
D = DAMAGE TO EPIDERMIS: OOZING, CRUSTING AND/OR SUPERFICIAL EROSIONS
P = PAPULAR RESPONSE >50%

PROGRAM: SUMMARY.SAS/USES: RESPONSE, PRODLIST, FINAL/21OCT03:09:20:46

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APPENDIX II

DATA LISTINGS

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TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
1	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
2	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
3	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
4	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
5	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
6	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
7	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
8	09/03/03	09/03/03		09/10/03	I1	L	8
9	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
10	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
11	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
12	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
13	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
14	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
15	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
16	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
17	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
18	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
19	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
20	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
21	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
22	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
23	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
24	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
25	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
26	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
27	09/03/03	09/03/03		09/19/03	I5	L	17
28	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
29	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
30	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
31	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
32	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
33	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
34	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
35	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
36	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
37	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
38	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
39	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38

KEY: LAST READING # (I=INDUCTION PHASE, C=CHALLENGE PHASE)
COMPLETION STATUS (C=COMPLETED, L=LOST TO FOLLOW-UP, S=VOLUNTARY WITHDRAWAL
V=PROTOCOL VIOLATION, AE=ADVERSE EVENT, O=OTHER)

PROGRAM: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
40	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
41	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
42	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
43	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
44	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
45	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
46	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
47	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
48	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
49	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
50	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
51	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
52	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
53	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
54	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
55	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
56	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
57	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
58	09/03/03	09/03/03		09/12/03	I3	S	10
59	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
60	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
61	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
62	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
63	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
64	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
65	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
66	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
67	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
68	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
69	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
70	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
71	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
72	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
73	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
74	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
75	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
76	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
77	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
78	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38

KEY: LAST READING # (I=INDUCTION PHASE, C=CHALLENGE PHASE)
COMPLETION STATUS (C=COMPLETED, L=LOST TO FOLLOW-UP, S=VOLUNTARY WITHDRAWAL
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TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
79	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
80	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
81	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
82	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
83	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
84	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
85	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
86	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
87	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
88	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
89	09/03/03	09/03/03		09/05/03	I0	S	3
90	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
91	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
92	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
93	09/03/03	09/03/03		09/19/03	I5	L	17
94	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
95	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
96	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
97	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
98	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
99	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
100	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
101	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
102	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
103	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
104	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
105	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
106	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
107	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38
108	09/03/03	09/03/03	10/07/03	10/10/03	C2	C	38

KEY: LAST READING # (I=INDUCTION PHASE, C=CHALLENGE PHASE)
COMPLETION STATUS (C=COMPLETED, L=LOST TO FOLLOW-UP, S=VOLUNTARY WITHDRAWAL
V=PROTOCOL VIOLATION, AE=ADVERSE EVENT, O=OTHER)

PROGRAM: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 2: SUBJECT DEMOGRAPHICS

SUBJECT NO.	AGE	GENDER	RACE
1	59.0	MALE	HISPANIC
2	45.1	FEMALE	HISPANIC
3	56.4	FEMALE	HISPANIC
4	53.6	FEMALE	CAUCASIAN
5	59.4	MALE	HISPANIC
6	44.1	FEMALE	HISPANIC
7	37.0	FEMALE	HISPANIC
8	37.2	FEMALE	HISPANIC
9	62.0	MALE	HISPANIC
10	58.2	MALE	HISPANIC
11	31.8	FEMALE	HISPANIC
12	56.3	MALE	HISPANIC
13	57.8	FEMALE	HISPANIC
14	55.8	FEMALE	HISPANIC
15	65.3	FEMALE	HISPANIC
16	61.4	FEMALE	HISPANIC
17	35.0	FEMALE	HISPANIC
18	66.0	FEMALE	HISPANIC
19	36.1	FEMALE	HISPANIC
20	39.0	MALE	HISPANIC
21	34.5	FEMALE	HISPANIC
22	63.3	FEMALE	HISPANIC
23	58.2	FEMALE	HISPANIC
24	28.3	FEMALE	HISPANIC
25	63.3	FEMALE	HISPANIC
26	56.3	FEMALE	HISPANIC
27	58.9	FEMALE	HISPANIC
28	42.8	MALE	HISPANIC
29	49.1	FEMALE	HISPANIC
30	56.3	MALE	HISPANIC
31	55.7	FEMALE	HISPANIC
32	50.1	FEMALE	HISPANIC
33	38.1	FEMALE	HISPANIC
34	44.7	FEMALE	HISPANIC
35	26.0	FEMALE	HISPANIC
36	35.4	FEMALE	HISPANIC
37	51.0	FEMALE	HISPANIC
38	48.8	FEMALE	HISPANIC
39	54.7	FEMALE	HISPANIC
40	47.7	MALE	HISPANIC

PROGRAM: DEMOLIST.SAS/USES: DEMOGS/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 2: SUBJECT DEMOGRAPHICS

SUBJECT NO.	AGE	GENDER	RACE
41	45.2	MALE	HISPANIC
42	53.1	FEMALE	HISPANIC
43	38.5	FEMALE	HISPANIC
44	29.5	FEMALE	HISPANIC
45	32.3	FEMALE	HISPANIC
46	37.6	FEMALE	HISPANIC
47	43.8	FEMALE	HISPANIC
48	54.6	MALE	HISPANIC
49	48.8	FEMALE	HISPANIC
50	53.6	FEMALE	HISPANIC
51	47.4	FEMALE	HISPANIC
52	23.7	FEMALE	HISPANIC
53	41.2	FEMALE	HISPANIC
54	35.9	FEMALE	HISPANIC
55	27.6	FEMALE	HISPANIC
56	25.6	FEMALE	HISPANIC
57	50.2	FEMALE	HISPANIC
58	20.0	MALE	HISPANIC
59	34.3	FEMALE	HISPANIC
60	53.8	FEMALE	HISPANIC
61	69.8	FEMALE	HISPANIC
62	56.3	FEMALE	CAUCASIAN
63	37.3	FEMALE	HISPANIC
64	34.7	FEMALE	HISPANIC
65	54.6	FEMALE	HISPANIC
66	50.6	FEMALE	HISPANIC
67	28.6	FEMALE	HISPANIC
68	41.1	FEMALE	HISPANIC
69	55.8	FEMALE	HISPANIC
70	46.5	FEMALE	CAUCASIAN
71	45.5	FEMALE	HISPANIC
72	69.2	FEMALE	HISPANIC
73	38.1	MALE	HISPANIC
74	64.1	FEMALE	HISPANIC
75	41.6	FEMALE	HISPANIC
76	66.9	FEMALE	HISPANIC
77	54.3	FEMALE	HISPANIC
78	41.6	FEMALE	HISPANIC
79	50.3	FEMALE	HISPANIC
80	65.1	FEMALE	HISPANIC

PROGRAM: DEMOLIST.SAS/USES: DEMOGS/21OCT03:09:20:24

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TKL STUDY NO. [redacted]
DATA LISTING 2: SUBJECT DEMOGRAPHICS

SUBJECT NO.	AGE	GENDER	RACE
81	66.7	FEMALE	HISPANIC
82	46.9	FEMALE	HISPANIC
83	53.9	FEMALE	HISPANIC
84	36.3	FEMALE	HISPANIC
85	58.3	FEMALE	HISPANIC
86	38.2	FEMALE	HISPANIC
87	69.9	FEMALE	HISPANIC
88	69.0	FEMALE	HISPANIC
89	44.5	MALE	HISPANIC
90	56.5	FEMALE	HISPANIC
91	38.8	MALE	HISPANIC
92	61.2	FEMALE	HISPANIC
93	23.0	MALE	HISPANIC
94	53.2	FEMALE	HISPANIC
95	55.8	MALE	CAUCASIAN
96	55.1	MALE	HISPANIC
97	39.5	FEMALE	HISPANIC
98	60.2	FEMALE	HISPANIC
99	68.5	FEMALE	HISPANIC
100	37.2	MALE	HISPANIC
101	49.8	FEMALE	HISPANIC
102	49.7	MALE	HISPANIC
103	48.9	FEMALE	HISPANIC
104	30.2	FEMALE	HISPANIC
105	52.5	FEMALE	HISPANIC
106	41.4	FEMALE	HISPANIC
107	49.9	MALE	HISPANIC
108	56.7	FEMALE	HISPANIC

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[redacted]
TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= TSIN: BCS578-098

SUBJECT	INDUCTION READING										CHALLENGE PHASE	
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR 96HR(*)
1	-	-	-	-	-	-	-	-	-		-	-
2	-	-	-	-	-	-	-	-	-		-	-
3	-	-	-	-	-	-	-	-	-		-	-
4	-	-	-	-	-	-	-	-	-		-	-
5	-	-	-	-	-	-	-	-	-		-	-
6	-	-	-	-	-	-	-	-	-		-	-
7	-	-	-	-	-	-	-	-	-		-	-
8	-	X	X	X	X	X	X	X	X		X	X
9	-	-	-	-	-	-	-	-	-		-	-
10	-	-	-	-	-	-	-	-	-		-	-
11	-	-	-	-	-	-	-	-	-		-	-
12	-	-	-	-	-	-	-	-	-		-	-
13	-	-	-	-	-	-	-	-	-		-	-
14	-	-	-	-	-	-	-	-	-		-	-
15	-	-	-	-	-	-	-	-	-		-	-
16	-	-	-	-	-	-	-	-	-		-	-
17	-	-	-	-	-	-	-	-	-		-	-
18	-	-	-	-	-	-	-	-	-		-	-
19	-	-	-	-	-	-	-	-	-		-	-
20	-	-	-	-	-	-	-	-	-		-	-

KEY TO SYMBOLS:

- = NO REACTION
? = MINIMAL OR DOUBTFUL RESPONSE, SLIGHTLY DIFFERENT FROM SURROUNDING NORMAL SKIN

+ = DEFINITE ERYTHEMA, NO EDEMA
++ = DEFINITE ERYTHEMA, DEFINITE EDEMA

+++ = DEFINITE ERYTHEMA, DEFINITE EDEMA AND VESICULATION

N9G = NO NINTH GRADING NA=NOT APPLIED NP=NOT PATCHED DUE TO REACTION ACHIEVED
X = READING NOT PERFORMED DUE TO MISSED VISIT OR SUBJECT DISCONTINUATION
D = DAMAGE TO EPIDERMIS: OOZING, CRUSTING AND/OR SUPERFICIAL EROSIONS
P = PAPULAR RESPONSE >50% NR=DATA NOT RECORDED
MU = MAKE-UP READING FOR MISSED INDUCTION VISIT

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/21OCT03:09:20:27

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TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= TSIN: BCS578-098

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
21	-	-	-	-	-	-	-	-	-		-	-	
22	-	-	-	-	-	-	-	-	-		-	-	
23	-	-	-	-	-	-	-	-	-		-	-	
24	-	-	-	-	-	-	-	-	-		-	-	
25	-	-	-	-	-	-	-	-	-		-	-	
26	-	-	-	-	-	X	-	-	-	-	-	-	
27	-	-	-	-	-	X	X	X	X		X	X	
28	-	-	-	-	-	-	-	-	-		-	-	
29	-	-	-	-	-	-	-	-	-		-	-	
30	-	-	-	-	-	-	-	-	-		-	-	
31	-	-	-	-	-	-	-	-	-		-	-	
32	-	-	-	-	-	-	-	-	-		-	-	
33	-	-	-	-	-	-	-	-	-		-	-	
34	-	-	-	-	-	-	-	-	-		-	-	
35	-	-	-	-	-	-	-	-	-		-	-	
36	-	-	-	-	-	-	-	-	-		-	-	
37	-	-	-	-	-	-	-	-	-		-	-	
38	-	X	-	-	-	-	-	-	-	-	-	-	
39	?	-	-	-	-	-	-	-	-		-	-	
40	-	-	-	-	-	-	-	-	-		-	-	
41	-	-	-	-	-	-	-	-	-		-	-	
42	-	-	-	-	-	-	-	X	-	-	-	-	
43	-	-	-	-	-	-	-	-	-		-	-	
44	-	X	-	-	-	-	-	-	-	-	-	-	
45	-	-	-	-	-	-	-	-	-		-	-	
46	-	-	-	-	-	-	-	-	-		-	-	
47	-	-	-	-	-	-	-	-	-		-	-	
48	-	-	-	-	-	-	-	-	-		-	-	
49	-	-	-	-	-	-	-	-	-		-	-	
50	-	-	-	-	-	-	-	-	-		-	-	
51	-	-	-	-	-	-	-	-	-		-	-	
52	-	-	-	-	-	-	-	-	-		-	-	

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/21OCT03:09:20:27

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[redacted]
TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= TSIN: BCS578-098

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
53	-	-	-	-	-	-	-	-	-		-	-	
54	-	-	-	-	-	-	-	-	-		-	-	
55	-	-	-	-	X	-	-	-	-	-	-	-	
56	-	-	-	-	-	-	-	-	-		-	-	
57	-	-	-	-	-	-	-	-	-		-	-	
58	X	-	-	X	X	X	X	X	X		X	X	
59	-	-	-	-	-	-	-	-	-		-	-	
60	-	-	-	-	-	-	-	-	-		-	-	
61	-	-	-	-	-	-	-	-	-		-	-	
62	-	-	-	-	-	-	-	-	-		-	-	
63	-	-	-	-	-	-	-	-	-		-	-	
64	-	-	-	-	-	-	-	-	-		-	-	
65	-	-	-	-	-	-	-	-	-		-	-	
66	-	-	-	-	-	-	-	-	-		-	-	
67	-	-	-	-	-	-	-	-	-		-	-	
68	-	-	-	-	-	-	-	-	-		-	-	
69	-	-	-	-	-	-	-	-	-		-	-	
70	-	-	-	-	-	-	-	-	-		-	-	
71	-	-	-	-	-	-	-	-	-		-	-	
72	-	-	-	-	-	-	-	-	-		-	-	
73	-	-	-	-	-	-	-	-	-		-	-	
74	-	-	-	-	-	-	-	-	-		-	-	
75	-	-	-	-	-	-	-	-	-		-	-	
76	-	X	-	-	-	-	-	-	-	-	-	-	
77	-	-	-	-	-	-	-	-	-		-	-	
78	-	-	-	-	-	-	-	-	-		-	-	
79	-	-	-	-	-	-	-	-	-		-	-	
80	-	-	-	-	-	-	-	-	-		-	-	
81	-	-	-	-	-	-	-	-	-		-	-	
82	-	-	-	-	-	-	-	-	-		-	-	
83	-	-	-	-	-	-	-	-	-		-	-	
84	-	-	-	-	-	-	-	-	-		-	-	

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/21OCT03:09:20:27

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[redacted]
TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= TSIN: BCS578-098

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
85	-	-	-	-	-	-	-	-	-		-	-	
86	-	-	-	-	-	-	-	-	-		-	-	
87	-	-	-	-	-	-	X	-	-	-	-	-	
88	-	-	-	-	-	-	-	-	-		-	-	
89	X	X	X	X	X	X	X	X	X		X	X	
90	-	-	-	-	-	-	-	-	-		-	-	
91	-	-	-	-	-	-	-	-	-		-	-	
92	-	-	X	-	-	-	-	-	-	-	-	-	
93	-	-	-	-	-	X	X	X	X		X	X	
94	-	-	-	-	-	-	-	-	-		-	-	
95	-	-	-	-	-	-	-	-	-		-	-	
96	-	-	-	-	-	-	-	-	-		-	-	
97	-	-	-	-	-	-	-	-	-		-	-	
98	-	-	-	-	-	-	-	-	-		-	-	
99	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	X	-	-	-	-	-	-	-	-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	X	-	-	-	-	-	-	-	-	
103	-	-	-	-	X	-	-	-	-	-	-	-	
104	-	-	-	-	-	X	-	-	-	-	-	-	
105	-	-	-	-	-	-	-	-	-		-	-	
106	-	-	-	-	-	-	-	-	-		-	-	
107	-	X	-	-	-	-	-	-	-	-	-	-	
108	-	X	-	-	-	-	-	-	-	-	-	-	

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/21OCT03:09:20:27

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[redacted]

HUMAN REPEAT INSULT PATCH TEST

[redacted] RE-0647.01

PEG-20 Almond Glycerides

100% Neat tested at 5%

To:

[redacted]

From:
Pharmaco UK Ltd
Townfield House
30-33 Townfield Street
Chelmsford
Essex CM1 1QL
England

Final: 23 May 1994

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[redacted]

HUMAN REPEAT INSULT PATCH TEST

[redacted] RE-0647.01

Pharmaco No [redacted]

I declare that the following report constitutes a true and faithful account of the procedures adopted and the results obtained in the performance of this study. The aspects of the study conducted by Pharmaco UK Ltd were performed, where relevant, in accordance with the principles of Good Clinical Research Practice.

A MacLennan, PhD
(Study Director)

A MacLennan
Date 12 July '94

I have reviewed this report and concur with its contents.

D B Galloway, MB, ChB, DObst, RCOG, FRCP, FFPM
(Medical Advisor)

D B Galloway
Date 13 July 1994

D Shuttleworth, MB, BS, MRCP
(Consultant Dermatologist)

D Shuttleworth
Date 14th July 1994

This report has been audited and is considered to be an accurate description of the methods used and an accurate presentation of the data obtained during the conduct of the study.

A J Dench, CBiol, MIBiol
(Quality Assurance Manager)

A J Dench
Date 17 July 1994

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[redacted]

TEST ARTICLE INFORMATION

Test Substance code	:	RE-0647.01
Study file code	:	[redacted]
Date sample received	:	1 March 1994
Sample weight	:	1016g
General characteristics	:	Clear yellow liquid
Storage conditions	:	Ambient room temperature
Expiration date	:	January 1995
Study start date	:	7 March 1994
Study completion date	:	14 April 1994

TEST ARTICLE ACCOUNTABILITY

At the end of the study, after test article reconciliation, a reserve sample was stored by Pharmaco under appropriate conditions (as defined by the Sponsor) in the Sample Archives at [redacted] for a minimum period of five years. On study completion all other test article was incinerated.

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[redacted]

SUMMARY

1. The one hundred and seven subjects recruited for the study received occlusive patches containing test materials, according to the protocol dated 15 January 1993. Ninety-three subjects completed the study.

2. Irritance scores for the ninety-three subjects who completed the study were:

[redacted] RR-0647.01

0	1	1P	2	NSG
1080	123	1	2	3

3. One subject (Nos 48) experienced an adverse event.

She reported feeling dizzy and ill when the challenge patches had been in place approximately 19 hours. She later vomited and fasted drinking only water. Pharmaco's Medical Advisor advised the subject to have a light meal only and to report to Pharmaco if symptoms persisted. All symptoms were resolved by the 72 hour challenge grading and was felt to be related to the challenge patching rather than the test articles.

4. The test article showed no evidence of skin sensitization during induction or at challenge.

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[redacted]

METHODS

In order to assess the sensitization potential of the test material in human volunteers, the protocol dated 15 January 1993 was followed without modification or deviation.

This consisted of a three week induction period during which an occlusive patch was generally applied to the upper arm each Monday, Wednesday and Friday. Each patch was left in place for 24 hours and then removed by the subject. Seventeen days after the last induction application, duplicate challenge patches were applied for 24 hours. The rest period for those subjects receiving a make-up patch was 14 days.

Patches consisted of a 5 cm wide strip of Blenderm® tape, to which four Webril® discs (ca 24 mm diameter) were fixed along the midline at equal intervals.

A 0.4 ml sample of [redacted] RE-0647.01 was tested in the study at a concentration of 5.0% (w/v) aqueous solution.

The Sponsor's test substance information sheet for RE-0647.01 is presented in Appendix 1.

Three other test articles was tested simultaneously and are reported separately as follows:

[redacted]

Grading of the induction sites was performed after a 24 hour rest period (48 hours over a weekend) and immediately preceding the next patch application. Challenge sites were scored 48 hours and 72 hours after application. Pharmaco's consultant dermatologist was in attendance at the 72 hour grading. All reactions were assessed by L Noakes according to the scoring scale in Appendix 2.

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[redacted]

RESULTS AND CONCLUSION

1. Location and dates of study
(Figure 1, Appendices 3, 4 and 5)

Two hundred and forty-five subjects were screened prior to participation in the study. One hundred and thirty-eight were found to be ineligible (see Appendix 3) and one hundred and seven subjects were admitted onto the study, which was conducted at the Five Star Youth Club, Brewsters Hall, Gooshays Drive, Harold Hill, Essex, England. This study was conducted between 7 March and 14 April 1994.

Fourteen subjects did not complete the study for reasons presented in Appendix 4. The composition of the panel who completed the study is presented by age and sex in Figure 1. Individual skin reactions observed during induction and challenge are presented in Appendix 5.

2. Adverse events

Subject No 48 reported feeling dizzy and ill when the challenge patches had been in place approximately 19 hours. She later vomited and fasted drinking only water. Pharmaco's Medical Advisor advised the subject to have a light meal only and to report to Pharmaco if symptoms persisted. All symptoms were resolved by the 72 hour challenge grading and are felt to be related to the challenge patching rather than the test articles.

3. Conclusion

There was no evidence of sensitization observed during induction or at challenge.

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[redacted]

Leberco • Celsis Testing

123 Hawthorne St
Roselle Park, NJ 07204-0
908.245.1933 / 800.523.L
Fax 908.245.6

Ocular Irritation Screen
#: SPDL11 PEG-10 sunflower glycerides
Using the
Chorioallantoic Membrane Vascular Assay (CAMVA)

[redacted]

Conducted for:

[redacted]

Final Report Date: May 12, 1997

Work Approved by:

Anthony T. Grilli, M.S.
Manager, Microbiology

LEBERCO.CELSIS TESTING

James W. Brown, Ph.D.
Director, Biological Services

[redacted]

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MEMB [redacted]

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May 12, 1997
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Client: [redacted]

May 12, 1997
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Conclusion:

The following samples were received at tested in the CAMVA test system:

[redacted] Lot# SPDL11 = PEG-10 sunflower glyceride

This sample was tested neat, 40µl per egg. This sample caused slight/moderate hemorrhage, against six eggs tested after 30 minutes of contact time. The RC50 was 80% therefore, the sample tested according to the approved protocol was nonirritating in a CAMVA model.

Sample Concentration	Number of Positive Responders	Percent of Positive Responders
90%	4/6	66.7%
80%	3/6	50.0%
70%	2/6	33.3%

RC50 = 80.0%
Range = 66.1 - 96.8%

Leberco • Celsis Testing

Client: [redacted]

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Protocol:

1.0 TITLE: Chorioallantoic Membrane Vascular Assay (CAMVA)

2.0 OBJECTIVE: To evaluate the potential for a test material to cause an effect on the chorioallantoic membrane of the developing chick embryo. This assay is indicative for evaluating the potential for ocular irritation.

3.0 TESTING FACILITY: Leberco-Celsis Testing
123 Hawthorne Street
Roselle Park, N.J. 07204

4.0 SPONSOR: [redacted]

5.0 STUDY DIRECTOR: Anthony Grilli

6.0 TEST DATES:

7.0 TEST SUBSTANCES:

1) [redacted]DL11

7.1 Identification: Test and control substances are identified by a sponsor supplied name, lot number, code number and a Leberco-Celsis Testing account number.

7.2 Storage: The test and appropriate control substances are stored at ambient room temperature and humidity, unless otherwise specified by the Sponsor, in the containers in which they were received.

7.3 Disposition: Unused test materials for GLP studies will be returned to the sponsor at the conclusion of the study. Remaining samples of test substance for non-GLP studies are stored for a period of 3 months prior to being discarded.

7.4 Hazards: Routine safety precautions will be exercised in the handling of the test substance. It is the responsibility of the Sponsor to identify special handling requirements.

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Client: [redacted]

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7.5 Test Substance Characterization: Data regarding the identity, characteristics, and stability of the test substance are established by the sponsor. Any information supplied to the testing facility is retained with the raw data and final report in the testing facilities archives.

7.6 Vehicle: No vehicle was used as initial screen of neat sample showed no irritablity. Therefore, no dilution was required..

8.0 GENERAL TEST SYSTEM PARAMETERS:

8.1 Egg Requirements: Varies according to study parameters. One to four concentrations of test substance will be used, depending on test substance characteristics and availability of existing data.

8.1.1 Number of Eggs: SCREEN - 1
STUDY - 6

8.1.4 Strain: Fertile DeKalb XL Eggs

8.1.5 Age at Receipt: less than 1 day

8.1.6 Supplier: Moyer's Chicks, Inc.
266 E. Palctown Road
Quakertown, PA 18951

8.2 Test System Justification: The CAMVA has been shown to be a qualitative method for assessing potential ocular hazards.

8.3 Husbandry: Upon receipt, the eggs are placed in a commercial incubator* which is maintained at 99 +/- 2 degrees F and 50 - 60 % relative humidity. Temperature and humidity are monitored daily.

9.0 EXPERIMENTAL DESIGN:

9.1 Development: Upon receipt, the eggs weree placed in a commercial incubator* and maintained at 99 +/- 2°F, 50-60% relative humidity. The eggs were incubated for a total of 14 days. The position of the egg trays in the incubator was rotated daily, Monday through Friday, to ensure even atmospheric exposure. The individual eggs were rotated from the day of receipt (day 1) through day 14.

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Leberco • Celsis Testing

Client: [redacted]

May 12, 1997
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*Model 1202 Circulated Air Incubator,GQF Manufacturing Savannah,GA

9.2 Day 4, Preparation:

9.2.1 The eggs were placed horizontally in the incubator for at least 30 minutes.

9.2.2 The eggs were kept warm with an infrared heating lamp (GE, 250R, 40/10) maintained at a distance of approximately 18 inches from the egg.

9.2.3 The eggs were candled to determine the presence and location of the embryo.

9.2.4 The eggs were wiped with 70% alcohol and drill a small hole at the narrow end of the egg using a Sterling Wohl Power Unit (Sterling ,IL).

9.2.5 Approximately 2.5 ml of albumen was removed with a needle and syringe.

9.2.6 The hole was sealed with hot sealing wax.

9.2.7 A small square hole was cut (Sterling Wohl Power Unit and a silicon abrasive disc), approximately 1 x 1 cm, through the shell directly over the embryo.

9.2.8 The cutting area was cleaned with "Dust-Off" to remove any powdered shell residue.

9.2.9 The square window in the shell was removed with forceps.

9.2.10 The window area was covered with Dermiclear tape.

9.2.11 The egg was returned to the incubator.

9.3 Day 14, Treatment:

9.3.1 The eggs were removed from the incubator. Peel back the tape and examine chorioallantoic membrane (CAM).

9.3.2 A Teflon ring (5/16" ID, 7/16" OD) was gently placed on the CAM and 40 ul of the test material is pipetted into the ring.

9.3.3 The window was resealed with Demiclear tape, identify the egg with an appropriate label and return it to the incubator.

Leberco•Colsis Testing

Client: [redacted]

May 12, 1997
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9.4 Day 14, Observation:

9.4.1 After 30 +/- 5 minutes incubation, the egg was removed from the incubator and the CAM was exposed by removing the tape and portions of the egg shell surrounding the pre-cut window.

9.4.2 The CAM was examined for the presence of vascular hemorrhage, capillary injection, ghost vessels or other abnormalities.

9.5 Group Sizes:

9.5.1 Screen: A preliminary screen was performed to select the appropriate concentration level for the CAMVA test.

1 egg/concentration level
1 - 4 concentration levels based on the sponsor's information regarding irritation potential of the test material. If no such information is available, the first concentration will be 100% (as received).

9.2.2 Study: Based on the results of the screen, the test concentrations are selected to achieve positive results which permit the calibration of the RC_{50}.

10.0 TEST MATERIAL:

10.1 The viscosity state of the dose concentration to be used was such that the volume dosed = 40 ul.

10.2 The dosage form was sufficiently transparent to allow the CAM surface area below the Teflon ring to be observed. A gentle stream of 0.9% saline was used to wash the area clean.

11.0 RESULTS:
None of the six eggs per sample showed any sign of irritation.

Leberco•Celsis Testing

Client: [redacted]

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12.0 INTERPRETATION: The irritation potential is based on the calculated RC_{50} as follows:

RC_{50}	Interpretation
< 3.0%	Irritant
3.0 - 5.0%	Indeterminate
> 5.0%	Non-irritant

The presence of vascular hemorrhage, capillary injection, ghost vessels, embryo mortality or any other abnormality would have been considered positive results.

13.0 RECORDS TO BE MAINTAINED:

13.1 Collection of Data: All data generated during the conduct of this study was recorded in ink in a bound notebook or on a Leberco-Celsis form. All entries are dated and initialed. Data was reviewed periodically by the department manager or his/her designee, and the date of review and the initials of the reviewer are documented.

13.2 Retention of Data:

13.2.1 Filed notebooks are retained indefinitely.

13.2.2 Final Reports are filed by sponsor name and project number.

14.0 REFERENCE: "An Improved CAM Method for Predicting Ocular Irritation." Bagley, D. M., et al (1988), Alternative Methods in Toxicology Vol.6, pp. 131-138.

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Raltech SCIENTIFIC SERVICES

P.O. Box 7305 • Madison, Wisconsin 53707 • 608/241 4471
A Division of Ralston Purina Company

Other Raltech Scientific Services Laboratories:
St. Louis MO
Gray Summit MO

Perfume Containing 4% PEG-6 Caprylic/Capric Glycerides

SKIN CORROSIVITY (DOT PROCEDURE) OF P0956

SPONSOR: [redacted]

STUDY NO. [redacted]
INITIATION: 3/6/81
COMPLETION: 3/9/81 (IN-LIFE)
REPORTED: 4/17/81

SAMPLE: Clear Liquid: P0956 [redacted]

ENCLOSED: METHOD, PAGE 2
SUMMARY, PAGE 3
QAU REPORT, PAGE 4
RAW DATA APPENDIX

SIGNED: [redacted]

SUPERVISORY PERSONNEL INVOLVED IN THIS STUDY: JAMES E. POMBIER, BS
TECHNICAL SUPERVISOR

BY AND FOR RALTECH SCIENTIFIC SERVICES

RAW DATA FOR THIS STUDY IS KEPT ON FILE AT RALTECH SCIENTIFIC SERVICES, MADISON, WISCONSIN.

RECEIVED BY
MAY 19 1981
[redacted]

Reports are furnished to clients on a confidential basis. No reference to our work, the results or to Raltech Scientific Services in any form of advertising, news release or other public communication may be made without written authorization from Raltech Scientific Services.

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RT LAB NUMBER [redacted]
SKIN CORROSIVITY (DOT)

Objective: To determine the skin corrosivity of a test substance when this substance is tested using the Department of Transportation (DOT) Procedure (49 CFR 173.240).

Test Material: Clear Liquid: P0956

Stability of Test Material: Has been determined by the sponsor.

Test Animal: Young adult rabbits (approximately 14 weeks of age) of the New Zealand white strain were maintained individually in screen bottom cages in temperature and humidity controlled quarters [illegible] continuous access to commercial laboratory feed and water, and held for an acclimation period of at least 7 days.

Three male and three female acclimated animals were chosen at random for the test, weighed, and maintained during the observation period as specified for the acclimation period. Test animals were identified by animal number and corresponding ear tag.

Method: Twenty-four hours prior to application, the hair was removed from the back of each rabbit with an electric clipper. All of the rabbits' skin remained intact. (Abraded sites were not used.) To the prepared [illegible] of each rabbit's back 0.5 mL of test material was applied under a [illegible] gauze patch secured with tape. The area of application was [illegible] wrapped with dental dam and secured with Elastoplast tape. Collars [illegible] applied during the 4-hour exposure period. At the end of the 4-hour [illegible] the bandages were removed and the area of application [illegible]. Thirty minutes after bandage removal, the degree of erythema and edema was recorded according to the Draize technique*. The examination was repeated at 48 hours.

Individual body weights were obtained immediately prior to initiation of the study.

Pathology: At study termination all animals were euthanized and discarded.

*Draize, J. H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics - Dermal Toxicity, Association of Food and Drug Officials of the United States: Topeka, Kansas, 49-51, (1965).

**Methods for Testing Corrosion to the Skin, 49 CFR 173.1200, Appendix A.

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RT LAB NUMBER [redacted]
SKIN CORROSIVITY (DOT)

Test Animals: New Zealand white strain rabbits
Source: Kuipers Rabbitry, Gary, IN
Date Animals Received: 2/25/81
Temperature and Humidity of Animal Room: 20 to 21°C,
43 to 51% relative humidity

Test Material: Clear Liquid: [illegible]

Date Test Started: 3/6/81 Date Test Completed: 3/6/81 (In-Life)

Average Dermal Irritation Scores*:	Erythema	Edema
4 Hours:	0.0	0.0
48 Hours:	1.0	[illegible]

Primary Dermal Irritation Index**: 0.5

*The average Dermal Irritation Score is the sum of the irritation scores for each animal divided by the number of animals at each observation period.
**The Primary Dermal Irritation Index is the sum of the average scores for erythema and edema at 4 and 48 hours (4 values) divided by 2 and rounded the nearest tenth.

Conclusions: The test material is not corrosive to the skin. The test material is considered to be mil[illegible] irritating according to Protocol [illegible]

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QUALITY ASSURANCE FINAL REPORT STATEMENT

Skin Corrosivity (DOT Procedure) of P0956

Raltech [redacted]

The final report as herein attached for the above-mentioned study has been reviewed by the assigned Quality Assurance Unit of Raltech Scientific Services in accordance with the Good Laboratory Practice Regulations as set forth in 21 CFR 58.35 (b) (6) (7). It has been found to accurately identify and/or describe the authorized methods and standard operating procedures followed in the conduct of the study and that the reported data accurately reflect the raw data of the laboratory study. Furthermore, the Quality Assurance Unit has conducted the following inspections of the testing facilities utilized in the conduct of this study and has submitted written reports of said inspections to the study director and/or management.

Date of Inspection	Type of Inspection	Date Issued to Management
3/06/81	Test Article Administration Body ... ht Data Collection Animal ...cement onto Study Data Recording Animal Preparation	3/06/81

[signature] DATE 3/11/81

Susan Glad Anderson, Inspector
Quality Assurance Unit

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PRIMARY DERMAL IRRITATION STUDY

Test Compound: Liquid: P0956 — RT No. 839403

Dose (g): NA — Vehicle: NA

Dose Volume (ml): 0.5 — Room No. 226

Date Animals Received: 2/25/81 — Source: Kuipers

Date Animals Clipped: 3/5/81, 3/6/81 ③ — Tech: TP

Test Site Location: Head A B C D Tail

Conducted By: SW JR — Date: 3-6-81

Verified By: [illegible] — Date: 3/6/81

OBSERVATION PERIOD: 4 (Hours/Days)

Animal No./Ear Tag No. 6510		1299*	1291*	1296*	1352*	① 1321* ~~1355~~	② 1328* ~~1335~~
Sex		♂	♂	♂	♀	♀	♀
Body Weight (Grams)		2159	2174	2097	[illegible]	~~[illegible]~~	2410
Intact Site	Erythema	0	0	0	0	0	0
	Edema	0	0	0	0	0	0
Intact Site	Erythema						
	Edema						
Abraded Site	Erythema						
	Edema						
Abraded Site	Erythema						
	Edema						
Technician		SW	SW	SW	SW	SW	SW
Recorded By		JR	JR	JR	JR	JR	JR
Date	1981	3/6	3/6	3/6	3/6	3/6	3/6
Scale Used		K-Tron 4809 SW 3/6/81 JR					

NA - Not Applicable
A - Subcutaneous hemorrhage
B - Blanching
C - Scab formation
D - Desquamation
F - Fissuring
* - No sign of corrosivity was observed on test site - JR 3/6/81

Dermal Irritation Score: 0.0 pg

Reviewed By: JV — Date: 3/6/81

① Replaced Rabbit - had diarrhea. SW 3/6/81
② Replaced Rabbit - too light. SW 3/6/81
③ Rabbits #6510-1321, #6510-1328 were clipped 3/6/81 as replacements. SW 3/6/81

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PRIMARY DERMAL IRRITATION STUDY

Test Compound: Liquid: PO 956 RT No. [redacted]

Test Site Location

Head
A | B
C | D
Tail

OBSERVATION PERIOD 48 (Hours/Days)

[illegible] No./Ear Tag No. 6510		1299*	1291*	1296*	1352*	① 1321-2 ~~1355~~	② 1328-2 ~~1338~~
Sex		♂	♂	♂	♀	♀	♀
Body Weight (Grams)		N/A	N/A	N/A	N/A	[illegible]	[illegible]
Intact Site	Erythema	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	Edema	0	0	0	0	0	0
Intact Site	Erythema						
	Edema						
Abraded Site	Erythema						
	Edema						
Abraded Site	Erythema						
	Edema						
Technician		NJA	NJA	NJA	NJA	NJA	NJA
Recorded By		NJA	NJA	NJA	NJA	NJA	NJA
Date	1981	3/8	3/8	3/8	3/8	3/8	3/8
Scale Used		N/A					

NA - Not Applicable
A - Subcutaneous hemorrhage
B - Blanching
C - Scab formation
D - Desquamation
F - Fissuring

Dermal Irritation Score: 1.0 pg. [illegible]

Reviewed By: SG Date: 3.9.81

① Replaced Rabbit - had diarrhea. Sw 3/6/81
② Replaced Rabbit - too light. Sw 3/6/81

Page 2 of 2

* - No signs of corrosivity observed on test site. 3/8/81 NJA

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[redacted]

PROTOCOL NO. C9A

Skin Corrosivity (DOT Procedure with Optional)

Issue Date: September 15, 1980
Superseded Issue Dated: January 1, 1980

Test Substance Identification Number (TSIN) # P0956

[redacted] Request Document Number [redacted]

Sponsor: [redacted]

Testing Facility: (To be filled in by Operations Section)
Raltech Scientific Services, Inc.
P. O. Box 7545
Madison, Wisconsin 53707

Study # [redacted] (To be filled in by Testing Facility)

Purpose: To determine the skin corrosivity of a test substance when this substance is tested using the Department of Transportation (DOT) Procedure. (49 CFR 173.240)

Justification for Selection of Test: Required by DOT Procedure. (49 CFR 173.240)

Route of Administration of Test Substance and Reason for Choice: Patch placed on intact skin clipped free of hair. Required by DOT Procedure. (49 CFR 173.240)

Diet and/or Water Analyses Required: None (no known contaminants expected which would interfere with this study)

Records to be Maintained: All records that would be required to reconstruct the study and demonstrate adherence to protocol.

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[redacted] PROTOCOL NO. C9A (Cont'd)

Skin Corrosivity (DOT Procedure with Options)

Issue Date: September 15, 1980

Test Substance(s) TSIN #	DRD Number	Description Color	Description Physical Form	Expiration Date
P0956	[redacted]	Clear ~~Amber~~	Liquid	2/82

Storage Conditions: (Check one)

[✓] Room temperature [ ] Refrigerator [ ] Freezer
[ ] Other

Hazards: (Check one)

[ ] None known. Take ordinary precautions in handling.
[✓] As follows: Flammable / will support combustion

Special Instructions: (Check one)

[ ] None
[✓] As follows: avoid temp. greater than 140° F.

Animals: Each test group will consist of six (6) New Zealand albino rabbits weighing ≥ 2.0 kg.

Animal Care: Follow the approved Standard Operating Procedures of the Test Facility. (Acclimation period must be a minimum of seven (7) days.)

Environmental Conditions: Follow the approved Standard Operating Procedures of the Test Facility.

Animal Identification: Follow the approved Standard Operating Procedures of the Test Facility.

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[redacted] PROTOCOL NO. C9A (Cont'd)

Skin Corrosivity (DOT Procedure with Options)

Issue Date: September 15, 1980

Site Preparation: Clip the back of each animal with a small animal clipper. Leave the test site on each animal intact.

Dose Preparation:

Test Group(s): (Check appropriate box)

[✓] Dose test substance undiluted
[ ] Dose as a _____% (w/w) solution/suspension of test substance in _____
_____.
[ ] Dose as a _____% (w/v) solution/suspension of test substance in _____
_____.
[ ] Dose per Special Instructions (see page 2)

Control Group

A control group should be [ ]; should not be [✓] included in this study. If included, the control substance _____ should be tested concurrently with the test substance at a dosage level of _____.

Note

A concentration analysis of the test substance - vehicle mixture(s) will [ ]; will not [✓] be required.

If a concentration analysis is required:

[ ] Prepare a sufficient quantity of the test substance - vehicle mixture(s) so that a portion can be returned to the Sponsor's designated facility.

Shipping Instructions

Send approximately _____ml. Send [ ] frozen; [ ] under ambient conditions; [ ] other_____
_____

[ ] Analyze the test substance - vehicle mixture(s) for test substance concentration using the analytical method in Appendix _____.

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[redacted]

PROTOCOL NO. C9A (Cont'd)

Skin Corrosivity (DOT Procedure with Options)

Issue Date: September 15, 1980

Dosing Instructions: Introduce 0.5 ml (in the case of liquids) or 0.5 gm (in the case of solids and semisolids) of the substance to be tested under a square surgical gauze patch measuring 1 inch x 1 inch and two single layers thick. Secure patches in place with adhesive tape by placing tape around the border of the patch. Wrap the entire trunk of each animal with impervious material such as rubberized cloth. (The impervious wrap should be applied in such a manner that the hand can easily be placed between the wrap and the animal's back.) Restrain the animal in appropriate harness or collar to prevent it from removing wrapping.

Observations: After 4 hours of exposure, remove the patches and evaluate the skin sites for corrosion. Readings are again made at the end of a total of 48 hours (44 hours after first reading). Corrosion is considered to have resulted if the substance in contact with the rabbit skin has caused destruction or irreversible alteration of the tissue. Tissue destruction is considered to have [illegible] of the [illegible], there is ulceration or necrosis. Tissue destruction does not include merely sloughing of the epidermis, [illegible] edema, or fissuring.

At study [illegible] surviving animals should be removed from [illegible] following the Standard Operating Procedures of the Test Facility.

Protocol Changes: If it becomes necessary to change the approved protocol, verbal agreement to make this change should be made between the Study Director and the Sponsor. As soon as practical, this change and the [illegible] should be put in writing and signed by both the Study Director and the Sponsor's Divisional Toxicologist. This document is then attached to the protocol as an addendum.

Report: Report should include how study was conducted, dates of initiation and termination, documentation of dose preparation, and whether the test substance was or was not corrosive.

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[redacted]

PROTOCOL NO. C9A (Cont'd)

Skin Corrosivity (DOT Procedure with Options)

Issue Date: September 15, 1980

Possible Options to the DOT Procedure:

Check the appropriate box(es) for any options desired and fill in any blank spaces.

[ ] 1. Immediately following the initial reading for corrosion, all test sites will be thoroughly washed with _____ to remove any residual test substance.

[ ] 2. Approximately 30 minutes after the removal of the patches, evaluate the test sites using the grading scale below.

Primary Irritation Scoring

(a) [illegible]

No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate-to-severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Highest possible erythema score	4

(b) [illegible]

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Highest possible edema score	4

Re-evaluate the test sites for these parameters 48 hours after initial application.

[ ] 3. If the test substance is judged to be corrosive at either reading, no primary irritation evaluation should be made. If the test substance is corrosive at the initial reading, the study is terminated.

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[redacted]

PROTOCOL NO. C9A (Cont'd)

Skin Corrosivity (DOT Procedure with Options)

Issue Date: September 15, 1980

Possible Options to the DOT Procedure (Cont'd):

[ ] 4. If the skin reaction is questionable, regarding corrosivity at 48 hours, then the study should be continued by maintaining the test animals with questionable reactions until the reactions can be properly classified.

If blank 2 is checked, the study report should include the erythema and edema scores for each animal at each observation time. The Primary Irritation Index equals the average of all the erythema scores plus the average of all the edema scores.

0	=	Nonirritating
0.1-2	=	Mildly irritating
>2-5	=	Moderately irritating
>5-6	=	Moderately to severely irritating
>6-8	=	Severely irritating

Report all skin reactions that are not covered by the above erythema and edema grading scale.

Sponsor: [redacted] Toxicologist

Date Approved by Sponsor's [redacted] Toxicologist 2/26/81

Proposed Starting Date: 3/4/81

Proposed Completion Date: 4/6/81
(Final Report Available)

Study Director: [redacted]

Date: 2/23/81

Study Cost: [redacted]

(To be completed by the Test Facility)

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SPRINGBORN INSTITUTE
FOR BIORESEARCH, INC.

(1)

RECEIVED BY
APR 20 1981
[redacted]

Perfume Containing
4% PEG-6
Caprylic / Capric Glycerides

RABBIT EYE IRRITATION STUDY
Sample: P0956
[redacted]

Lab Study No.: [redacted]
Report Date: 04/16/81

Protocol: Rabbit Eye Irritation #C2

Sponsor: [redacted]

Enclosed:

Summary	-	Page 2
GLP Requirements	-	" 3
Quality Assurance Statements	-	" 4
Raw Data Appendix	-	" 5-8
Protocol	-	" 9-18
Protocol Amendment	-	" Not applicable

Signed: Barbara Foraker
Laboratory Technician

Richard A. Hiles
Richard A. Hiles, Ph.D.
Vice President and
Director of Acute and
Subchronic Toxicology
(Study Director)

Jon C. Fulfs
Jon C. Fulfs, Ph.D.
Executive Vice President
and Director of Toxicology

Date 4/16/81

/lks

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[redacted]

(2)

RABBIT EYE IRRITATION STUDY - SUMMARY

Report of a biological test performed at:
Springborn Institute for BioResearch, Inc.
553 North Broadway
Spencerville, Ohio 45887

During the period: 03/09/81 - 04/16/81
According to the attached protocol and addenda (if any).
Deviations from Protocol: None

***

Lab Study No. [redacted]

Sponsor's [redacted] No. [redacted]

Test Substance (TSIN) P0956

Description: Clear liquid

Storage Conditions: Room temperature

Sponsor's [redacted] Toxicologist: [redacted]

Strain and Source of Animals: Rabbit - New Zealand White Isaacs Lab Stock

Concentration and Amount of Test Substance Dosed: 100%, 10% w/v aqueous - 0.1 ml

RESULTS

Treatment Group	Maximum Ave. Score (MAS)	Cornea No. Eyes Affected/ Treated	Iris No. Eyes Affected/ Treated	Conjunctiva No. Eyes Affected/ Treated	Days To Clear
Group I - 100% (no rinse)	0.0	0/3	0/3	0/3	1
Group II-100% (rinse)	0.0	0/3	0/3	0/3	1
Group III-10% w/v aqueous (no rinse)	0.0	0/3	0/3	0/3	1

CONCLUSIONS:

The test article did not cause irritation to the eye.

[redacted]

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[redacted]

GLP REPORT REQUIREMENTS

GLP Requirement	Page
Name and Address of Test Facility	2
Date Study Initiated	2
Date Study Completed	2
Objective and Procedures	9-16
Statistical Methods Used	NA
Test and Control Article Identification	2
Stability of Test and Control Articles	NA
Description of Methods	9-16
Description of Test System Species, Strain, Substrain, Source of Supply, Age, Sex, Body Weight Range, Number of Animals Used, and Procedure Used for Identification	13
Dosage Information	2
Description Circumstances Which May Have Affected the Data	NA
Name of the Study Director	1
Names of the Scientists, Professionals, and Personnel Involved in the Study	1
Description of Operations Performed on the Data	14
A Summary and Analysis of the Data	2
A Statement of Conclusions Drawn from the Analysis	2
Signed and Dated Reports of Individual Scientists or Other Professionals Involved in the Study	1
Locations Where All Specimens, Raw Data, and Final Report are to be Stored	4
Quality Assurance Statement (signed)	4

NA = not applicable

LETTERS AND REPORTS [illegible]

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[redacted]

Quality Assurance Statement

Study No. [redacted] Test Substance P0956

Type of Study Rabbit Eye Irritation #C2

Listed below are dates that this study was inspected by the Quality Assurance Unit and the dates findings were reported to the Study Director and to Management.

Dates of Inspection	Dates Findings Reported to Study Director	Date Findings Reported to Management
04/15/81	04/15/81	04/15/81
03/09/81	03/09/81	04/15/81
03/[illegible]/81	04/08/81	04/15/81

Location of Raw Data Storage Statement

The original copy of the final report and all raw data will be on file at the testing facility.

Date 4/15/81

Carol Davis
Manager/Coordinator Quality Assurance Unit

LETTERS AND REPORTS [illegible]

[redacted]

TABLE I

DOSE SOLUTION PREPARATION WEIGH SHEET

Study # [redacted] Test Material PO 5 Type of Test Rabbit Eye Irritation

Test Material Concentration 10% % w/w X w/v

Specific Gravity NA ml weighed at °C °F Room Temp.

Specific Gravity NA gm/ml

Nominal Conc. w/w or w/v	Test Material: Weight Container (gm) or mg	Test Material: Weight of Container and Test Material	Test Material: Weight of Test Mat. (gm) or mg	Diluent w/w: Weight of Container gm or mg	Diluent w/w: Weight of Container Plus Dilu. gm or mg	Diluent w/w: Weight of Diluent gm or mg	Diluent w/v: Amount of Test Mat. Plus Dilu. ml	Diluent w/v: Type of Vessel
10% w/v	35.6721	36.6909	1.0	NA	NA	NA	Brought up to 10 ml w/ distilled H_2O	10 ml grad. cylinder
NA	NA	NA	NA	NA	NA	NA	NA	NA (5)
NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA

Special Instructions:
NA = not applicable

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[redacted]

TABLE II (6)

ACUTE EYE IRRITATION
GROUP I
100% - 0.1 ml (no rinse)

Rabbit Number	Observ Time	Cornea A	Cornea B	Score AXBX5	Iris A	Score AX5	Conjunctivae A	Conjunctivae B	Conjunctivae C	Score (A+B+C)2
Rb-2145-81	Day 1	0	0	0	0	0	0	0	0	0
Rb-2146-81	Day 1	0	0	0	0	0	0	0	0	0
Rb-2147-81	Day 1	0	0	0	0	0	0	0	0	0

Primary Irritation Score:
Day 1 0.0

Maximum Average Score:
0.0 @ Day 1

No animal squealed upon instillation of test article.

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TABLE II (7)

ACUTE EYE IRRITATION

GROUP II

100% - 0.1 ml (rinse)

Rabbit Number	Observ Time	Cornea A	Cornea B	Score AXBX5	Iris A	Score AX5	Conjunctivae A	Conjunctivae B	Conjunctivae C	Score (A+B+C)2
Rb-2148-81*	Day 1	0	0	0	0	0	0	0	0	0
Rb-2149-81	Day 1	0	0	0	0	0	0	0	0	0
Rb-2150-81	Day 1	0	0	0	0	0	0	0	0	0

Primary Irritation Scores:
Day 1 0.0

Maximum Average Score:
0.0 @ Day 1

No animal squealed upon instillation of test article.

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[redacted]

TABLE II (8)

ACUTE EYE IRRITATION
GROUP II

10% w/v aqueous - 0.1 [redacted] (no rinse)

Rabbit Number	Observ Time	Cornea A	Cornea B	Score AXBX5	Iris A	Score AX5	Conjunctivae A	Conjunctivae B	Conjunctivae C	Score (A+B+C)2
Rb-2151-81	Day 1	0	0	0	0	0	0	0	0	0
Rb-2127-81	Day 1	0	0	0	0	0	0	0	0	0
Rb-2099-81	Day 1	0	0	0	0	0	0	0	0	0

Primary Irritation Scores:
Day [redacted] 0.0

Maximum Average Score:
0.0 @ Day 1

No animal squealed upon instillation of test article.

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[redacted]

(9)

PROTOCOL NO. C2

10004

Rabbit Eye Irritation

Issue Date: September 15, 1980
Supersedes Issue of: January 1, 1980

Test Substance Identification Number (TSIN) # P0956

[redacted]

Sponsor: [redacted]

Testing Facility: (To be filled in by Operations Section) Springborn Institute for Bioresearch, Inc. Spencerville, Ohio 45887

Study # [redacted] (To be filled in by Testing Facility)

Purpose: To determine the relative level of eye irritation of a test substance in the rabbit so that it may be compared with more familiar substances.

Justification for Selection of Test System: The New Zealand albino rabbit is the animal of choice based on large orbit and nonpigmented iris.

Site of Administration of Test Substance and Reason for Choice: Place the test substance into the conjunctival sac of one eye. Historical - Based on method of Draize.

Diet and/or Water Analyses Required: None (no known contaminants expected which would interfere with this study)

Records to be Maintained: All records that would be required to reconstruct the study and demonstrate adherence to protocol.

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[redacted]

(10)

PROTOCOL NO. C2 (Cont'd)

0006

Rabbit Eye Irritation

Issue Date: September 15, 1980

Test Substance(s)	Description		Expiration Date
	Color	Physical Form	
TSIN # [redacted]	Clear ~~Amber~~	liquid	2/82 2/20/81
P0956			
[redacted]			

Storage Conditions: (Check one)

[✓] Room temperature [ ] Refrigerator [ ] Freezer
[ ] Other

Hazards: (Check one)

[ ] None known. Take ordinary precautions in handling.
[✓] As follows: Flammable / will support combustion

Special Instructions: (Check one)

[ ] None
[ ] As follows: avoid temps. greater than 140° F

Animals: Rabbits, New Zealand albino. Each test group will consist of three (3) young animals per test group. Animals are to weigh ≥ 1.5 kg.

Animal Care: Follow the approved Standard Operating Procedures of the Test Facility. (Acclimation period must be a minimum of seven (7) days.)

Environmental Conditions: Follow the approved Standard Operating Procedures of the Test Facility.

Animal Identification: Follow the approved Standard Operating Procedures of the Test Facility.

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Non-discretionary

[redacted]

Date: 8/26/81

Work Done: 2/18/81 - 3/27/81

Human Sensitization Test of [redacted] Perfume [redacted]

Summary and Test Material:

[redacted] P0956, 0.1% in mineral oil (v/v), 69 subjects, no sensitization, [redacted]

Sponsor: [redacted]

↳ Perfume containing 4% PEG-6 Caprylic / Capric Glycerides

Additional Sample Information: Appendix I

Procedure:

Performed according to standard [redacted] human sensitization test protocol dated 1/2/80 with any modifications noted below:

[redacted] group was not used for this sample. The test concentration and prior safety [redacted] indicated that the main group could be tested without unacceptable risk to the subjects.

Test Volunteers From:

[redacted]

Subjects Excused at Pre-Test Interview: Appendix II

Allergy/Dermatologic Comment Summary: Appendix III

Subject Groups and Dates of Participation:

	Pilot Group	Main Group
[redacted]	--	1-81

Calendars are Appendix IV

Field Supervisor and Scorer: [redacted]

Dermatologist Available for Consultation: [redacted]

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RESULTS

Subjects Completing Test/Scores/Number Dropped: Table I

Reasons for drops in Appendix V. No dropped subject has responded in a manner [illegible] sensitization.

Summary of Scores by Visit: Table II

Subject Deviations:

[redacted]-24: Subject was unable to appear at test site for 96 hour challenge scoring. Challenge scores are for 24 hours and 48 hours.

[redacted]-27: On 2/25/81 the subject reported to the test grader she developed a dermatitis on the left side of her neck on 2/24/81. She had worn three patches. At this time (2/25/81) there was no evidence of dermatitis in the patch area, and the fourth patch was applied. When the subject returned to the test site on 2/27/81, she reported that a dermatitis appeared on both cheeks early in the day of 2/26/81, and that later, in the afternoon and evening of the same day, the patch area itself became reddened with numerous eruptions visible. When the subject's arm was graded on 2/27/81 there was some evidence of a mild dermatitis in the area of the Blenderm tape, but no unusual response to the test material. The subject requested to remain on the test and the patch was applied (moved) to the back part of the arm with all excess tape trimmed. All subsequent induction patches [illegible] trimmed and worn on the back part of the arm without further [illegible]. The dermatitis gradually cleared and the subject wore challenge patches likewise without further problem. It may, therefore, be concluded that the test material itself did not cause the dermatitis.

[illegible]: Subject was unable to appear at test site for 48 hour challenge scoring. Challenge graders are for 72 hours and 96 hours.

Sensitization:

No sensitization was seen during this test in any of the subjects.

[redacted]

[redacted]

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Appendix I

Composition of Materials:

[redacted] Perfume [redacted] P0936) ← 4% PEG-6 Caprylic/capric glyceride in perfume

Perfume formula is attached to the test request.

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APPENDIX II

EXCUSED PERSONS AND REASONS
TEST NO. [redacted]

PANELIST	SEX	AGE	
XA	F	35-44	OTHER ACTIVE DERMATITIS
XB	F	25-34	OTHER--SEE REPORT
XC	F	35-44	OTHER ACTIVE DERMATITIS
XD	F	25-34	ECZEMA
XE	M	65 OR OLDER	OTHER ACTIVE DERMATITIS
XF	F	45-54	DECLINED PARTICIPATION

TOTAL QUESTIONED = 87
TOTAL EXCUSED = 6
TOTAL STARTING = 81

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APPENDIX III

SUMMARY OF ALLERGY/DERMATOLOGIC HISTORY BY SUBJECT

TEST NO. [redacted] DATE 2/18/81 TO 3/27/81

PANELIST	SEX	AGE	
001	F	65 OR OLDER	NONE
002	F	35-44	NONE
003	F	65 OR OLDER	NONE
004	F	65 OR OLDER	NONE
005	F	25-34	NONE
006	F	35-44	HISTORY OF DERMATITIS LAUNDRY DETERGENTS DISHWASHING LIQUIDS CLEANING PRODUCTS PERFUMES ANTIPERSPIRANTS/DEODORANTS FOODS MEDICINES
007	F	45-54	NONE
008	F	25-34	POISON IVY/OAK MEDICINES
009	F	35-44	NONE
010	F	35-44	HISTORY OF DERMATITIS
011	F	35-44	NONE
012	F	45-54	SHAMPOOS MEDICINES
013	F	25-34	HAY FEVER DISHWASHING LIQUIDS
014	M	55-64	HISTORY OF DERMATITIS
015	F	55-64	POISON IVY/OAK
016	F	45-54	NONE
017	F	65 OR OLDER	NONE
018	F	65 OR OLDER	NONE
019	F	25-34	NONE
020	F	25-34	NONE
021	F	25-34	POISON IVY/OAK
[illegible]	[illegible]	45-54	COSMETICS CLOTHING MEDICINES
[illegible]	[illegible]	18-24	NONE
[illegible]	[illegible]	35-44	HISTORY OF DERMATITIS MEDICINES
[illegible]	F	45-54	POISON IVY/OAK
026	M	25-34	NONE
027	F	35-44	FABRIC SOFTENERS BAR SOAPS POISON IVY/OAK MEDICINES
028	F	35-44	NONE
029	F	25-34	HISTORY OF ECZEMA HISTORY OF DERMATITIS LAUNDRY DETERGENTS DISHWASHING LIQUIDS CLEANING PRODUCTS BAR SOAPS ANTIPERSPIRANTS/DEODORANTS OTHER
030	F	35-44	HISTORY OF DERMATITIS BAR SOAPS POISON IVY/OAK
031	F	45-54	NONE
032	F	35-44	HISTORY OF ECZEMA DISHWASHING LIQUIDS CLEANING PRODUCTS POISON IVY/OAK
033	F	18-24	NONE
034	M	25-34	POISON IVY/OAK
035	F	25-34	HAY FEVER
036	M	55-64	HAY FEVER ASTHMA
037	F	25-34	HISTORY OF DERMATITIS HAY FEVER
038	F	25-34	HISTORY OF DERMATITIS POISON IVY/OAK JEWELRY/METALS
039	F	25-34	NONE
040	F	45-54	CLOTHING POISON IVY/OAK FOODS
041	F	25-34	DISHWASHING LIQUIDS MEDICINES OTHER

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APPENDIX III (cont'd)

SUMMARY OF ALLERGY/DERMATOLOGIC HISTORY BY SUBJECT

TEST NO. [redacted] DATE 2/16/81 TO 3/27/81

PANEL LIST	SEX	AGE	
042	F	18-24	HISTORY OF DERMATITIS
043	F	25-34	NONE
044	F	25-34	CLOTHING MEDICINES
045	F	45-54	HAY FEVER FABRIC SOFTENERS LAUNDRY DETERGENTS DISHWASHING LIQUIDS CLEANING PRODUCTS SHAMPOOS SOAP SCRUBS PERFUMES CLOTHING POISON IVY/OAK OTHER
046	F	65 OR OLDER	MEDICINES
047	F	65 OR OLDER	NONE
048	F	18-24	HISTORY OF DERMATITIS LAUNDRY DETERGENTS CLEANING PRODUCTS POISON IVY/OAK
049	F	25-34	POISON IVY/OAK
050	F	55-64	ASTHMA ANTIPERSPIRANTS/DEODORANTS CLOTHING MEDICINES
051	F	45-54	SHAMPOOS CLOTHING OTHER
052	F	55-64	POISON IVY/OAK
053	F	35-44	JEWELRY/METALS
054	F	35-44	NONE
055	M	18-24	POISON IVY/OAK
056	M	25-34	POISON IVY/OAK
057		35-44	MASTECTOMY-PATCHES ON LEFT SIDE
058	F	25-34	POISON IVY/OAK
059	F	18-24	HISTORY OF DERMATITIS POISON IVY/OAK
060		55-64	NONE
061		25-34	NONE
062	F	35-44	NONE
063	F	25-34	NONE
064	M	18-24	HAY FEVER
065	F	35-44	HAY FEVER ASTHMA BAR SOAPS CLOTHING POISON IVY/OAK FOODS MEDICINES
066	M	18-24	POISON IVY/OAK
067	F	65 OR OLDER	SHAMPOOS BAR SOAPS ANTIPERSPIRANTS/DEODORANTS
068	M	18-24	NONE
069	M	18-24	NONE
070	F	18-24	NONE
071	F	18-24	NONE
072	F	35-44	NONE
073	M	18-24	POISON IVY/OAK
074	F	35-44	NONE
075	F	25-34	POISON IVY/OAK
076	F	45-54	POISON IVY/OAK MEDICINES
077	M	55-64	NONE
078	F	35-44	NONE
079	F	25-34	NONE
080	M	35-44	POISON IVY/OAK JEWELRY/METALS
081	F	35-44	HISTORY OF ECZEMA CLOTHING

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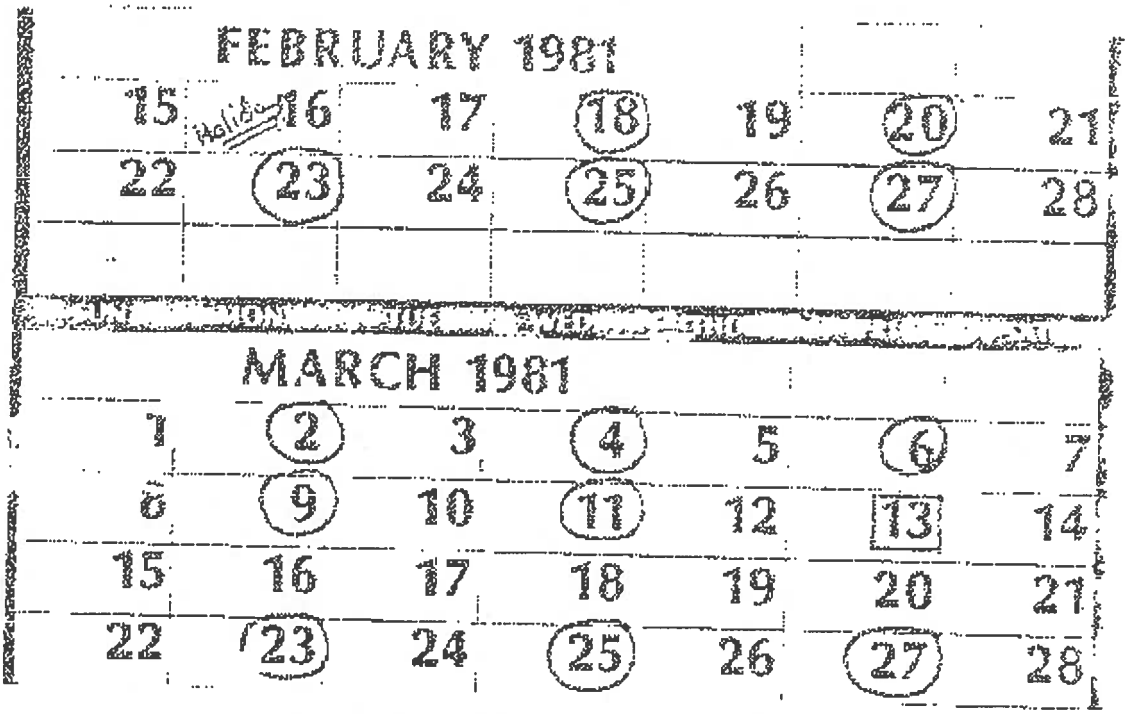
[redacted]

APPENDIX IV

[redacted] SKIN PATCH TEST SCHEDULE

As a participant in the [redacted] Patch Test for [redacted] we would like for you to be present between 1:30 p.m. and 3:45 p.m. on the following days:



March 13 - Make Up Day

A pa[illegible] to [redacted] for your participation then you [illegible] the test. If you are absent on any of the test days from February 18 to March 11, you [illegible] on the make-up day, March 13. You cannot miss more than one visit during this period of the test. YOU MUST BE PRESENT ON EACH OF THE THREE DAYS OF THE LAST WEEK OF THE TEST, March 23, 25 &27 FOR THE ORGANIZATION TO RECEIVE PAYMENT FOR YOUR PARTICIPATION IN THE TEST. Your organization <u>will not</u> receive <u>any</u> payment for your partial participation.

Please remove and throw away your patch 24 hours (1 day) after it is applied. After removing, you may wish to rinse the skin under the patch to remove any remaining materials. However, please do not apply any cream or lotion to the patch area at any time during the test. You will notice that the purple dots applied to your arm have remained on your skin. Please <u>do not wash them off</u>. While wearing the patch, try to keep it as dry as possible and do not immerse your arm in water. Water splashed on the patch during bathing should not loosen it; however, please wash the patch arm with care so that the patch remains secure for 24 hours (1 day).

When you come to the test please remember to wear clothing which will enable us to easily place a patch on the upper part of your arm.

If you wish to contact us for any reason you may use the following telephone numbers:

[redacted]

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Appendix V

Reasons for Failure to Complete Test

[redacted]

Subject No.	Date	Reason
1	2/23/81	Unable to make final test day.
9	3/4/81	No longer works at the school.
12	2/27/81	Had the flu.
17	3/4/81	Had a stroke.
43	3/6/81	Absent from school.
46	2/25/81	Had diabetes; doctor suggested that she not participate.
54	3/4/81	Absent from school.
55	3/9/81	No longer has school custodian job.
56	3/27/81	Had the flu.
63	2/25/81	Husband does not want her to participate.
64	3/6/81	Absent from school.
69	3/6/81	Absent from school.

TABLE 1

SCORES FOR ALL SUBJECTS

[redacted] [redacted] PERFUME MAIN [illegible]

P0956 2/18/81 - 3/27/81

SUBJECT NUMBER	INDUCTION 1	2	3	4	5	6	7	8	9	MAKE-UP	CHALLENGE 01	A1	02	A2	
1	0	0	-	-	-	-	-	-	-		-	-	-	-	DROP
2	0	0	0	0	0	0	0	0	0	1	0	0	0	0	
3	0	0	0	0	0	0	0	0	0		0	0	0	0	
4	0	1	0	0	1	0	1	0	-	0	0	0	0	0	
5	1	0	0	0	0	0	0	0	0		0	0	1	1	
6	0	0	0	0	0	0	0	0	0		0	0	0	0	
7	0	-	0	0	0	0	0	0	0	0	0	0	0	0	
8	1	0	0	-	0	0	0	0	0	0	0	0	0	0	
9	0	0	0	0	-	0	0	0	-	-	-	-	-	-	DROP
10	0	0	0	0	0	0	0	0	0		0	0	0	0	
11	1	1	0	0	1	0	1	1	-	0	0	0	0	0	
12	0	0	-	-	-	0	-	-	-	-	-	-	-	-	DROP
13	0	0	0	0	0	0	0	0	0		0	0	0	0	
14	0	0	0	0	0	0	0	0	0		0	0	0	0	
15	0	0	0	0	0	0	0	0	0		0	0	0	0	
16	0	0	0	0	0	0	0	0	0		0	0	0	0	
17	0	-	0	0	-	0	-	-	-	-	-	-	-	-	DROP
18	0	-	0	0	0	0	0	0	0	0	0	0	0	0	
19	0	0	0	0	0	0	0	0	0		0	0	0	0	
20	0	0	0	0	0	0	0	0	0		0	0	0	0	
21	0	-	1	0	0	0	0	0	1		0	0	0	0	
22	0	0	0	0	0	0	0	0	0		0	0	0	0	
23	0	0	0	0	0	0	0	0	0		0	0	0	0	
24	0	-	0	0	0	0	0	0	0	0	0	0	0	0	
25	0	0	0	0	0	0	0	0	1		0	0	0	0	
26	0	0	0	0	0	0	0	0	0		0	0	0	0	
27	0	0	0	NA	NO	0	0	0	0		-	-	-	-	

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TABLE 1

SCORES OF ALL SUBJECTS

[redacted] [redacted] PERFUME MAIN GROUP

P0956 2/18/81 - 3/27/81

SUBJECT NUMBER	INDUCTION 1	2	3	4	5	6	7	8	9	MAKE-UP	CHALLENGE 01	A1	02	A2	
28	0	0	0	0	0	0	0	0	0		0	0	0	0	
29	-	0	0	0	0	0	0	0	0	0	0	0	0	0	
30	0	0	0	0	0	0	0	0	0		0	0	0	0	
31	0	0	0	0	0	0	0	0	0		0	0	0	0	
32	0	0	0	-	0	0	0	0	0	0	0	0	0	0	
33	0	0	0	0	0	0	-	0	0	0	0	0	0	0	
34	0	0	0	0	0	0	0	0	0		0	0	0	0	
35	0	0	0	0	-	0	0	0	0	1	0	0	0	0	
36	0	0	0	0	0	0	0	0	0		0	0	0	0	
37	0	0	0	0	0	0	0	0	0		0	0	0	1	
38	0	0	0	0	1	0	0	0	0		0	0	0	0	
39	0	0	0	0	0	0	0	-	0	0	0	0	0	0	
40	0	0	0	0	0	0	0	0	0		0	0	0	0	
41	0	0	0	0	0	0	0	0	0		0	0	0	0	
42	0	0	0	-	0	0	0	0	0	0	0	0	0	0	
43	0	0	0	0	-	0	-	-	-	-	-	-	-	-	DROP
44	0	0	0	0	0	0	0	0	-	1	0	1	0	0	
45	0	0	0	0	0	0	0	0	1		0	0	0	0	
46	0	-	0	-	-	-	-	-	-	-	-	-	-	-	DROP
47	-	0	0	0	0	0	0	0	0	0	0	0	0	0	
48	0	0	-	0	0	0	-	-	-	-	-	-	-	-	DROP
49	0	0	0	1	0	0	0	1	0		0	0	0	0	
50	0	0	0	0	0	0	0	0	0		0	0	0	0	
51	0	0	0	0	0	0	-	0	0	0	0	0	0	0	
52	0	1	0	0	0	0	0	0	0		0	0	0	0	
53	0	0	0	0	0	0	0	0	0		0	0	0	0	
54	0	0	1	0	0	0	0	-	0	0	0	1	0	0	

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TABLE 1

SCORES FOR ALL SUBJECTS

[redacted] PERFUME MAIN GROUP

PD950 2/18/81 - 3/27/81

SUBJECT NUMBER	INDUCTION 1	2	3	4	5	6	7	8	9	MAKE-UP	CHALLENGE U1	A1	U2	A2	
55	0	0	0	1	1	0	1	1	1	1	1	1	1	1	DROP
56	0	0	0	0	0	0	0	0	0		0	0	0	0	DROP
57	0	0	0	0	0	0	0	0	0		0	0	0	0	
58	0	0	0	0	0	0	0	0	0		0	0	0	0	
59	0	0	0	0	0	0	0	0	0		0	0	0	0	
60	0	0	0	0	0	0	0	0	0		0	0	0	0	
61	0	0	0	0	0	0	0	0	0		0	0	0	0	
62	0	0	0	0	0	0	0	0	0		0	0	0	0	
63	0	1	1	1	1	1	1	1	1	1	1	1	1	1	DROP
64	0	0	0	0	0	1	1	1	1	1	1	1	1	1	DROP
65	0	0	0	0	1	0	0	0	0	0	0	0	0	0	
66	0	0	0	0	0	0	0	0	0		0	0	0	0	
67	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
68	0	0	0	0	0	0	1	1	1	1	1	1	1	1	DROP
69	0	0	0	0	0	0	0	0	0		0	0	0	0	
70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
71	0	0	0	0	0	0	0	0	0		0	0	0	0	
72	0	0	0	0	0	0	0	0	0		0	0	0	0	
73	0	0	0	0	0	1	0	0	0		0	0	0	0	
74	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
75	0	0	0	0	0	0	0	0	0		0	0	0	0	
76	0	0	0	0	0	0	0	0	0		0	0	0	0	
77	0	0	0	1	1	1	1	1	0		0	0	0	0	
78	0	0	0	0	0	0	0	0	0		0	0	0	0	
79	0	0	0	0	0	0	0	0	0		0	0	0	0	
80		0	0	0	0	0	0	0	0	0	0	0	0	0	
81		0	0	0	0	0	0	0	0	0	0	0	0	0	

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TABLE 1

SOURCE: [redacted] ALL SUBJECTS

[redacted] PERFUME MATCH - UP

PERIOD 2/18/81 - 3/27/81

SUBJECT NUMBER	INDUCTION 1	2	3	4	5	6	7	8	9	MATCH UP	UP	AT	DOWN	AWAY	CHALLENGE

TOTAL SUBJECTS 81

DROPPED 12

COMPLETED TEST 69

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TABLE II

SUMMARY OF SCORES BY VISIT

[redacted] [redacted] PERFUME MAIN (DY

P0956 2/18/81 - 3/27/81

SCORES	INDUCTION 1	2	3	4	5	6	7	8	9	MAKE-UP	CHALLENGE VISITS C1	A1	C2	A2	TOTAL
0	74	72	75	68	67	70	64	64	64	20	70	68	68	66	910
1	3	4	2	3	6	2	4	3	3	3	0	1	1	2	37
1E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
A	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
X	0	0	0	0	0	0	0	0	0	0	0	1	0	1	2
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-	2	5	4	10	7	9	13	14	14	10	11	11	12	12	134
NO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: June 24, 2014

SUBJECT: Comments on the Scientific Literature Review: Safety Assessment of PEGylated Alkyl Glycerides as Used in Cosmetics

The Council has no suppliers listed for the following ingredients:

PEG-6 Almond Glycerides
PEG-35 Almond Glycerides
PEG-14 Avocado Glycerides
PEG-11 Babassu Glycerides
PEG-4 Caprylic/Capric Glycerides
PEG-11 Cocoa Butter Glycerides
PEG-75 Cocoa Butter Glycerides
PEG-20 Corn Glycerides
PEG-20 Evening Primrose Glycerides
PEG-5 Hydrogenated Corn Glycerides
PEG-8 Hydrogenated Fish Glycerides
PEG-20 Hydrogenated Palm Glycerides
PEG-13 Mink Glycerides
PEG-25 Moringa Glycerides
PEG-2 Olive Glycerides
PEG-6 Olive Glycerides
PEG-7 Olive Glycerides
PEG-40 Olive Glycerides
PEG-12 Palm Glycerides
PEG-6 Hydrogenated Palm/Palm Kernel 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-13 Sunflower Glycerides

Key Issue

The CIR report on plant seed oils states that *Moringa pterygosperma* and *Moringa oleifera* are two names for the same species, and only shows composition information for *Moringa oleifera*. Table 2 of the current report should indicate that the plant oil report included information on *Moringa oleifera* rather than *Moringa pterygosperma*. The composition information from *Moringa oleifera* needs to be added to Table 4 of this report. After it was discovered that these were two names for the same species, the INCI name Moringa

Pterygosperma Seed Oil was removed from the Dictionary. To be consistent with name now used in the Dictionary for this species, the definition of PEG-25 Moringa Glycerides has been changed from *Moringa pterygosperma* to *Moringa oleifera*.

Additional Comments

Most of the text under figures is not straight when the report is printed.

Cosmetic Use - The paragraph concerning potential spray products suggests that the VCRP reported products containing up to 1.9% PEG-45 Palm Kernel Glyceride in a pump spray product. This does not make sense as the VCRP does not include use concentrations.

Irritation and Sensitization - Please correct: "and the researched stated"

Irritation and Sensitization - The dosing solution used in reference 34 is not clear. It says "100 µl of diclofenac epolamine in a microemulsion containing 30% propylene glycol monocapryate, 50% PEG-8 caprylic/capric glycerides/ethoxydiglycol (1:2 w/w), and 20% water". Does 100 µl represent the amount of diclofenac epolamine, or the total amount of the dosing solution? If it is the total amount of the dosing solution, what was the concentration of diclofenac epolamine?

Table 2 - It would be helpful to state if the PEG report included any information on Triethylene Glycol. Please indicate that concentrations of Caprylic/Capric Triglyceride, palm oil and safflower that were not sensitizing. What was the route of injection, e.g., i.v., used in the study of PEG-60 Hydrogenated Castor Oil in dogs?

Table 5 - The 0.01% concentration of PEG-20 Almond Glycerides, and the 0.2% concentration of PEG-10 Olive Glycerides were in the hair tonics category. This category is also shown in the incidental inhalation- spray row for the other compounds. For PEG-75 Shea Butter Glycerides, it is not clear why the powder row has two 0.1% values. There were three 0.1% values in the concentration of use information provided by the Council, shampoo, bath soaps and detergents, and foot products. Of these categories, only the foot product category is put in the incidental inhalation - powder row.