
Amended Safety Assessment of Monoglyceryl Monoesters as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: August 28, 2015
Panel Meeting Date: September 21-22, 2015

The 2015 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/Writer and Bart Heldreth, Ph.D., Chemist.

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
 From: Monice M. Fiume *MMF*
 Assistant Director/Senior Scientific Analyst
 Date: August 28, 2015
 Subject: Amended Safety Assessment of Monoglyceryl Monoesters as Used in Cosmetics

Enclosed is the Re-Review of the Amended Safety Assessment of Monoglyceryl Monoesters as Used in Cosmetics. (It is identified as *glyest092015rep* in the pdf document.) In 1982, the Panel concluded that glyceryl stearate and glyceryl stearate SE are safe for topical application to humans. In accordance with its Procedures, CIR evaluates the conclusions of previously-issued reports every 15 years to determine whether the conclusion should be reaffirmed. There is no record of glyceryl stearate being re-reviewed, so that process is now being initiated.

The Panel has issued 4 final reports on 35 similar ingredients that seem appropriate to include in this re-review; all of those ingredients are safe as used. Also, there are 8 additional cosmetic ingredients that have not yet been reviewed that have been identified as appropriate for inclusion. Table 1 provides a complete list of all 45 ingredients.

All of the ingredients that are being proposed for inclusion in this report are similar because they are structurally-constituted of the esterification products of glycerin and fatty acids. A report strategy was presented to the Panel at the December 2014 meeting (see *glyest092015strat_memo*), proposing that a much larger group be included as part of the re-review of glyceryl stearate. However, after further consideration by the CIR staff, it was determined that two separate documents should actually be developed: 1.) the monoglyceryl monoesters report (enclosed), and 2.) a report on the polyglyceryl fatty acid esters (to be presented at the December meeting).

Two other issues need to be acknowledged. First, is one of the ingredients previously-reviewed (in 2004) glyceryl arachidonate. The data were insufficient to support the safety of this ingredient, and therefore glyceryl arachidonate is not part of the current re-review because ingredients with insufficient data are not re-reviewed. Second, that same report included an ingredient identified as glyceryl stearate/maleate. Although that name was listed in the *International Cosmetic Ingredient Dictionary* as an ingredient, that was an error. It is actually glyceryl stearate/malate that is an ingredient, and glyceryl stearate/malate is proposed for inclusion in the re-review.

Concentration of use data were received from the Council and are included in this package (*glyest092015data*). Also included are VCRP data (*glyest092015FDA*). You will note that, with the exception of glyceryl rosinat and glyceryl hydrogenated rosinat (for which concentration of use has increased), the frequency of use of these ingredients has increased, but the concentration of use generally has not.

The original review of glyceryl stearate and the four safety assessments referred to above are also provided:

glyest092015prev_1: Final Report on the Safety Assessment of Glyceryl Stearate and Glyceryl Stearate/SE (1982)

glyest092015prev_2: Final Report on the Safety Assessment of Glyceryl Oleate (1986)

glyest092015prev_3: Final Report of the Amended Safety Assessment of [Glyceryl Monoesters] (2004)

glyest092015prev_4: Final Report on the Safety Assessment of Glyceryl Ricinoleate (1988)

glyest092015prev_5: Final Report on the Safety Assessment of Ricinus Communis (Castor) Seed Oil [-derived ingredients] (2007)

The Panel is now being asked to consider whether a re-review of this ingredient group is appropriate, first considering whether new data are a reason to re-open the review. If the new data presented in the report simply reaffirm the original conclusion, then is it appropriate to re-open the review to include the proposed “add-ons”.



Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members, CIR SSC Members, and Liaisons
From: Bart Heldreth, PhD, Chemist
Date: October 9, 2014
Subject: Request for Endorsement of a Review Strategy for Glyceryl Esters as Used in Cosmetics

In 1982, the Journal of the American College of Toxicology published the Panel's safety assessment of the cosmetic ingredients Glyceryl Stearate and Glyceryl Stearate SE (*Journal of the American College of Toxicology* 1(4):169-192, 1982).

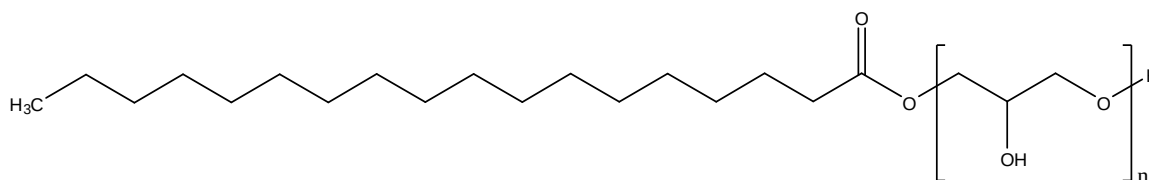


Figure 1. Glyceryl Stearate, wherein n is one.

At that time the Panel's conclusion was:

On the basis of the available animal data and clinical experience presented in this report, the Panel concludes that Glyceryl Stearate and Glyceryl Stearate SE are safe for topical application to humans in the present practices of use and concentration.

And of note in the discussion:

Clinical safety data are limited, but long clinical experience and abundant animal studies prove these compounds to be nonsensitizing, nonphototoxic and nonphotosensitizing. Human phototesting, single and repeated patch testing has been carried out on too few subjects, but none of the available data provides suspicion of risk associated with the use of Glyceryl Stearate and Glyceryl Stearate SE as cosmetic ingredients. Furthermore, chemical manufacturing worker experience for 14 years has produced no adverse employee reactions.

According to CIR procedures, the time to consider this assessment for re-review has transpired. In agreement with our 2014 Re-Review Priority document, we had proposed the addition of seventy-three ingredients comprising other mono-glyceryl fatty acid mono-esters, sharing the core structure depicted in Figure 2, to this re-review.

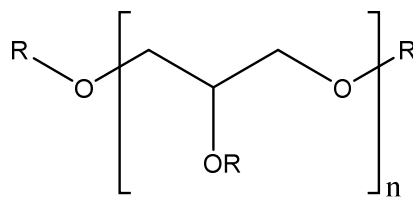


Figure 2. Generic structure of mono-glyceryl fatty acid mono-esters, wherein one R group represents the residue of a certain fatty acid, the other two R groups each represent hydrogen, and n is one.

However, a related group of ingredients is also slated on the 2015 new report Priority List. This grouping was given the draft report name “Polyglyceryl-X Fatty Acid Esters.” The ingredients in this group of two hundred eighty-two share in common the core structure depicted in Figure 3 and are each **Glyceryl Esters**, comprising at least one, and no more than twenty, glyceryl repeat unit(s) and at least one fatty acid ester.

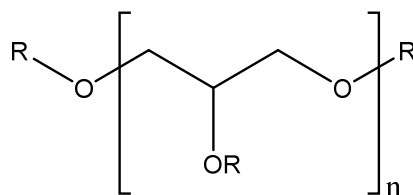


Figure 3. Generic structure, wherein R represents hydrogen or the residue of certain fatty acids, and n varies from 1 to 20.

Since the ingredients in our originally proposed re-review of Glyceryl Stearate share the same structural core as those ingredients of our new report, we herein propose the assemblage of these two groupings into one report, **Glyceryl Esters**. The ingredients in this combined report, the **Glyceryl Esters**, are each structurally constituted of the esterification products of glycerin and fatty acids. Therein, the ingredient grouping would be broken down into sub-groups, delineated by structural characteristics such as the value of “n” or how many “R” groups are representative of fatty acid residues. Accordingly, if some rationale to separate these ingredients along those structural lines becomes apparent, once the culmination of toxicological data is available and summarized, such lysing into two or more concurrent reports will be rather straight-forward. A rough draft of the sub-groupings is included herein, as Table 1.

In consideration of the size of this proposed report, please remember the success of the even larger CIR safety assessment titled Alkyl PEG Ethers, the 369 ingredients of which also varied by the number of polyether (polyethylene glycol instead of polyglycerol) repeat units and the number of attached fatty alkyl chains.

Accordingly, the question being asked is, should an SLR be prepared comprising all 331 of the ingredients listed in Table 1?

- 3 -

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

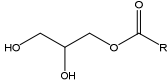
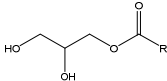
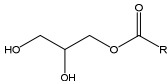
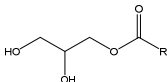
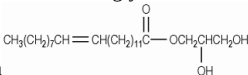
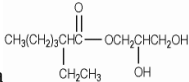
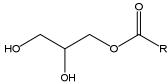
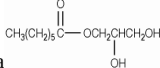
Ingredient CAS No.	Definition & Structure
Glyceryl Caprylate/Caprate	Glyceryl Caprylate/Caprate is a monoester of glycerin esterified with a mixture of caprylic and capric acids.  wherein RC(O)- represents the residue of Caprylic or Capric Acid
Glyceryl Citrate/Lactate/Linoleate/Oleate	Glyceryl Citrate/Lactate/Linoleate/Oleate is glycerin esterified with a blend of citric, lactic, linoleic and oleic acids.  wherein RC(O)- represents the residue of citric, lactic, linoleic, or oleic acid
Glyceryl Cocoate 61789-05-7	Glyceryl Cocoate is the monoester of glycerin and coconut fatty acids. It conforms generally to the formula:  where RC(O)- represents the fatty acids derived from coconut oil
Glyceryl Cocoate/Citrate/Lactate	Glyceryl Cocoate/Citrate/Lactate is glycerin esterified with a blend of coconut, citric and lactic acids.  wherein RC(O)- represents the residue of coconut, citric, or lactic acid
Glyceryl Erucate 28063-42-5	Glyceryl Erucate is the monoester of glycerin and erucic acid. It conforms generally to the formula 
Glyceryl Ethylhexanoate	Glyceryl Ethylhexanoate is the ester of glycerin and ethylhexanoic acid that conforms to the formula 
Glyceryl Ethylhexanoate/Stearate/Adipate	Glyceryl Ethylhexanoate/Stearate/Adipate is Glycerin esterified with a blend of 2-ethylhexanoic acid, Stearic Acid and Adipic Acid.  wherein RC(O)- represents the residue of 2-ethylhexanoic, stearic, or adipic acid
Glyceryl Heptanoate 26402-24-4	Glyceryl Heptanoate is the glyceryl ester of heptanoic acid that conforms to the formula 

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

Ingredient CAS No.	Definition & Structure
Glyceryl Hydrogenated Rapeseedate	Glyceryl Hydrogenated Rapeseedate is the monoester of glycerin and the fatty acids derived from Hydrogenated Rapeseed Oil. wherein RC(O)- represents the residue of the fatty acids derived from Hydrogenated Rapeseed Oil
Glyceryl Hydrogenated Rosinate	Glyceryl Hydrogenated Rosinate is the monester of glycerin and hydrogenated mixed long chain acids derived from rosin. wherein RC(O)- represents the residue of the hydrogenated mixed long chain acids derived from rosin
Glyceryl Hydrogenated Soyate	Glyceryl Hydrogenated Soyate is the monoester of Glycerin and hydrogenated mixed long chain acids derived from soy. wherein RC(O)- represents the residue of the hydrogenated mixed long chain acids derived from soy
Glyceryl Hydroxystearate 1323-42-8	Glyceryl Hydroxystearate is the monoester of glycerin and Hydroxystearic Acid. It conforms generally to the formula
Glyceryl Hydroxystearate/Oleate Esters	Glyceryl Hydroxystearate/Oleate Esters is a mixture of esters formed by the reaction of Glycerin with a blend of Hydroxystearic Acid and Oleic Acid. wherein RC(O)- represents the residue of hydroxystearic or oleic acid
Glyceryl Isopalmitate	Glyceryl Isopalmitate is the monoester of glycerin and a branched chain 16 carbon aliphatic acid. It conforms to the formula
Glyceryl Isostearate 61332-02-3 66085-00-5	Glyceryl Isostearate is the monoester of glycerin and Isostearic Acid. It conforms generally to the formula
Glyceryl Isostearate/Myristate	Glyceryl Isostearate/Myristate is the monoester of glycerin esterified with a blend of isostearic and myristic acids. wherein RC(O)- represents the residue of isostearic or myristic acid

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

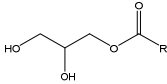
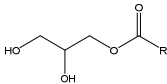
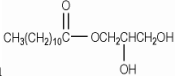
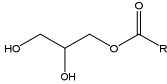
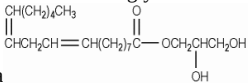
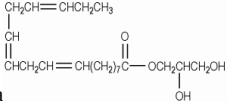
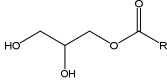
Ingredient CAS No.	Definition & Structure
Glyceryl Isotridecanoate/Stearate/Adipate	Glyceryl Isotridecanoate/Stearate/Adipate is Glycerin esterified with a blend of isotridecanoic acid, Stearic Acid and Adipic Acid.  wherein RC(O)- represents the residue of isotridecanoic, stearic, or adipic acid
Glyceryl Lanolate	Glyceryl Lanolate is the monoester of glycerin and Lanolin Acid.  wherein RC(O)- represents the residue of lanolin acid
Glyceryl Laurate 142-18-7 27215-38-9 37318-95-9	Glyceryl Laurate is the monoester of glycerin and lauric acid. It conforms generally to the formula 
Glyceryl Laurate SE	Glyceryl Laurate SE is a self-emulsifying grade of Glyceryl Laurate that contains some sodium and/or potassium laurate.
Glyceryl Laurate/Oleate	Glyceryl Laurate/Oleate is the monoester of glycerin esterified with a blend of lauric and oleic acids.  wherein RC(O)- represents the residue of lauric or oleic acid
Glyceryl Linoleate 2277-28-3 26545-74-4 37348-65-5	Glyceryl Linoleate is the monoester of glycerin and linoleic acid. It conforms to the formula 
Glyceryl Linolenate 18465-99-1 56554-41-7	Glyceryl Linolenate is the monoester of glycerin and linolenic acid. It conforms to the formula 
Glyceryl Montanate 68476-38-0 71035-02-4	Glyceryl Montanate is the monoester of glycerin and Montan Acid Wax.  wherein RC(O)- represents the residue of montan acid wax

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

Ingredient CAS No.	Definition & Structure
Glyceryl Myristate 27214-38-6 589-68-4	Glyceryl Myristate is the monoester of glycerin and myristic acid. It conforms generally to the formula $\text{CH}_3(\text{CH}_2)_{12}\text{C}(=\text{O})\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$
Glyceryl Oleate 111-03-5 161403-66-3 25496-72-4 37220-82-9 68424-61-3	Glyceryl Oleate is the monoester of glycerin and oleic acid. It conforms generally to the formula $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$
Glyceryl Oleate SE	Glyceryl Oleate SE is a self-emulsifying grade of Glyceryl Oleate that contains some sodium and/or potassium oleate.
Glyceryl Oleate/Elaidate	Glyceryl Oleate/Elaidate is a mixture of monoglycerides of oleic and elaidic acids. wherein RC(O)- represents the residue of elaidic or oleic acid
Glyceryl Olivatate	Glyceryl Olivatate is the monoester of glycerin and the fatty acids derived from olive oil. It conforms generally to the formula wherein RC(O)- represents the fatty acids derived from olive oil
Glyceryl Palmitate 26657-96-5 542-44-9	Glyceryl Palmitate is the monoester of glycerin and palmitic acid. It conforms to the formula $\text{CH}_3(\text{CH}_2)_{14}\text{C}(=\text{O})\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$
Glyceryl Palmitate/Stearate 68002-71-1	Glyceryl Palmitate/Stearate is the monoester of glycerin esterified with a blend of palmitic and stearic acids. wherein RC(O)- represents the residue of palmitic or stearic acid
Glyceryl Palmitoleate	Glyceryl Palmitoleate is the monoester of glycerin and palmitoleic acid. It conforms to the formula $\text{CH}_3(\text{CH}_2)_5\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$
Glyceryl Pentadecanoate 122636-37-7	Glyceryl Pentadecanoate is the monoester of glycerin and pentadecanoic acid. It conforms generally to the formula

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

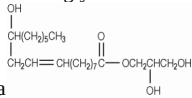
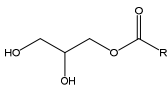
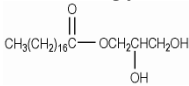
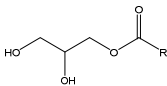
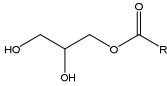
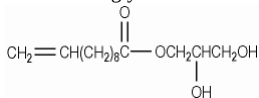
Ingredient CAS No.	Definition & Structure
Glyceryl Ricinoleate 1323-38-2 141-08-2 5086-52-2	Glyceryl Ricinoleate is the monoester of glycerin and ricinoleic acid. It conforms generally to the formula 
Glyceryl Ricinoleate SE	Glyceryl Ricinoleate SE is a self-emulsifying grade of Glyceryl Ricinoleate containing sodium and/or potassium stearate.
Glyceryl Rosinate 8050-31-5	Glyceryl Rosinate is the monoester of glycerin and mixed long chain acids derived from Rosin.  wherein RC(O)- represents the residue of mixed long chain acids derived from Rosin
Glyceryl Stearate 11099-07-3 123-94-4 31566-31-1 85666-92-8	Glyceryl Stearate is the monoester of glycerin and stearic acid. It conforms generally to the formula 
Glyceryl Stearate SE 11099-07-3 85666-92-8	Glyceryl Stearate SE is a self-emulsifying grade of Glyceryl Stearate that contains some sodium and/or potassium stearate.
Glyceryl Stearate/Malate	Glyceryl Stearate/Malate is the ester of glycerin esterified with a blend of stearic and malic acids.  wherein RC(O)- represents the residue of stearic or malic acid
Glyceryl Tallowate	Glyceryl Tallowate is the monoester of glycerin and tallow fatty acids. It conforms generally to the formula  wherein RC(O)- represents the residue of the fatty acids derived from tallow
Glyceryl Undecylenate 123759-97-7 62285-15-8	Glyceryl Undecylenate is the ester of glycerin and undecylenic acid that conforms to the formula 

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

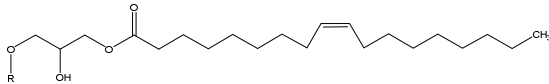
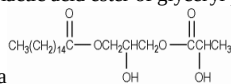
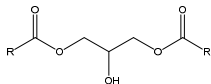
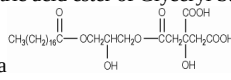
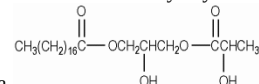
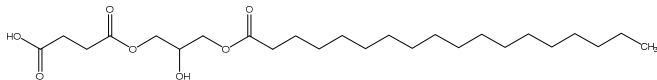
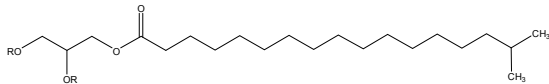
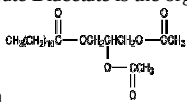
Ingredient CAS No.	Definition & Structure	
Monoglyceryl Diesters (a.k.a. Diglycerides) and Monoglyceryl Sesquiesters (a.k.a. mixtures of Mono- and Diglycerides)		
Glyceryl Sesquioleate	Glyceryl Sesquioleate is a mixture of mono- and diesters of glycerin and oleic acid.  wherein R- represents hydrogen or the residue of oleic acid	Glyceryl Sesquioleate
Glyceryl Palmitate Lactate	Glyceryl Palmitate Lactate is the lactic acid ester of glyceryl palmitate. It conforms generally to the formula 	Glyceryl Palmitate Lactate
Glyceryl Stearate/Acetate	Glyceryl Stearate/Acetate is the diester of glycerin esterified with a blend of stearic and acetic acids.  wherein RC(O)- represents the residue of acetic or stearic acid	
Glyceryl Stearate Citrate	Glyceryl Stearate Citrate is the citric acid ester of Glyceryl Stearate. It conforms generally to the formula 	
39175-72-9		
55840-13-6		
Glyceryl Stearate Lactate	Glyceryl Stearate Lactate is the lactic acid ester of Glyceryl Stearate. It conforms generally to the formula 	
Glyceryl Stearate Succinate	Glyceryl Stearate Succinate is the succinic acid ester of Glyceryl Stearate. 	
Monoglyceryl Triesters (a.k.a. Triglycerides) & mixtures of Monoglyceryl Mono-, Di-, & Triesters (a.k.a. Mono-, Di, & Triglycerides)		
Glyceryl Isostearates	Glyceryl Isostearates is a mixture of the mono-, di- and triesters of glycerin and isostearic acid.  wherein R represents hydrogen or the residue of isostearic acid (one example of an "iso")	Glyceryl Isostearates
Glyceryl Laurate Diacetate	Glyceryl Laurate Diacetate is the organic compound that conforms generally to the formula 	
30899-62-8	to the formula	

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

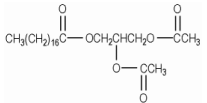
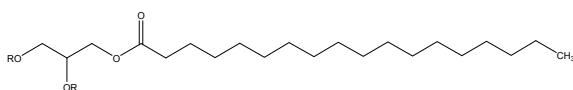
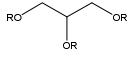
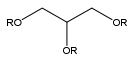
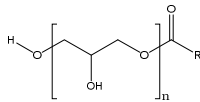
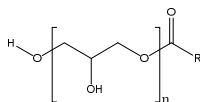
Ingredient CAS No.	Definition & Structure
Glyceryl Stearate Diacetate 84931-78-2	Glyceryl Stearate Diacetate is the organic compound that conforms to the  formula
Glyceryl Stearates	Glyceryl Stearates is a mixture of the mono-, di- and triesters of glycerin and stearic acid.  wherein R represents hydrogen or the residue of stearic acid
Glyceryl Tribehenate/Isostearate/Eicosandioate	Glyceryl Tribehenate/Isostearate/Eicosandioate is the triester of glycerin with a mixture of Behenic Acid, Isostearic Acid, and eicosandioic acid.  wherein R represents the residue of behenic, isostearic, or eicosandioic acid
Glyceryl Tripalmate/Palm Kernelate/Olivate/Macadamate/Rapeseedate	Glyceryl Tripalmate/Palm Kernelate/Olivate/Macadamate/Rapeseedate is the triester of glycerin with a mixture of fatty acids derived from palm oil, palm kernel oil, olive oil, macadamia nut oil and rapeseed oil.  wherein R represents the residue of the fatty acids derived from palm oil, palm kernel oil, olive oil, macadamia nut oil and rapeseed oil
Polyglyceryl Monoesters	
Acacia Decurrens/Jojoba/Sunflower Seed Wax Polyglyceryl-3 Esters	Acacia Decurrens/Jojoba/Sunflower Seed Wax Polyglyceryl-3 Esters is a product obtained by the transesterification of Polyglycerin-3 with a mixture of Acacia Decurrens Flower Wax, Simmondsia Chinensis (Jojoba) Seed Wax and Helianthus Annuus (Sunflower) Seed Wax.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification of the respective tryglyceride waxes) from Acacia Decurrens Flower Wax, Simmondsia Chinensis (Jojoba) Seed Wax and Helianthus Annuus (Sunflower) Seed Wax, and n is 3
Adansonia Digitata Seed Oil Polyglyceryl-6 Esters	Adansonia Digitata Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Adansonia Digitata Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Adansonia Digitata Seed Oil, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

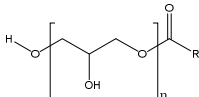
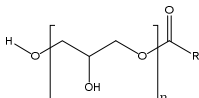
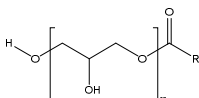
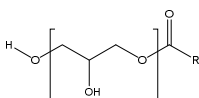
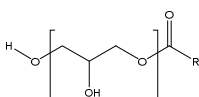
Ingredient CAS No.	Definition & Structure
Almond Oil/Polyglyceryl-10 Esters	Almond Oil/Polyglyceryl-10 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Sweet Almond) Oil and Polyglycerin-10.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Amygdalus Dulcis (Sweet Almond) Oil, and n is 10
Apricot Kernel Oil Polyglyceryl-3 Esters	Apricot Kernel Oil Polyglyceryl-3 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and Polyglycerin-3.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Armeniaca (Apricot) Kernel Oil, and n is 3
Apricot Kernel Oil Polyglyceryl-4 Esters	Apricot Kernel Oil Polyglyceryl-4 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Armeniaca (Apricot) Kernel Oil, and n is 4
Apricot Kernel Oil Polyglyceryl-5 Esters	Apricot Kernel Oil Polyglyceryl-5 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and Polyglycerin-5.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Armeniaca (Apricot) Kernel Oil, and n is 5
Apricot Kernel Oil Polyglyceryl-6 Esters	Apricot Kernel Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Armeniaca (Apricot) Kernel Oil, and n is 5

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

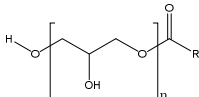
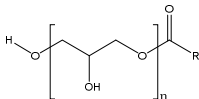
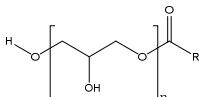
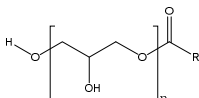
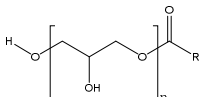
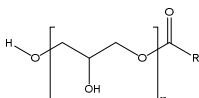
Ingredient CAS No.	Definition & Structure
Apricot Kernel Oil Polyglyceryl-10 Esters	Apricot Kernel Oil Polyglyceryl-10 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and Polyglycerin-10.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Armeniaca (Apricot) Kernel Oil, and n is 10
Argan Oil Polyglyceryl-6 Esters	Argan Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Argania Spinosa Kernel Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Argania Spinosa Kernel Oil, and n is 6
Astrocaryum Vulgare Oil Polyglyceryl-6 Esters	Astrocaryum Vulgare Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Astrocaryum Vulgare Kernel Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Astrocaryum Vulgare Kernel Oil, and n is 6
Avocado Oil Polyglyceryl-6 Esters	Avocado Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Persea Gratissima (Avocado) Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Persea Gratissima (Avocado) Oil, and n is 6
Babassu Oil Polyglyceryl-4 Esters	Babassu Oil Polyglyceryl-4 Esters is the product of the transesterification of Orbignya Oleifera Seed Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Orbignya Oleifera Seed Oil, and n is 4
Babassu Oil Polyglyceryl-6 Esters	Babassu Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Orbignya Oleifera Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Orbignya Oleifera Seed Oil, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

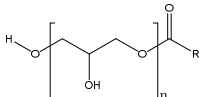
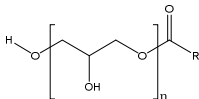
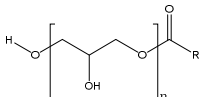
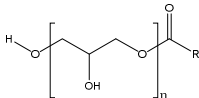
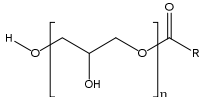
Ingredient CAS No.	Definition & Structure
Bertholletia Excelsa Seed Oil Polyglyceryl-6 Esters	Bertholletia Excelsa Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Bertholletia Excelsa Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Bertholletia Excelsa Seed Oil, and n is 6
Borage Seed Oil Polyglyceryl-4 Esters	Borage Seed Oil Polyglyceryl-4 Esters is the product obtained by the transesterification of Borago Officinalis Seed Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Borago Officinalis Seed Oil, and n is 4
Borage Seed Oil Polyglyceryl-6 Esters	Borage Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Borago Officinalis Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Borago Officinalis Seed Oil, and n is 6
Candelilla/Joboba/Rice Bran Polyglyceryl-3 Esters	Candelilla/Joboba/Rice Bran Polyglyceryl-3 Esters is a product obtained by the transesterification of Polyglycerin-3 and Euphorbia Cerifera (Candelilla) Wax, and Simmondsia Chinensis (Jojoba) Seed Wax and Oryza Sativa (Rice) Bran Wax.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Euphorbia Cerifera (Candelilla) Wax, and Simmondsia Chinensis (Jojoba) Seed Wax and Oryza Sativa (Rice) Bran Wax, and n is 3
Carapa Guaianensis Oil Polyglyceryl-6 Esters	Carapa Guaianensis Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Carapa Guaianensis Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Carapa Guaianensis Seed Oil, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

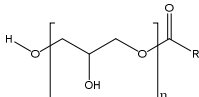
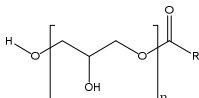
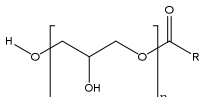
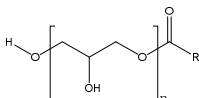
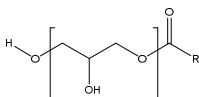
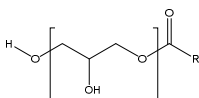
Ingredient CAS No.	Definition & Structure
Castor Oil Polyglyceryl-6 Esters	Castor Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Ricinus Communis (Castor) Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Ricinus Communis (Castor) Seed Oil, and n is 6
Cocoa Butter Polyglyceryl-6 Esters	Cocoa Butter Polyglyceryl-6 Esters is the product obtained by the transesterification of Theobroma Cacao (Cocoa) Seed Butter and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Theobroma Cacao (Cocoa) Seed Butter, and n is 6
Coconut Oil Polyglyceryl-6 Esters	Coconut Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Cocos Nucifera (Coconut) Oil with Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Cocos Nucifera (Coconut) Oil, and n is 6
Coffee Seed Oil Polyglyceryl-6 Esters	Coffee Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Polyglycerin-6 and Coffea Arabica (Coffee) Seed Oil.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Coffea Arabica (Coffee) Seed Oil, and n is 6
Glyceryl/Polyglyceryl-6 Isostearate/Behenate Esters	Glyceryl/Polyglyceryl-6 Isostearate/Behenate Esters is the mixture of esters formed by the reaction of Glycerin and Polyglycerin-6 with Isostearic Acid and Behenic Acid.  wherein RC(O)- represents the residue of isostearic or behenic acid, and n is 1 or 6
Hazelnut Seed Oil Polyglyceryl-6 Esters	Hazelnut Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Corylus Avellana (Hazelnut) Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Corylus Avellana (Hazelnut) Seed Oil, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

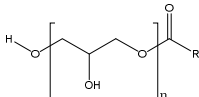
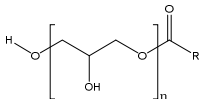
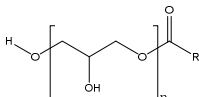
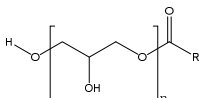
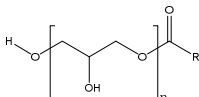
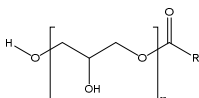
Ingredient CAS No.	Definition & Structure
Linseed Oil Polyglyceryl-4 Esters	Linseed Oil Polyglyceryl-4 Esters is the product obtained by the transesterification of <i>Linum Usitatissimum</i> (Linseed) Seed Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Linum Usitatissimum</i> (Linseed) Seed Oil, and n is 4
Macadamia Seed Oil Polyglyceryl-6 Esters	Macadamia Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Macadamia <i>Ternifolia</i> Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Macadamia <i>Ternifolia</i> Seed Oil, and n is 6
Mauritia Flexuosa Seed Oil Polyglyceryl-6 Esters	Mauritia Flexuosa Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of the oil obtained from the seeds of <i>Mauritia flexuosa</i> and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from the seeds of <i>Mauritia flexuosa</i>, and n is 6
Olive Oil Polyglyceryl-3 Esters	Olive Oil Polyglyceryl-3 Esters is the product obtained by the transesterification of Polyglycerin-3 and <i>Olea Europaea</i> (Olive) Fruit Oil.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Olea Europaea</i> (Olive) Fruit Oil, and n is 3
Olive Oil Polyglyceryl-4 Esters	Olive Oil Polyglyceryl-4 Esters is the product obtained by the transesterification of <i>Olea Europaea</i> (Olive) Fruit Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Olea Europaea</i> (Olive) Fruit Oil, and n is 4
Olive Oil Polyglyceryl-6 Esters	Olive Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of <i>Olea Europaea</i> (Olive) Fruit Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Olea Europaea</i> (Olive) Fruit Oil, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

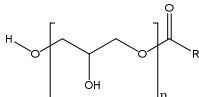
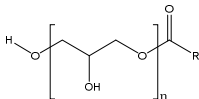
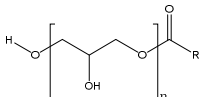
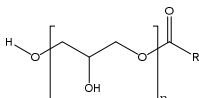
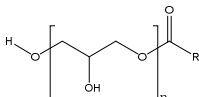
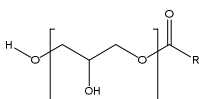
Ingredient CAS No.	Definition & Structure
Palm Kernel Oil Polyglyceryl-4 Esters	Palm Kernel Oil Polyglyceryl-4 Esters is the product obtained by the transesterification of <i>Elaeis Guineensis</i> (Palm) Kernel Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Elaeis Guineensis</i> (Palm) Kernel Oil, and n is 4
Palm Oil Polyglyceryl-3 Esters	Palm Oil Polyglyceryl-3 Esters is the product obtained by the transesterification of Polyglycerin-3 and <i>Elaeis Guineensis</i> (Palm) Oil.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Elaeis Guineensis</i> (Palm) Oil, and n is 3
Palm Oil Polyglyceryl-4 Esters	Palm Oil Polyglyceryl-4 Esters is the product obtained by the transesterification of Polyglycerin-4 and <i>Elaeis Guineensis</i> (Palm) Oil.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Elaeis Guineensis</i> (Palm) Oil, and n is 4
Palm Oil Polyglyceryl-5 Esters	Palm Oil Polyglyceryl-5 Esters is the product obtained by the transesterification of a glycerin polymer containing 5 units of glycerin and <i>Elaeis Guineensis</i> (Palm) Oil.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Elaeis Guineensis</i> (Palm) Oil, and n is 5
Palm Oil Polyglyceryl-6 Esters	Palm Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Polyglycerin-6 and <i>Elaeis Guineensis</i> (Palm) Oil.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from <i>Elaeis Guineensis</i> (Palm) Oil, and n is 6
Parinari Curatellifolia Oil Polyglyceryl-6 Esters	Parinari Curatellifolia Oil Polyglyceryl-6 Esters is the product of the transesterification of the oil obtained from the seeds of <i>Parinari curatellifolia</i> and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from the seeds of <i>Parinari curatellifolia</i>, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

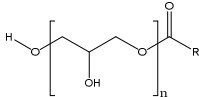
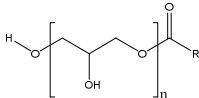
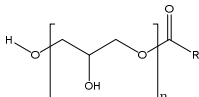
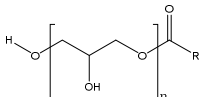
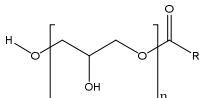
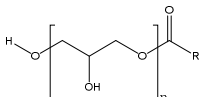
Ingredient CAS No.	Definition & Structure
Pinus Sibirica Seed Oil Polyglyceryl-6 Esters	Pinus Sibirica Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Pinus Sibirica Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Pinus Sibirica Seed Oil, and n is 6
Polyglyceryl-6 Adansonia Digitata Seedate	Polyglyceryl-6 Adansonia Digitata Seedate is the ester of the fatty acids obtained from Adansonia Digitata Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Adansonia Digitata Seed Oil, and n is 6
Polyglyceryl-4 Almond/Shea Butterate	Polyglyceryl-4 Almond/Shea Butterate is an ester of a mixture of fatty acids derived from almond oil and Butyrospermum Parkii (Shea) Butter with Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Butyrospermum Parkii (Shea) Butter, and n is 4
Polyglyceryl-6 Apricot Kernelate	Polyglyceryl-6 Apricot Kernelate is the ester of the fatty acids derived from Prunus Armeniaca (Apricot) Kernel Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Armeniaca (Apricot) Kernel Oil, and n is 6
Polyglyceryl-10 Apricot Kernelate	Polyglyceryl-10 Apricot Kernelate is the ester of the fatty acids derived from Prunus Armeniaca (Apricot) Kernel Oil and Polyglycerin-10.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Armeniaca (Apricot) Kernel Oil, and n is 10
Polyglyceryl-6 Argan Kernelate	Polyglyceryl-6 Argan Kernelate is the ester of Polyglycerin-6 and the fatty acids obtained from Argania Spinosa Kernel Oil.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Argania Spinosa Kernel Oil, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

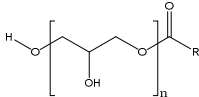
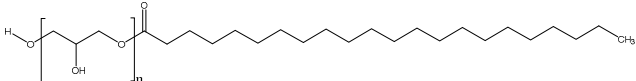
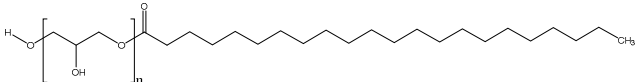
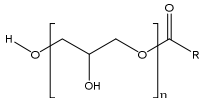
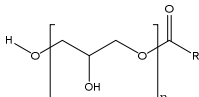
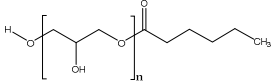
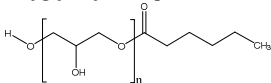
Ingredient CAS No.	Definition & Structure
Polyglyceryl-3 Beeswax 136097-93-3	Polyglyceryl-3 Beeswax is an ester of beeswax fatty acids and Polyglycerin-3.  wherein RC(O)- represents the residue of beeswax fatty acids, and n is 3
Polyglyceryl-3 Behenate	Polyglyceryl-3 Behenate is the ester of behenic acid and Polyglycerin-3.  wherein n is 3
Polyglyceryl-6 Behenate	Polyglyceryl-6 Behenate is the monoester of Behenic Acid and Polyglycerin-6.  wherein n is 6
Polyglyceryl-10 Behenate/Eicosadioate	Polyglyceryl-10 Behenate/Eicosadioate is the monoester of Polyglycerin-10 and a blend of behenic and eicosadioic acids.  wherein RC(O)- represents the residue of behenic or eicosadioic acid, and n is 10
Polyglyceryl-8 C12-20 Acid Ester	Polyglyceryl-8 C12-20 Acid Ester is the ester of a glycerin polymer containing 8 units of glycerin and a synthetic mixture of saturated acids containing 12 to 20 carbons in the alkyl chain.  wherein RC(O)- represents the residue of a fatty acid containing 12 to 20 carbons in the alkyl chain, and n is 8
Polyglyceryl-2 Caprate 156153-06-9	Polyglyceryl-2 Caprate is the ester of capric acid and Diglycerin.  wherein n is 2
Polyglyceryl-3 Caprate 133654-02-1 51033-30-8 74504-65-7	Polyglyceryl-3 Caprate is an ester of capric acid and Polyglycerin-3.  wherein n is 3

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

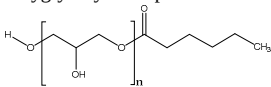
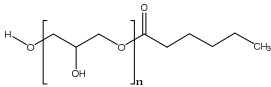
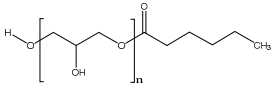
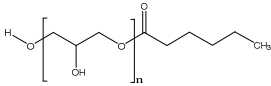
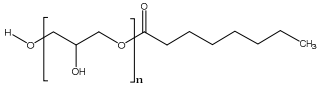
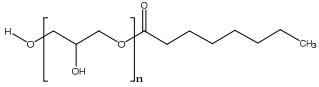
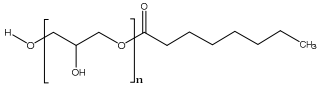
Ingredient CAS No.	Definition & Structure
Polyglyceryl-4 Caprate 160391-93-5 74504-65-7	Polyglyceryl-4 Caprate is the ester of Capric Acid and Polyglycerin-4.  wherein n is 4
Polyglyceryl-5 Caprate	Polyglyceryl-5 Caprate is the monoester of capric acid and Polyglycerin-5.  wherein n is 5
Polyglyceryl-6 Caprate	Polyglyceryl-6 Caprate is the monoester of Capric Acid and Polyglycerin-6.  wherein n is 6
Polyglyceryl-10 Caprate	Polyglyceryl-10 Caprate is the ester of capric acid and Polyglycerin-10.  wherein n is 10
Polyglyceryl-2 Caprylate	Polyglyceryl-2 Caprylate is the ester of Caprylic Acid and Diglycerin.  wherein n is 2
Polyglyceryl-3 Caprylate 108777-93-1	Polyglyceryl-3 Caprylate is the ester of caprylic acid and Polyglycerin-3.  wherein n is 3
Polyglyceryl-4 Caprylate	Polyglyceryl-4 Caprylate is the monoester of Caprylic Acid and Polyglycerin-4  wherein n is 4

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

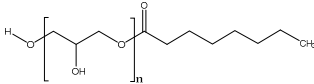
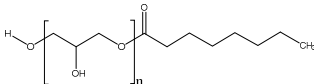
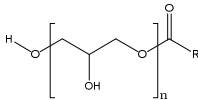
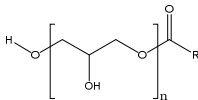
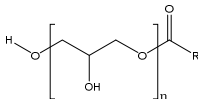
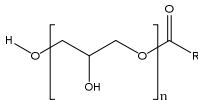
Ingredient CAS No.	Definition & Structure
Polyglyceryl-6 Caprylate	Polyglyceryl-6 Caprylate is the monoester of caprylic acid and Polyglycerin-6  wherein n is 6
Polyglyceryl-10 Caprylate 51033-41-1	Polyglyceryl-10 Caprylate is the monoester of caprylic acid and Polyglycerin-10.  wherein n is 10
Polyglyceryl-4 Caprylate/Caprate	Polyglyceryl-4 Caprylate/Caprate is the monoester of Polyglycerin-4 and a mixture of caprylic and capric acids.  wherein RC(O)- represents the residue of capric or caprylic acid, and n is 4
Polyglyceryl-6 Caprylate/Caprate	Polyglyceryl-6 Caprylate/Caprate is the monoester of Polyglycerin-6 and a mixture of caprylic and capric acids  wherein RC(O)- represents the residue of capric or caprylic acid, and n is 6
Polyglyceryl-10 Caprylate/Caprate	Polyglyceryl-10 Caprylate/Caprate is the monoester of Polyglycerin-10 and a blend of caprylic and capric acids.  wherein RC(O)- represents the residue of capric or caprylic acid, and n is 10
Polyglyceryl-6 Citrullus Lanatus Seedate	Polyglyceryl-6 Citrullus Lanatus Seedate is the ester of the fatty acids derived from Citrullus Lanatus (Watermelon) Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Citrullus Lanatus (Watermelon) Seed Oil, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

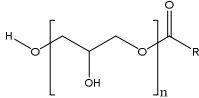
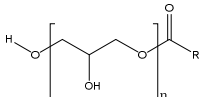
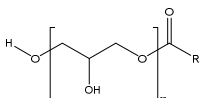
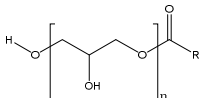
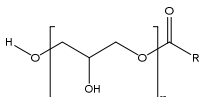
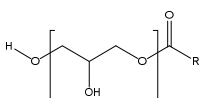
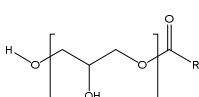
Ingredient CAS No.	Definition & Structure
Polyglyceryl-3 Cocoate	Polyglyceryl-3 Cocoate is the ester of Coconut Acid and Polyglycerin-3.  wherein RC(O)- represents the residue of Coconut Acid, and n is 3
Polyglyceryl-4 Cocoate	Polyglyceryl-4 Cocoate is an ester of Coconut Acid and Polyglycerin-4.  wherein RC(O)- represents the residue of Coconut Acid, and n is 4
Polyglyceryl-10 Cocoate	Polyglyceryl-10 Cocoate is the ester of Coconut Acid and Polyglycerin-10.  wherein RC(O)- represents the residue of Coconut Acid, and n is 10
Polyglyceryl-2 Isopalmitate/Sebacate	Polyglyceryl-2 Isopalmitate/Sebacate is the mixed ester of isopalmitic acid, Sebacic Acid and Diglycerin.  wherein RC(O)- represents the residue of isopalmitic or sebacic acid, and n is 2
Polyglyceryl-2 Isostearate	Polyglyceryl-2 Isostearate is the ester of isostearic acid and Diglycerin.  wherein RC(O)- represents the residue of isostearic acid, and n is 2
Polyglyceryl-3 Isostearate	Polyglyceryl-3 Isostearate is the ester of isostearic acid and Polyglycerin-3.  wherein RC(O)- represents the residue of isostearic acid, and n is 3
Polyglyceryl-4 Isostearate	Polyglyceryl-4 Isostearate is an ester of Isostearic Acid and Polyglycerin-4.  wherein RC(O)- represents the residue of isostearic acid, and n is 4

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

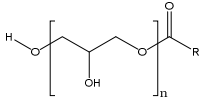
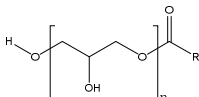
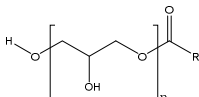
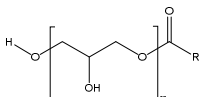
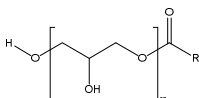
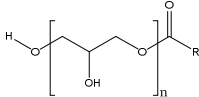
Ingredient CAS No.	Definition & Structure
Polyglyceryl-5 Isostearate	Polyglyceryl-5 Isostearate is the ester of isostearic acid and a glycerin polymer containing an average of 5 glycerin units.  wherein RC(O)- represents the residue of isostearic acid, and n is 5
Polyglyceryl-6 Isostearate 126928-07-2	Polyglyceryl-6 Isostearate is the ester of isostearic acid and Polyglycerin-6.  wherein RC(O)- represents the residue of isostearic acid, and n is 6
Polyglyceryl-10 Isostearate 133738-23-5	Polyglyceryl-10 Isostearate is the ester of isostearic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of isostearic acid, and n is 10
Polyglyceryl-10 Eicosanedioate/ Tetradecanedioate	Polyglyceryl-10 Eicosanedioate/Tetradecanedioate is the ester of Polyglycerin-10 with a mixture of eicosanedioic and tetradecanedioic acids.  wherein RC(O)- represents the residue of eicosanedioic or tetradecanedioic acid, and n is 10
Polyglyceryl-4 Hazelnutseedate	Polyglyceryl-4 Hazelnutseedate is an ester of the fatty acids derived from Corylus Avellana (Hazelnut) Seed Oil with Polyglycerin-4.  wherein RC(O)- represents the residue of the fatty acids derived from Corylus Avellana (Hazelnut) Seed Oil, and n is 4
Polyglyceryl-2 Isopalmitate	Polyglyceryl-2 Isopalmitate is an ester of isopalmitic acid and Diglycerin.  wherein RC(O)- represents the residue of isopalmitic acid, and n is 2

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

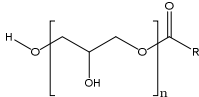
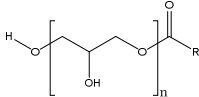
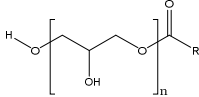
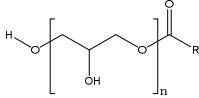
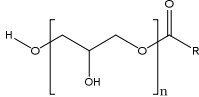
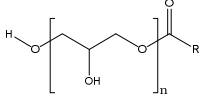
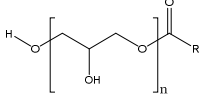
Ingredient CAS No.	Definition & Structure
Polyglyceryl-4 Isostearate/Laurate	Polyglyceryl-4 Isostearate/Laurate is the ester of a mixture of isostearic and lauric acids with Polyglycerin-4.
	 wherein RC(O)- represents the residue of isostearic or lauric acid, and n is 4
Polyglyceryl-2 Laurate	Polyglyceryl-2 Laurate is the ester of lauric acid and Diglycerin.
96499-68-2	 wherein RC(O)- represents the residue of lauric acid, and n is 2
Polyglyceryl-3 Laurate	Polyglyceryl-3 Laurate is the ester of lauric acid and Polyglycerin-3.
51033-31-9	 wherein RC(O)- represents the residue of lauric acid, and n is 3
Polyglyceryl-4 Laurate	Polyglyceryl-4 Laurate is the ester of lauric acid and Polyglycerin-4.
74504-64-6	 wherein RC(O)- represents the residue of lauric acid, and n is 4
75798-42-4	
Polyglyceryl-5 Laurate	Polyglyceryl-5 Laurate is the ester of lauric acid and a glycerin polymer containing an average of 5 glycerin units.
128738-83-0	 wherein RC(O)- represents the residue of lauric acid, and n is 5
Polyglyceryl-6 Laurate	Polyglyceryl-6 Laurate is the ester of lauric acid and Polyglycerin-6.
51033-38-6	 wherein RC(O)- represents the residue of lauric acid, and n is 6
Polyglyceryl-10 Laurate	Polyglyceryl-10 Laurate is an ester of lauric acid and Polyglycerin-10.
34406-66-1	 wherein RC(O)- represents the residue of lauric acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

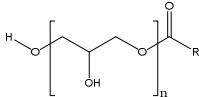
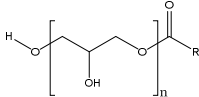
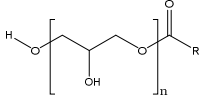
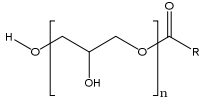
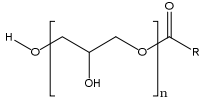
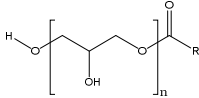
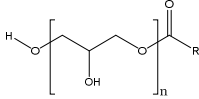
Ingredient CAS No.	Definition & Structure
Polyglyceryl-10 Linoleate	Polyglyceryl-10 Linoleate is the monoester of linoleic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of linoleic acid, and n is 10
Polyglyceryl-2 Myristate	Polyglyceryl-2 Myristate is the monoester of myristic acid and Diglycerol.  wherein RC(O)- represents the residue of myristic acid, and n is 2
Polyglyceryl-3 Myristate	Polyglyceryl-3 Myristate is the ester of myristic acid and Polyglycerin-3.  wherein RC(O)- represents the residue of myristic acid, and n is 3
Polyglyceryl-5 Myristate	Polyglyceryl-5 Myristate is the monoester of myristic acid and a glycerin polymer containing 5 units of glycerin.  wherein RC(O)- represents the residue of myristic acid, and n is 5
Polyglyceryl-6 Myristate	Polyglyceryl-6 Myristate is the monoester of myristic acid and Polyglycerin-6.  wherein RC(O)- represents the residue of myristic acid, and n is 6
Polyglyceryl-10 Myristate	Polyglyceryl-10 Myristate is an ester of myristic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of myristic acid, and n is 10
87390-32-7	
Polyglyceryl-2 Oleate	Polyglyceryl-2 Oleate is an ester of oleic acid and Diglycerin.  wherein RC(O)- represents the residue of oleic acid, and n is 2
49553-76-6	
9007-48-1 (generic)	

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

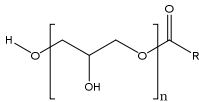
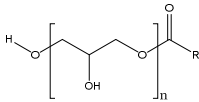
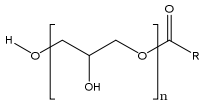
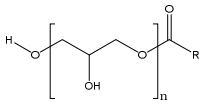
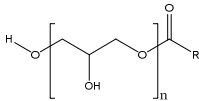
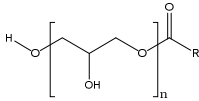
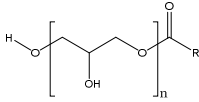
Ingredient CAS No.	Definition & Structure
Polyglyceryl-3 Oleate 33940-98-6 9007-48-1 (generic)	Polyglyceryl-3 Oleate is an ester of oleic acid and Polyglycerin-3.  wherein RC(O)- represents the residue of oleic acid, and n is 3
Polyglyceryl-4 Oleate 71012-10-7 9007-48-1 (generic)	Polyglyceryl-4 Oleate is an ester of oleic acid and Polyglycerin-4.  wherein RC(O)- represents the residue of oleic acid, and n is 4
Polyglyceryl-5 Oleate 86529-98-8 9007-48-1 (generic)	Polyglyceryl-5 Oleate is the ester of oleic acid and a glycerin polymer containing an average of 5 glycerin units.  wherein RC(O)- represents the residue of oleic acid, and n is 5
Polyglyceryl-6 Oleate 79665-92-2 9007-48-1 (generic)	Polyglyceryl-6 Oleate is the ester of oleic acid and Polyglycerin-6.  wherein RC(O)- represents the residue of oleic acid, and n is 6
Polyglyceryl-8 Oleate 75719-56-1 9007-48-1 (generic)	Polyglyceryl-8 Oleate is an ester of oleic acid and a glycerin polymer containing an average of 8 glycerin units.  wherein RC(O)- represents the residue of oleic acid, and n is 8
Polyglyceryl-10 Oleate 79665-93-3 9007-48-1 (generic)	Polyglyceryl-10 Oleate is an ester of oleic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of oleic acid, and n is 10
Polyglyceryl-10 Palmate 	Polyglyceryl-10 Palmate is the ester of Palm Acid and Polyglycerin-10.  wherein RC(O)- represents the residue of palm acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

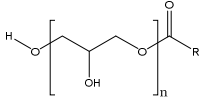
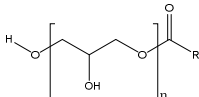
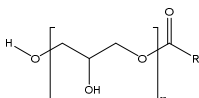
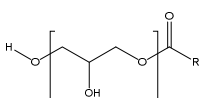
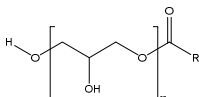
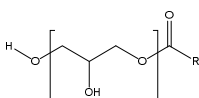
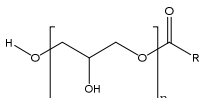
Ingredient CAS No.	Definition & Structure
Polyglyceryl-2 Palmitate	Polyglyceryl-2 Palmitate is the monoester of palmitic acid and Diglycerol.  wherein RC(O)- represents the residue of palmitic acid, and n is 2
Polyglyceryl-3 Palmitate	Polyglyceryl-3 Palmitate is an ester of Palmitic Acid and Polyglycerin-3.  wherein RC(O)- represents the residue of palmitic acid, and n is 3
Polyglyceryl-6 Palmitate	Polyglyceryl-6 Palmitate is the ester of Palmitic Acid and Polyglycerin-6.  wherein RC(O)- represents the residue of palmitic acid, and n is 6
Polyglyceryl-10 Palmitate	Polyglyceryl-10 Palmitate is the ester of palmitic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of palmitic acid, and n is 10
Polyglyceryl-6 Palmitate/Succinate	Polyglyceryl-6 Palmitate/Succinate is the monoester of Polyglycerin-6 and a mixture of palmitic and succinic acids.  wherein RC(O)- represents the residue of palmitic or succinic acid, and n is 6
Polyglyceryl-4 Punicate	Polyglyceryl-4 Punicate is the ester of Polyglycerin-4 and punicic acid.  wherein RC(O)- represents the residue of punicic acid, and n is 4
Polyglyceryl-3 Rice Branate	Polyglyceryl-3 Rice Branate is the monoester of Polyglycerin-3 and Rice Bran Acid.  wherein RC(O)- represents the residue of rice bran acid, and n is 3

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

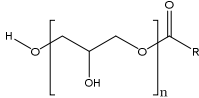
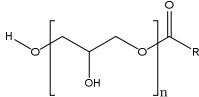
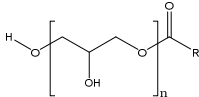
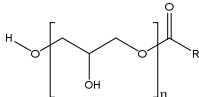
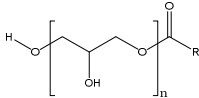
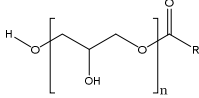
Ingredient CAS No.	Definition & Structure
Polyglyceryl-3 Ricinoleate	Polyglyceryl-3 Ricinoleate is an ester of ricinoleic acid and Polyglycerin-3.
29894-35-7 (generic)	 wherein RC(O)- represents the residue of ricinoleic acid, and n is 3
Polyglyceryl-5 Ricinoleate	Polyglyceryl-5 Ricinoleate is the product obtained by the reaction of Ricinoleic Acid with a glycerin polymer containing 5 glycerin units.
	 wherein RC(O)- represents the residue of ricinoleic acid, and n is 5
Polyglyceryl-6 Ricinoleate	Polyglyceryl-6 Ricinoleate is the ester of Polyglycerin-6 and Ricinoleic Acid.
	 wherein RC(O)- represents the residue of ricinoleic acid, and n is 6
Polyglyceryl-6 Schinziophyton Rautanenii Kernelate	Polyglyceryl-6 Schinziophyton Rautanenii Kernelate is the ester of Polyglycerin-6 and the fatty acids obtained from Schinziophyton Rautanenii Kernel Oil.
	 wherein RC(O)- represents the residue of the fatty acids obtained from Schinziophyton Rautanenii Kernel Oil, and n is 6
Polyglyceryl-6 Sclerocarya Birrea Seedate	Polyglyceryl-6 Sclerocarya Birrea Seedate is the ester of Polyglycerin-6 and the fatty acids obtained from ~~Schinziophyton Rautanenii Kernel~~ Sclerocarya Birrea Seed Oil.
	 wherein RC(O)- represents the residue of the fatty acids obtained from Sclerocarya Birrea Seed Oil, and n is 6
Polyglyceryl-3 Soyate/Shea Butterate	Polyglyceryl-3 Soyate/Shea Butterate is an ester of a mixture of fatty acids derived from Glycine Soja (Soybean) Oil and Butyrospermum Parkii (Shea) Butter with Polyglycerin-3.
	 wherein RC(O)- represents the residue of the fatty acids obtained from Glycine Soja (Soybean) Oil and Butyrospermum Parkii (Shea) Butter, and n is 3

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

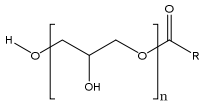
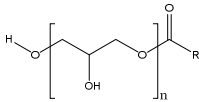
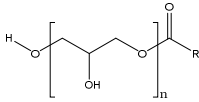
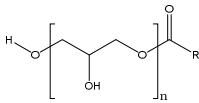
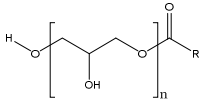
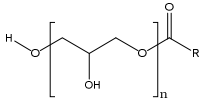
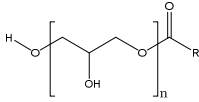
Ingredient CAS No.	Definition & Structure
Polyglyceryl-2 Stearate 12694-22-3 9009-32-9 (generic)	Polyglyceryl-2 Stearate is the ester of stearic acid and Diglycerin.  wherein RC(O)- represents the residue of stearic acid, and n is 2
Polyglyceryl-3 Stearate 26855-43-6 27321-72-8 37349-34-1 (generic)	Polyglyceryl-3 Stearate is an ester of stearic acid and Polyglycerin-3.  wherein RC(O)- represents the residue of stearic acid, and n is 3
Polyglyceryl-4 Stearate 26855-44-7 37349-34-1 (generic) 68004-11-5	Polyglyceryl-4 Stearate is an ester of stearic acid and Polyglycerin-4.  wherein RC(O)- represents the residue of stearic acid, and n is 4
Polyglyceryl-5 Stearate 37349-34-1 (generic)	Polyglyceryl-5 Stearate is the monoester of stearic acid and a glycerin polymer containing 5 units of glycerin.  wherein RC(O)- represents the residue of stearic acid, and n is 5
Polyglyceryl-6 Stearate 95461-65-7	Polyglyceryl-6 Stearate is the ester of Stearic Acid and Polyglycerin-6.  wherein RC(O)- represents the residue of stearic acid, and n is 6
Polyglyceryl-8 Stearate 37349-34-1 (generic) 75719-57-2	Polyglyceryl-8 Stearate is an ester of stearic acid and a glycerin polymer containing an average of 8 glycerin units.  wherein RC(O)- represents the residue of stearic acid, and n is 8
Polyglyceryl-10 Stearate 79777-30-3 9009-32-9 (generic)	Polyglyceryl-10 Stearate is an ester of stearic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of stearic acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

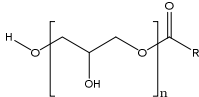
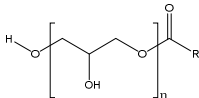
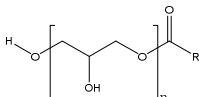
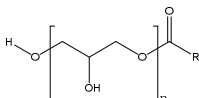
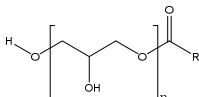
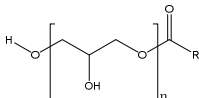
Ingredient CAS No.	Definition & Structure
Polyglyceryl-3 Stearate SE	Polyglyceryl-3 Stearate SE is a self-emulsifying grade of Polyglyceryl-3 Stearate that contains some sodium and/or potassium stearate.
Polyglyceryl-4 Sweet Almondate	Polyglyceryl-4 Sweet Almondate is an ester of the fatty acids derived from sweet almond oil and Polyglycerin-4.  wherein RC(O)- represents the residue of the fatty acids obtained from sweet almond oil, and n is 4
Polyglyceryl-6 Trichilia Emetica Seedate	Polyglyceryl-6 Trichilia Emetica Seedate is the ester of Polyglycerin-6 and the fatty acids obtained from Trichilia Emetica Seed Butter.  wherein RC(O)- represents the residue of the fatty acids obtained from Trichilia Emetica Seed Butter, and n is 6
Polyglyceryl-6 Undecylenate	Polyglyceryl-6 Undecylenate is the an ester of Undecylenic Acid and Polyglycerin-6.  wherein RC(O)- represents the residue of undecylenic acid, and n is 6
Polyglyceryl-10 Undecylenate	Polyglyceryl-10 Undecylenate is an ester of Undecylenic Acid and Polyglycerin-10.  wherein RC(O)- represents the residue of undecylenic acid, and n is 10
Polyglyceryl-6 Ximenia Americana Seedate	Polyglyceryl-6 Ximenia Americana Seedate is the ester of Polyglycerin-6 and the fatty acids obtained from Ximenia Americana Seed Oil.  wherein RC(O)- represents the residue of the fatty acids obtained from ximenia americana seed oil, and n is 6
Pumpkin Seed Oil Polyglyceryl-4 Esters	Pumpkin Seed Oil Polyglyceryl-4 Esters is the complex mixture of esters formed by the transesterification of Cucurbita Pepo (Pumpkin) Seed Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Cucurbita Pepo (Pumpkin) Seed Oil, and n is 4

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

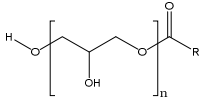
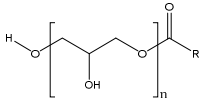
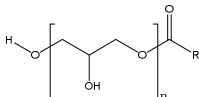
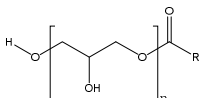
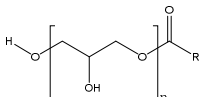
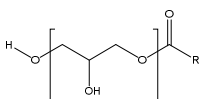
Ingredient CAS No.	Definition & Structure
Rice Bran Oil Polyglyceryl-3 Esters	Rice Bran Oil Polyglyceryl-3 Esters is the product obtained by the transesterification of Oryza Sativa (Rice) Bran Oil and Polyglycerin-3.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Oryza Sativa (Rice) Bran Oil, and n is 3
Rosa Rubiginosa Seed Oil Polyglyceryl-6 Esters	Rosa Rubiginosa Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Rosa Rubiginosa Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Rosa Rubiginosa Seed Oil, and n is 6
Safflower Seed Oil Polyglyceryl-6 Esters	Safflower Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Carthamus Tinctorius (Safflower) Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Carthamus Tinctorius (Safflower) Seed Oil, and n is 6
Schinziophyton Rautanenii Kernel Oil Polyglyceryl-6 Esters	Schinziophyton Rautanenii Kernel Oil Polyglyceryl-6 Esters is the product formed by the transesterification of Schinziophyton Rautanenii Kernel Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Schinziophyton Rautanenii Kernel Oil, and n is 6
Sclerocarya Birrea Seed Oil Polyglyceryl-6 Esters	Sclerocarya Birrea Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Sclerocarya Birrea Seed Oil with Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Sclerocarya Birrea Seed Oil, and n is 6
Sclerocarya Birrea Seed Oil Polyglyceryl-10 Esters	Sclerocarya Birrea Seed Oil Polyglyceryl-10 Esters is the product obtained by the transesterification of Sclerocarya Birrea Seed Oil with Polyglycerin-10.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Sclerocarya Birrea Seed Oil, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

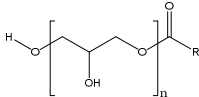
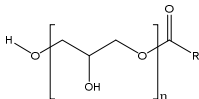
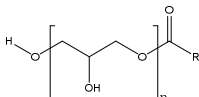
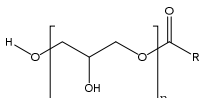
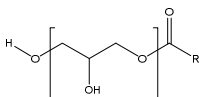
Ingredient CAS No.	Definition & Structure
Sesame Oil Polyglyceryl-6 Esters	Sesame Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Sesamum Indicum (Sesame) Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Sesamum Indicum (Sesame) Oil, and n is 6
Shea Butter Polyglyceryl-3 Esters	Shea Butter Polyglyceryl-3 Esters is the product obtained by the transesterification of Polyglycerin-3 and Butyrospermum Parkii (Shea) Butter.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Butyrospermum Parkii (Shea) Butter, and n is 3
Shea Butter Polyglyceryl-6 Esters	Shea Butter Polyglyceryl-6 Esters is the product obtained by the transesterification of Butyrospermum Parkii (Shea) Butter and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Butyrospermum Parkii (Shea) Butter, and n is 6
Soybean Oil Polyglyceryl-6 Esters	Soybean Oil Polyglyceryl-6 Esters is the product of the transesterification of Glycine Soja (Soybean) Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Glycine Soja (Soybean) Oil, and n is 6
Sunflower Seed Oil Polyglyceryl-3 Esters	Sunflower Seed Oil Polyglyceryl-3 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and Polyglycerin-3.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Helianthus Annuus (Sunflower) Seed Oil, and n is 3

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

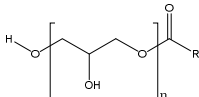
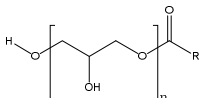
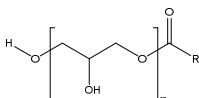
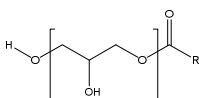
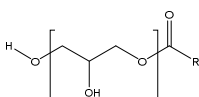
Ingredient CAS No.	Definition & Structure
Sunflower Seed Oil Polyglyceryl-4 Esters	Sunflower Seed Oil Polyglyceryl-4 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Helianthus Annuus (Sunflower) Seed Oil, and n is 4
Sunflower Seed Oil Polyglyceryl-5 Esters	Sunflower Seed Oil Polyglyceryl-5 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and a glycerin polymer containing 5 units of glycerin.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Helianthus Annuus (Sunflower) Seed Oil, and n is 5
Sunflower Seed Oil Polyglyceryl-6 Esters	Sunflower Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Helianthus Annuus (Sunflower) Seed Oil, and n is 6
Sunflower Seed Oil Polyglyceryl-10 Esters	Sunflower Seed Oil Polyglyceryl-10 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and Polyglycerin-10.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Helianthus Annuus (Sunflower) Seed Oil, and n is 10
Sweet Almond Oil Polyglyceryl-4 Esters 1072006-19-9 [generic for n]	Sweet Almond Oil Polyglyceryl-4 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Sweet Almond) Oil and Polyglycerin-4.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Amygdalus Dulcis (Sweet Almond) Oil, and n is 4

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

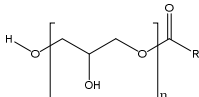
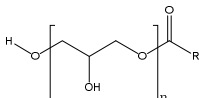
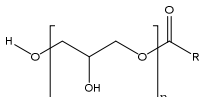
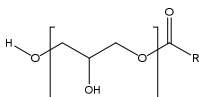
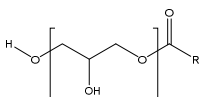
Ingredient CAS No.	Definition & Structure
Sweet Almond Oil Polyglyceryl-6 Esters	Sweet Almond Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Sweet Almond) Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Prunus Amygdalus Dulcis (Sweet Almond) Oil, and n is 6
Theobroma Grandiflorum Seed Butter Polyglyceryl-6 Esters	Theobroma Grandiflorum Seed Butter Polyglyceryl-6 Esters is the product obtained by the transesterification of Theobroma Grandiflorum Seed Butter and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Theobroma Grandiflorum Seed Butter, and n is 6
Trichilia Emetica Seed Oil Polyglyceryl-6 Esters	Trichilia Emetica Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Trichilia Emetica Seed Butter and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Trichilia Emetica Seed Butter, and n is 6
Watermelon Seed Oil Polyglyceryl-6 Esters	Watermelon Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Citrullus Lanatus (Watermelon) Seed Oil with Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Citrullus Lanatus (Watermelon) Seed Oil, and n is 6
Watermelon Seed Oil Polyglyceryl-10 Esters	Watermelon Seed Oil Polyglyceryl-10 Esters is the product obtained by the transesterification of Citrullus Lanatus (Watermelon) Seed Oil with Polyglycerin-10.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Citrullus Lanatus (Watermelon) Seed Oil, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

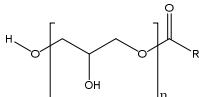
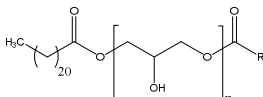
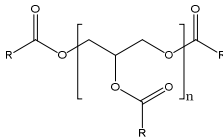
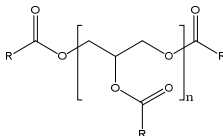
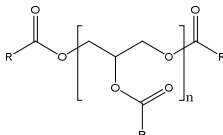
Ingredient CAS No.	Definition & Structure
Ximenia Americana Seed Oil Polyglyceryl-6 Esters	Ximenia Americana Seed Oil Polyglyceryl-6 Esters is the product obtained by the transesterification of Ximenia Americana Seed Oil and Polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Ximenia Americana Seed Oil, and n is 6
Polyglyceryl Multi-esters (i.e., not mono-esters and not “polyesters”)	
Macadamia Seed Oil Polyglyceryl-6 Esters Behenate	Macadamia Seed Oil Polyglyceryl-6 Esters Behenate is the behenic acid ester of the product obtained by the transesterification of macadamia seed oil and polyglycerin-6.  wherein RC(O)- represents the residue of fatty acids derived (via transesterification) from Macadamia Ternifolia Seed Oil, and n is 6
Polyglyceryl-8 Decabehenate/Caprate	Polyglyceryl-8 Decabehenate/Caprate is the decaester of a mixture of Behenic Acid and Capric Acid with a glycerin polymer containing 8 units of glycerin.  wherein RC(O)- represents the residue of capric or behenic acid, and n is 8
Polyglyceryl-8 Decaerucate/Decaisostearate/ Decaricinoleate	Polyglyceryl-8 Decaerucate/Decaisostearate/Decaricinoleate is the decaester of a glycerin polymer containing 8 units of glycerin with a mixture of Erucic Acid, Isostearic Acid and Ricinoleic Acid.  wherein RC(O)- represents the residue of erucic, isostearic, or ricinoleic acid, and n is 8
Polyglyceryl-10 Decaethylhexanoate	Polyglyceryl-10 Decaethylhexanoate is the decaester of 2-ethylhexanoic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of ethylhexanoic acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

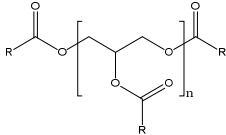
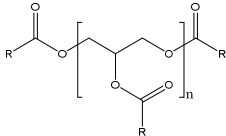
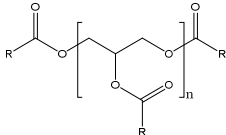
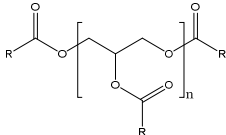
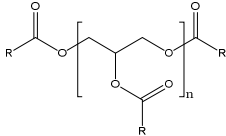
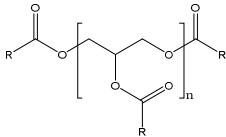
Ingredient CAS No.	Definition & Structure
Polyglyceryl-10 Decahydroxystearate	Polyglyceryl-10 Decahydroxystearate is the decaester of Hydroxystearic Acid and Polyglycerin-10.  wherein RC(O)- represents the residue of hydroxystearic acid, and n is 10
Polyglyceryl-10 Decaisostearate	Polyglyceryl-10 Decaisostearate is the ester of Polyglycerin-10 and Isostearic Acid.  wherein RC(O)- represents the residue of isostearic acid, and n is 10
Polyglyceryl-10 Decalinoleate 68900-96-9	Polyglyceryl-10 Decalinoleate is a decaester of linoleic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of linoleic acid, and n is 10
Polyglyceryl-10 Decamacadamiate	Polyglyceryl-10 Decamacadamiate is a decaester of Polyglycerin-10 and the fatty acids derived from macadamia nut oil.  wherein RC(O)- represents the residue of the fatty acids derived from macadamia nut oil, and n is 10
Polyglyceryl-10 Decaoleate 11094-60-3	Polyglyceryl-10 Decaoleate is a decaester of oleic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of oleic acid, and n is 10
Polyglyceryl-10 Decastearate 39529-26-5	Polyglyceryl-10 Decastearate is a decaester of stearic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of stearic acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

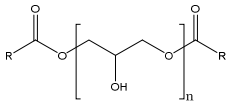
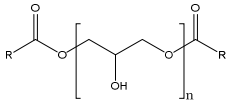
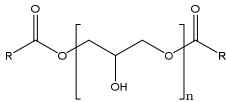
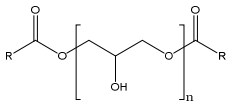
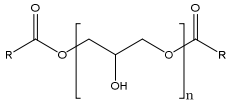
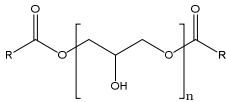
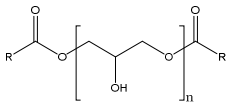
Ingredient CAS No.	Definition & Structure
Polyglyceryl-3 Dicaprate	Polyglyceryl-3 Dicaprate is the diester of capric acid and Polyglycerin-3.  wherein RC(O)- represents the residue of capric acid, and n is 3
Polyglyceryl-6 Dicaprate	Polyglyceryl-6 Dicaprate is the diester of Capric Acid and Polyglycerin-6.  wherein RC(O)- represents the residue of capric acid, and n is 6
Polyglyceryl-5 Dicaprylate 108777-93-1 (generic)	Polyglyceryl-5 Dicaprylate is the diester of Caprylic Acid with a glycerin polymer containing 5 glycerin units.  wherein RC(O)- represents the residue of caprylic acid, and n is 5
Polyglyceryl-3 Dicitrate/Stearate	Polyglyceryl-3 Dicitrate/Stearate is the diester of Polyglycerin-3 with a mixture of Citric Acid and Stearic Acid.  wherein RC(O)- represents the residue of citric or stearic acid, and n is 3
Polyglyceryl-3 Dicocoate	Polyglyceryl-3 Dicocoate is the diester of Coconut Acid and Polyglycerin-3.  wherein RC(O)- represents the residue of Coconut Acid, and n is 3
Polyglyceryl-10 Dicocoate	Polyglyceryl-10 Dicocoate is the diester of Coconut Acid and Polyglycerin-10.  wherein RC(O)- represents the residue of Coconut Acid, and n is 10
Polyglyceryl-10 Didecanoate 182015-59-4	Polyglyceryl-10 Didecanoate is the diester of decanoic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of decanoic acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

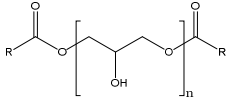
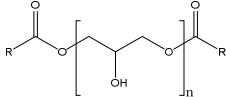
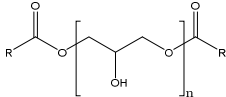
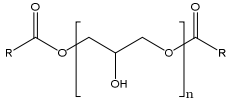
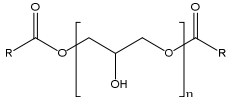
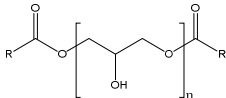
Ingredient CAS No.	Definition & Structure
Polyglyceryl-3 Di-Hydroxystearate	Polyglyceryl-3 Di-Hydroxystearate is the diester of Hydroxystearic Acid and Polyglycerin-3.  wherein RC(O)- represents the residue of Hydroxystearic Acid, and n is 3
Polyglyceryl-2 Diisostearate 63705-03-3 (generic) 67938-21-0	Polyglyceryl-2 Diisostearate is the diester of Isostearic Acid and Diglycerin.  wherein RC(O)- represents the residue of Isostearic Acid, and n is 2
Polyglyceryl-3 Diisostearate 63705-03-3 (generic) 66082-42-6	Polyglyceryl-3 Diisostearate is a diester of Isostearic Acid and Polyglycerin-3.  wherein RC(O)- represents the residue of Isostearic Acid, and n is 3
Polyglyceryl-6 Diisostearate	Polyglyceryl-6 Diisostearate is the diester of Isostearic Acid and Polyglycerin-6.  wherein RC(O)- represents the residue of Isostearic Acid, and n is 6
Polyglyceryl-10 Diisostearate 102033-55-6 63705-03-3 (generic)	Polyglyceryl-10 Diisostearate is a diester of Isostearic Acid and Polyglycerin-10.  wherein RC(O)- represents the residue of Isostearic Acid, and n is 10
Polyglyceryl-15 Diisostearate	Polyglyceryl-15 Diisostearate is a diester of Isostearic Acid and a glycerin polymer containing 15 glycerin units.  wherein RC(O)- represents the residue of Isostearic Acid, and n is 15

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

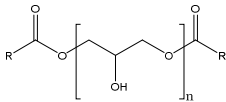
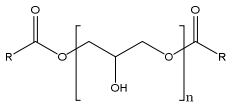
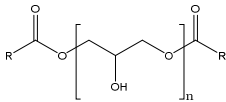
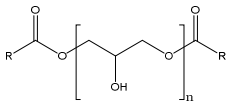
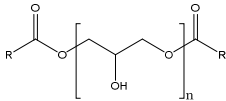
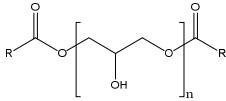
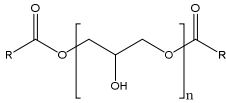
Ingredient CAS No.	Definition & Structure
Polyglyceryl-4 Dilaurate	Polyglyceryl-4 Dilaurate is the diester of Lauric Acid and Polyglycerin-4.  wherein RC(O)- represents the residue of Lauric Acid, and n is 4
Polyglyceryl-5 Dilaurate	Polyglyceryl-5 Dilaurate is the diester of lauric acid and a glycerin polymer containing 5 units of glycerin.  wherein RC(O)- represents the residue of Lauric Acid, and n is 5
Polyglyceryl-10 Dilaurate	Polyglyceryl-10 Dilaurate is the diester of lauric acid and Polyglycerin-10.  wherein RC(O)- represents the residue of Lauric Acid, and n is 10
Polyglyceryl-10 Dimyristate	Polyglyceryl-10 Dimyristate is the diester of myristic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of myristic acid, and n is 10
Polyglyceryl-2 Dioleate 60219-68-3 67965-56-4	Polyglyceryl-2 Dioleate is a diester of oleic acid and Diglycerin.  wherein RC(O)- represents the residue of oleic acid, and n is 2
Polyglyceryl-3 Dioleate 79665-94-4	Polyglyceryl-3 Dioleate is a diester of oleic acid and Polyglycerin-3.  wherein RC(O)- represents the residue of oleic acid, and n is 3
Polyglyceryl-5 Dioleate	Polyglyceryl-5 Dioleate is the diester of Oleic Acid and a glycerin polymer containing 5 units of glycerin.  wherein RC(O)- represents the residue of oleic acid, and n is 5

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

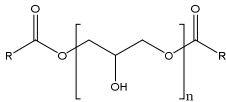
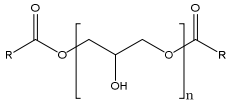
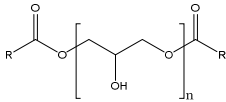
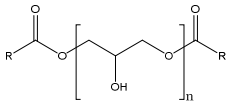
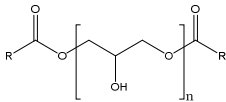
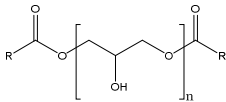
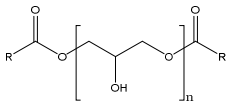
Ingredient CAS No.	Definition & Structure
Polyglyceryl-6 Dioleate	Polyglyceryl-6 Dioleate is a diester of oleic acid and Polyglycerin-6.
76009-37-5	 wherein RC(O)- represents the residue of oleic acid, and n is 6
Polyglyceryl-10 Dioleate	Polyglyceryl-10 Dioleate is a diester of oleic acid and Polyglycerin-10.
33940-99-7	 wherein RC(O)- represents the residue of oleic acid, and n is 10
Polyglyceryl-6 Dipalmitate	Polyglyceryl-6 Dipalmitate is the diester of Palmitic Acid and Polyglycerin-6.
	 wherein RC(O)- represents the residue of Palmitic Acid, and n is 6
Polyglyceryl-10 Dipalmitate	Polyglyceryl-10 Dipalmitate is the diester of Palmitic Acid and Polyglycerin-10.
	 wherein RC(O)- represents the residue of Palmitic Acid, and n is 10
Polyglyceryl-2 Distearate	Polyglyceryl-2 Distearate is the diester of stearic acid and Diglycerin.
9009-32-9	 wherein RC(O)- represents the residue of stearic acid, and n is 2
Polyglyceryl-3 Distearate	Polyglyceryl-3 Distearate is the diester of stearic acid and Polyglycerin-3.
9009-32-9 (generic)	
94423-19-5	 wherein RC(O)- represents the residue of stearic acid, and n is 3
Polyglyceryl-4 Distearate	Polyglyceryl-4 Distearate is a diester of Polyglycerin-4 with Stearic Acid.
	 wherein RC(O)- represents the residue of stearic acid, and n is 4

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

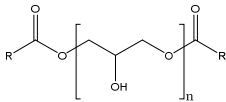
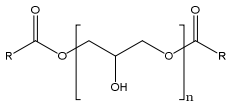
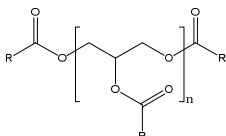
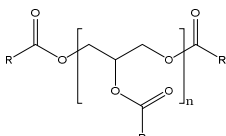
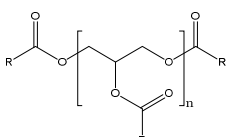
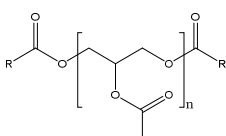
Ingredient CAS No.	Definition & Structure
Polyglyceryl-6 Distearate 34424-97-0 9009-32-9 (generic)	Polyglyceryl-6 Distearate is a diester of stearic acid and Polyglycerin-6.  wherein RC(O)- represents the residue of stearic acid, and n is 6
Polyglyceryl-10 Distearate 12764-60-2 9009-32-9 (generic)	Polyglyceryl-10 Distearate is the diester of stearic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of stearic acid, and n is 10
Polyglyceryl-20 Docosabehenate/Isostearate	Polyglyceryl-20 Docosabehenate/Isostearate is the docosaester of Polyglycerin-20 with a mixture of behenic and isostearic acids.  wherein RC(O)- represents the residue of behenic or isostearic acid, and n is 20
Polyglyceryl-20 Docosabehenate/Laurate	Polyglyceryl-20 Docosabehenate/Laurate is the docosaester of Polyglycerin-20 with a mixture of behenic and lauric acids.  wherein RC(O)- represents the residue of behenic or lauric acid, and n is 20
Polyglyceryl-20 Docosabehenate/Oleate	Polyglyceryl-20 Docosabehenate/Oleate is the docosaester of Polyglycerin-20 with a mixture of behenic and oleic acids.  wherein RC(O)- represents the residue of behenic or oleic acid, and n is 20
Polyglyceryl-10 Dodecabehenate	Polyglyceryl-10 Dodecabehenate is the dodecaester of behenic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of behenic, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

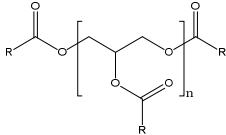
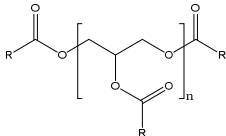
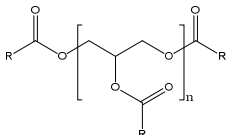
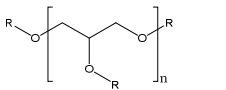
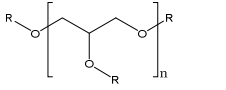
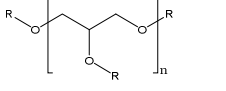
Ingredient CAS No.	Definition & Structure
Polyglyceryl-10 Dodecacaprate	Polyglyceryl-10 Dodecacaprate is the dodecaester of capric acid and Polyglycerin-10.  wherein RC(O)- represents the residue of capric acid, and n is 10
Polyglyceryl-10 Dodecaprylate	Polyglyceryl-10 Dodecaprylate is the dodecaester of caprylic acid and Polyglycerin-10.  wherein RC(O)- represents the residue of caprylic acid, and n is 10
Polyglyceryl-10 Dodeca-Caprylate/Caprate	Polyglyceryl-10 Dodeca-Caprylate/Caprate is the dodecaester of a mixture of caprylic and capric acids with Polyglycerin-10.  wherein RC(O)- represents the residue of capric or caprylic acid, and n is 10
Polyglyceryl-10 Hepta(Behenate/Stearate)	Polyglyceryl-10 Hepta(Behenate/Stearate) is the heptaester of Polyglycerin-10 with a mixture of Behenic Acid and Stearic Acid.  wherein R- represents hydrogen or the residue of behenic acid and stearic acid, and n is 10
Polyglyceryl-6 Heptacaprylate	Polyglyceryl-6 Heptacaprylate is the heptaester of caprylic acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 6
Polyglyceryl-20 Heptacaprylate	Polyglyceryl-20 Heptacaprylate is the heptaester of Caprylic Acid and Polyglycerin-20.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 20

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

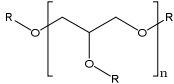
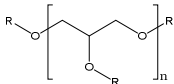
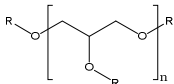
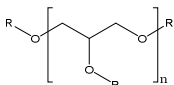
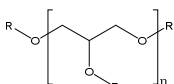
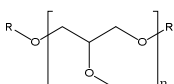
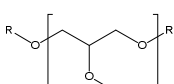
Ingredient CAS No.	Definition & Structure
Polyglyceryl-20 Heptadecabehenate/Laurate	Polyglyceryl-20 Heptadecabehenate/Laurate is the heptadecaester of Polyglycerin-20 with a mixture of behenic and lauric acids.  wherein R- represents hydrogen or the residue of behenic or lauric acid, and n is 20
Polyglyceryl-10 Heptahydroxystearate	Polyglyceryl-10 Heptahydroxystearate is a heptaester of Hydroxystearic Acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of hydroxystearic acid, and n is 10
Polyglyceryl-10 Heptaoleate 103175-09-3	Polyglyceryl-10 Heptaoleate is a heptaester of oleic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of oleic acid, and n is 10
Polyglyceryl-10 Heptastearate 9009-32-9 (generic) 99126-54-2	Polyglyceryl-10 Heptastearate is the heptaester of stearic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of stearic acid, and n is 10
Polyglyceryl-20 Hexacaprylate	Polyglyceryl-20 Hexacaprylate is the hexaester of Caprylic Acid and Polyglycerin-20.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 20
Polyglyceryl-10 Hexaerucate	Polyglyceryl-10 Hexaerucate is the hexaester of Polyglycerin-10 and Erucic Acid.  wherein R- represents hydrogen or the residue of erucic acid, and n is 10
Polyglyceryl-10 Hexaisostearate	Polyglyceryl-10 Hexaisostearate is the hexaester of Polyglycerin-10 and isostearic acid.  wherein R- represents hydrogen or the residue of isostearic acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

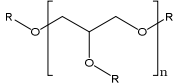
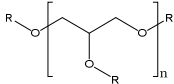
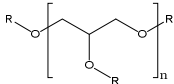
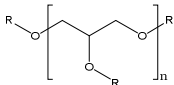
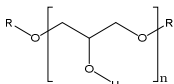
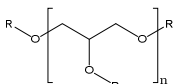
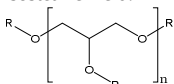
Ingredient CAS No.	Definition & Structure
Polyglyceryl-6 Hexaoleate	Polyglyceryl-6 Hexaoleate is a hexaester of oleic acid and Polyglycerin-6.
95482-05-6	 wherein R- represents hydrogen or the residue of oleic acid, and n is 6
Polyglyceryl-10 Hexaoleate	Polyglyceryl-10 Hexaoleate is the hexaester of Oleic Acid and Polyglycerin-10.
65573-03-7	 wherein R- represents hydrogen or the residue of oleic acid, and n is 10
Polyglyceryl-5 Hexastearate	Polyglyceryl-5 Hexastearate is the hexaester of stearic acid and a glycerin polymer containing 5 units of glycerin.
	 wherein R- represents hydrogen or the residue of oleic acid, and n is 5
Polyglyceryl-6 Hexastearate	Polyglyceryl-6 Hexastearate is the hexaester of stearic acid and Polyglycerin-6.
	 wherein R- represents hydrogen or the residue of stearic acid, and n is 6
Polyglyceryl-10 Mono/Dioleate	Polyglyceryl-10 Mono/Dioleate is a mixture of mono- and diesters of oleic acid and Polyglycerin-10.
	 wherein R- represents hydrogen or the residue of oleic acid, and n is 10
Polyglyceryl-10 Nonaerucate	Polyglyceryl-10 Nonaerucate is the nonaester of Erucic Acid and Polyglycerin-10.
155808-79-0	 wherein R- represents hydrogen or the residue of erucic acid, and n is 10
Polyglyceryl-10 Nonaisostearate	Polyglyceryl-10 Nonaisostearate is the nonaester of Polyglycerin-10 and Isostearic Acid.
	 wherein R- represents hydrogen or the residue of isostearic acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

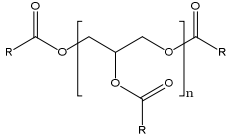
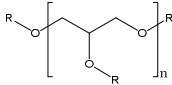
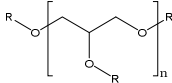
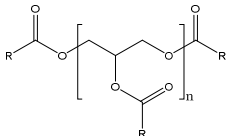
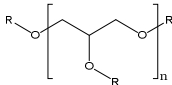
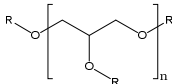
Ingredient CAS No.	Definition & Structure
Polyglyceryl-6 Octacaprylate	Polyglyceryl-6 Octacaprylate is the octaester of Polyglycerin-6 and caprylic acid.  wherein RC(O)- represents the residue of caprylic acid, and n is 6
Polyglyceryl-20 Octadecabehenate/Laurate	Polyglyceryl-20 Octadecabehenate/Laurate is the octadecaester of Polyglycerin-20 and a mixture of behenic and lauric acids.  wherein R- represents hydrogen or the residue of behenic or lauric acid, and n is 20
Polyglyceryl-20 Octaisiononanoate	Polyglyceryl-20 Octaisiononanoate is the octaester of isononanoic acid and Polyglycerin-20.  wherein R- represents hydrogen or the residue of isononanoic acid, and n is 20
Polyglyceryl-6 Octastearate	Polyglyceryl-6 Octastearate is the octaester of stearic acid and Polyglycerin-6.  wherein RC(O)- represents the residue of stearic acid, and n is 6
Polyglyceryl-6 Pentacaprylate	Polyglyceryl-6 Pentacaprylate is the pentaester of caprylic acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 6
Polyglyceryl-10 Pentacaprylate	Polyglyceryl-10 Pentacaprylate is the pentaester of Caprylic Acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

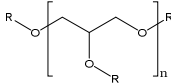
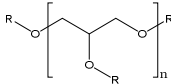
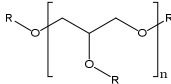
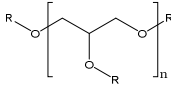
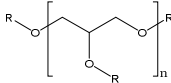
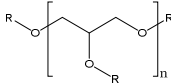
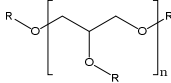
Ingredient CAS No.	Definition & Structure
Polyglyceryl-3 Pentacaprylate/Caprates	Polyglyceryl-3 Pentacaprylate/Caprates is the pentaester of a mixture of Caprylic Acid and Capric Acid with Polyglycerin-3.  wherein R- represents hydrogen or the residue of capric or caprylic acid, and n is 3
Polyglyceryl-10 Pentahydroxystearate	Polyglyceryl-10 Pentahydroxystearate is the pentaester of hydroxystearic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of hydroxystearic acid, and n is 10
Polyglyceryl-10 Pentaisostearate	Polyglyceryl-10 Pentaisostearate is the pentaester of isostearic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of isostearic acid, and n is 10
Polyglyceryl-10 Pentalaurate	Polyglyceryl-10 Pentalaurate is the pentaester of Lauric Acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of lauric acid, and n is 10
Polyglyceryl-10 Pentalinoleate	Polyglyceryl-10 Pentalinoleate is the pentaester of Linoleic Acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of linoleic acid, and n is 10
Polyglyceryl-5 Pentamyristate	Polyglyceryl-5 Pentamyristate is the pentaester of myristic acid and a glycerin polymer containing 5 units of glycerin.  wherein R- represents hydrogen or the residue of myristic acid, and n is 5
Polyglyceryl-4 Pentaoleate 103230-29-1	Polyglyceryl-4 Pentaoleate is the pentaester of Oleic Acid and Polyglycerin-4.  wherein R- represents hydrogen or the residue of oleic acid, and n is 4

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

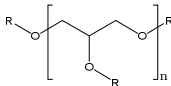
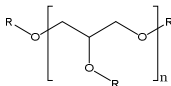
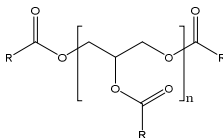
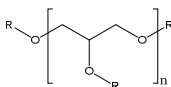
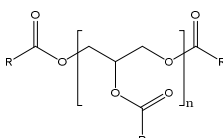
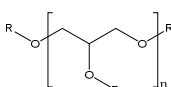
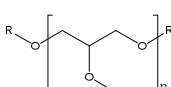
Ingredient CAS No.	Definition & Structure
Polyglyceryl-6 Pentaoleate 104934-17-0	Polyglyceryl-6 Pentaoleate is the pentaester of oleic acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of oleic acid, and n is 6
Polyglyceryl-10 Pentaoleate 86637-84-5	Polyglyceryl-10 Pentaoleate is the pentaester of oleic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of oleic acid, and n is 10
Polyglyceryl-3 Pentaoliveate	Polyglyceryl-3 Pentaoliveate is the pentaester of Polyglycerin-3 and Olive Acid.  wherein RC(O)- represents the residue of olive acid, and n is 3
Polyglyceryl-4 Pentapalmitate/Stearate	Polyglyceryl-4 Pentapalmitate/Stearate is the pentaester of a mixture of Palmitic Acid and Stearic Acid with Polyglycerin-4.  wherein R- represents hydrogen or the residue of palmitic or stearic acid, and n is 4
Polyglyceryl-3 Pentaricinoleate	Polyglyceryl-3 Pentaricinoleate is the pentaester of Ricinoleic Acid and Polyglycerin-3.  wherein RC(O)- represents the residue of ricinoleic acid, and n is 3
Polyglyceryl-6 Pentaricinoleate	Polyglyceryl-6 Pentaricinoleate is the pentaester of Ricinoleic Acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of ricinoleic acid, and n is 6
Polyglyceryl-10 Pentaricinoleate	Polyglyceryl-10 Pentaricinoleate is the pentaester of Ricinoleic Acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of ricinoleic acid, and n is 10

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

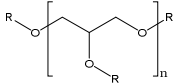
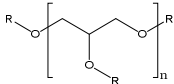
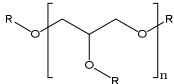
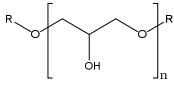
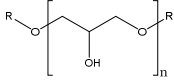
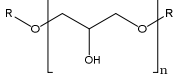
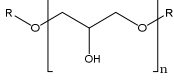
Ingredient CAS No.	Definition & Structure
Polyglyceryl-4 Pentastearate 99570-00-0	Polyglyceryl-4 Pentastearate is the pentaester of Stearic Acid and Polyglycerin-4.  wherein R- represents hydrogen or the residue of stearic acid, and n is 4
Polyglyceryl-6 Pentastearate 9009-32-9 (generic) 99734-30-2	Polyglyceryl-6 Pentastearate is the pentaester of stearic acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of stearic acid, and n is 6
Polyglyceryl-10 Pentastearate 9009-32-9 (generic) 95461-64-6	Polyglyceryl-10 Pentastearate is a pentaester of stearic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of stearic acid, and n is 10
Polyglyceryl-2 Sesquicaprylate	Polyglyceryl-2 Sesquicaprylate is a mixture of mono- and diesters of caprylic acid and Diglycerin.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 2
Polyglyceryl-6 Sesquicaprylate 108777-93-1 (generic) 946492-22-4 (generic) 946492-23-5 (generic)	Polyglyceryl-6 Sesquicaprylate is a mixture of mono- and diesters of Caprylic Acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 6
Polyglyceryl-2 Sesquiosostearate	Polyglyceryl-2 Sesquiosostearate is a mixture of mono and diesters of Isostearic Acid and Diglycerin.  wherein R- represents hydrogen or the residue of isostearic acid, and n is 2
Polyglyceryl-6 Sesquiosostearate	Polyglyceryl-6 Sesquiosostearate is a mixture of mono- and diesters of Isostearic Acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of isostearic acid, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

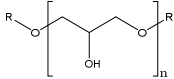
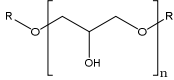
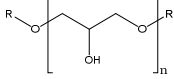
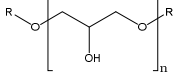
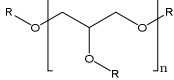
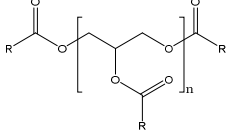
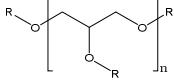
Ingredient CAS No.	Definition & Structure
Polyglyceryl-2 Sesquioleate	Polyglyceryl-2 Sesquioleate is a mixture of mono and diesters of oleic acid and Diglycerin.  wherein R- represents hydrogen or the residue of oleic acid, and n is 2
Polyglyceryl-2 Sesquistearate 9009-32-9 (generic)	Polyglyceryl-2 Sesquistearate is a mixture of mono- and diesters of stearic acid and Diglycerin.  wherein R- represents hydrogen or the residue of stearate acid, and n is 2
Polyglyceryl-6 Sesquistearate 112939-69-2	Polyglyceryl-6 Sesquistearate is a mixture of mono- and diesters of stearic acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of stearate acid, and n is 6
Polyglyceryl-10 Sesquistearate	Polyglyceryl-10 Sesquistearate is a mixture of mono- and diesters of stearic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of stearate acid, and n is 10
Polyglyceryl-6 Tetrabehenate	Polyglyceryl-6 Tetrabehenate is the tetraester of Behenic Acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of behenic acid, and n is 6
Polyglyceryl-2 Tetrabehenate/ Macadamate/Sebacate	Polyglyceryl-2 Tetrabehenate/Macadamate/Sebacate is the tetraester of a mixture of behenic, sebacic and macadamia acids with a dimer of glycerin.  wherein RC(O)- represents the residue of behenic, sebacic, or macadamia acid, and n is 2
Polyglyceryl-6 Tetracaprylate	Polyglyceryl-6 Tetracaprylate is the tetraester of caprylic acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 6

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

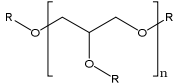
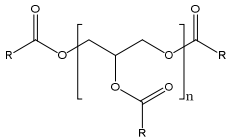
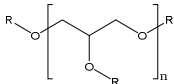
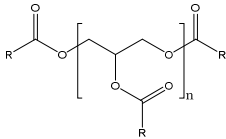
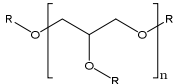
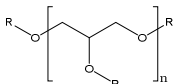
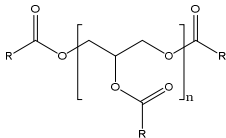
Ingredient CAS No.	Definition & Structure
Polyglyceryl-10 Tetradecanedioate	Polyglyceryl-10 Tetradecanedioate is the ester of tetradecanedioic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of tetradecanoic acid, and n is 10
Polyglyceryl-2 Tetraisostearate 121440-30-0	Polyglyceryl-2 Tetraisostearate is the tetraester of isostearic acid and a dimer of glycerin.  wherein RC(O)- represents the residue of isostearic acid, and n is 2
Polyglyceryl-10 Tetralaurate	Polyglyceryl-10 Tetralaurate is the tetraester of lauric acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of lauric acid, and n is 10
Polyglyceryl-2 Tetraoleate	Polyglyceryl-2 Tetraoleate is the tetraester of oleic acid and Diglycerin.  wherein RC(O)- represents the residue of oleic acid, and n is 2
Polyglyceryl-6 Tetraoleate 128774-95-8	Polyglyceryl-6 Tetraoleate is the tetraester of Oleic Acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of oleic acid, and n is 6
Polyglyceryl-10 Tetraoleate 34424-98-1	Polyglyceryl-10 Tetraoleate is a tetraester of oleic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of oleic acid, and n is 10
Polyglyceryl-2 Tetrastearate 72347-89-8 9009-32-9 (generic)	Polyglyceryl-2 Tetrastearate is the tetraester of stearic acid and Diglycerin.  wherein RC(O)- represents the residue of stearic acid, and n is 2

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

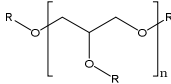
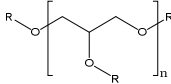
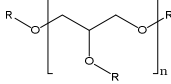
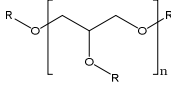
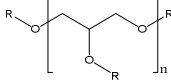
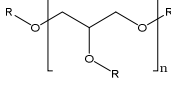
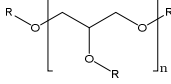
Ingredient CAS No.	Definition & Structure
Polyglyceryl-5 Tribehenate	Polyglyceryl-5 Tribehenate is the triester of behenic acid and a glycerin polymer containing 5 units of glycerin.  wherein R- represents hydrogen or the residue of behenic acid, and n is 5
Polyglyceryl-6 Tricaprylate	Polyglyceryl-6 Tricaprylate is the triester of Caprylic Acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of caprylic acid, and n is 6
Polyglyceryl-10 Tricoate	Polyglyceryl-10 Tricoate is the triester of Coconut Acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of coconut acid, and n is 10
Polyglyceryl-10 Tridecanoate 217782-56-4	Polyglyceryl-10 Tridecanoate is the triester of decanoic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of decanoic acid, and n is 10
Polyglyceryl-10 Trierucate	Polyglyceryl-10 Trierucate is the triester of Polyglycerin-10 and Erucic Acid.  wherein R- represents hydrogen or the residue of erucic acid, and n is 10
Polyglyceryl-2 Triisostearate 120486-24-0	Polyglyceryl-2 Triisostearate is the triester of isostearic acid and Diglycerin.  wherein R- represents hydrogen or the residue of isostearic acid, and n is 2
Polyglyceryl-3 Triisostearate 66082-43-7	Polyglyceryl-3 Triisostearate is the triester of Isostearic Acid and Polyglycerin-3.  wherein R- represents hydrogen or the residue of isostearic acid, and n is 3

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

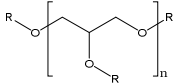
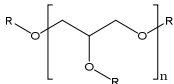
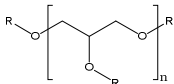
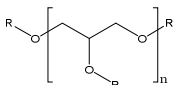
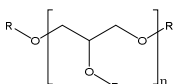
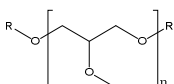
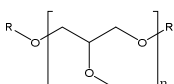
Ingredient CAS No.	Definition & Structure
Polyglyceryl-5 Triisostearate	Polyglyceryl-5 Triisostearate is the triester of Isostearic Acid and a glycerin polymer containing 5 units of glycerin.  wherein R- represents hydrogen or the residue of isostearic acid, and n is 5
Polyglyceryl-10 Triisostearate	Polyglyceryl-10 Triisostearate is the triester of Polyglycerin-10 and Isostearic Acid.  wherein R- represents hydrogen or the residue of isostearic acid, and n is 10
Polyglyceryl-10 Trilaurate	Polyglyceryl-10 Trilaurate is the triester of lauric acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of lauric acid, and n is 10
Polyglyceryl-5 Trimyristate	Polyglyceryl-5 Trimyristate is the triester of myristic acid and a glycerin polymer containing 5 units of glycerin.  wherein R- represents hydrogen or the residue of myristic acid, and n is 5
Polyglyceryl-5 Trioleate	Polyglyceryl-5 Trioleate is the triester of oleic acid and a glycerin polymer containing 5 units of glycerin.  wherein R- represents hydrogen or the residue of oleic acid, and n is 5
Polyglyceryl-10 Trioleate	Polyglyceryl-10 Trioleate is the triester of oleic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of oleic acid, and n is 10
102051-00-3	
Polyglyceryl-3 Trioliveate	Polyglyceryl-3 Trioliveate is the triester of Polyglycerin-3 and Olive Acid.  wherein R- represents hydrogen or the residue of olive acid, and n is 3

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.
(INCI Dictionary; CIR Staff)

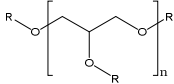
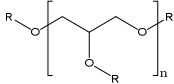
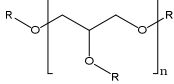
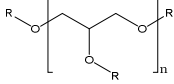
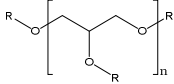
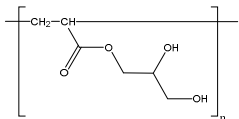
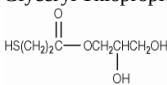
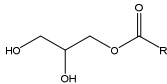
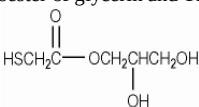
Ingredient CAS No.	Definition & Structure
Polyglyceryl-4 Tristearate 99734-29-9	Polyglyceryl-4 Tristearate is the triester of Stearic Acid and Polyglycerin-4.  wherein R- represents hydrogen or the residue of stearic acid, and n is 4
Polyglyceryl-5 Tristearate 9009-32-9 (generic)	Polyglyceryl-5 Tristearate is the triester of stearic acid and a glycerin polymer containing 5 units of glycerin.  wherein R- represents hydrogen or the residue of stearic acid, and n is 5
Polyglyceryl-6 Tristearate 71185-87-0 9009-32-9 (generic)	Polyglyceryl-6 Tristearate is the triester of stearic acid and Polyglycerin-6.  wherein R- represents hydrogen or the residue of stearic acid, and n is 6
Polyglyceryl-10 Tristearate 12709-64-7 9009-32-9 (generic)	Polyglyceryl-10 Tristearate is the triester of stearic acid and Polyglycerin-10.  wherein R- represents hydrogen or the residue of stearic acid, and n is 10
Triisostearoyl Polyglyceryl-3 Dimer Dilinoleate	Triisostearoyl Polyglyceryl-3 Dimer Dilinoleate is the diester of Dilinoleic Acid and Polyglyceryl-3 Triisostearate.  wherein R- represents the residue of isostearic acid or dilinoleic acid, and n is 3

Table 2. **Other structure types from prior CIR reports, proposed for EXCLUSION from this report**

IJT 23 (Suppl. 2:55-94,)2004 Some Glyceryl Stearates from this issue of IJT are included in Table 1, but the ingredients recited below appear to be structurally too dissimilar.	
Glyceryl Polyacrylate	Glyceryl Polyacrylate is the ester of Glycerin and Polyacrylic Acid.
104365-75-5	
Glyceryl/Sorbitol Oleate/Hydroxystearate	Glyceryl/Sorbitol Oleate/Hydroxystearate is the mixed esterification product of glycerin and sorbitol with hydroxystearic and oleic acids.
Glyceryl Thiopropionate	Glyceryl Thiopropionate is the organic compound that conforms to the formula
67874-65-1	
Glyceryl Collagenate	Glyceryl Collagenate is the ester of glycerin and Collagen. (<i>Collagen is the protein found in cartilage and other connective tissues in animals.</i>)
	 wherein RC(O)- represents the residue of collagen
IJT 28(Suppl. 1):68-133, 2009 While technically a glyceryl ester, the thio-group in the following ingredient is too dissimilar from the alkyl chains of the Glyceryl Esters.	
Glyceryl Thioglycolate	Glyceryl Thioglycolate is the monoester of glycerin and Thioglycolic Acid. It
30618-84-9	 conforms generally to the formula

Monoglyceryl Monoesters (RR of Glyceryl Stearate and Glyceryl Stearate SE)

1982: Panel concluded that glyceryl stearate and glyceryl stearate SE are safe for topical application to humans

1986: Panel concluded glyceryl oleate is safe as a cosmetic ingredient in the present practices of use and concentration; the conclusion was reaffirmed in 2004

1999: Panel concluded data were insufficient to determine safety of Glyceryl Ricinoleate

2007: Panel concluded Glyceryl Ricinoleate and Glyceryl Ricinoleate SE were safe as a cosmetic ingredient in the practices of use and concentrations

2004: Panel concluded a group of glyceryl monoesters were safe as a cosmetic ingredient in the practices of use and concentrations

Monoglyceryl Monoesters (new data only) - Sept 2015 - Monice Fiume

[illegible]

Monoglyceryl Monoesters (new data only) – Sept 2015 – Monice Fiume

[illegible]

	CAS No.	PrevRev	in Use	NTIS	FDA/CFR	NTP	ECHA	HPVIS	IUCLID/SIDS	EU	NICNAS	Web
Glyceryl Stearate FCC/NF; RIFM	11099-07-3 123-94-4 31566-31-1 85666-92-8	1982	VCRP PCPC		X	no	X (for 31566-31-1)	no	X	X	no	
Glyceryl Stearate SE	11099-07-3 85666-92-8	1982	VCRP PCPC			no	no	no	X	X	no	
Glyceryl Acetate	26446-35-5	---	---		X	X	preR	no	no	X	no	
Glyceryl Adipate	26699-71-8	2004	---		no	no	preR	no	no	X	no	
Glyceryl Alginate	-----	2004	---		no	no	no	no	no	X	no	
Glyceryl Arachidate	30208-87-8 50906-68-8	2004	---		no	no	no	no	no	X	no	
Glyceryl Behenate check FCC; NF	6916-74-1 77538-19-3 30233-64-8	2004	VCRP PCPC		X		X (for 77538-19-3)			X	no	
Glyceryl Caprate	11139-88-1 26402-22-2	2004	VCRP PCPC		X	no	preR	no	no	X	no	
Glyceryl Caprylate	26402-26-6	2004	VCRP PCPC		X	no	preR	no	no	X	no	
Glyceryl Caprylate/Caprate	-----	2004	VCRP		X	no	no	no	no	X	no	
Glyceryl Citrate/Lactate/Linoleate/Oleate	-----	2004	PCPC		no	no	no	no	no	X	no	
Glyceryl Cocoate	61789-05-7	2004	VCRP PCPC		X	no	preR	no	no	X	no	
Glyceryl Cocoate/Citrate/Lactate	-----	---	---		no	no	no	no	no	X	no	
Glyceryl Erucate	28063-42-5	2004	---		X	no	preR	no	no	X	no	
Glyceryl Ethylhexanoate	-----	---	---		no	no	no	no	no	X	no	
Glyceryl Ethylhexanoate/Stearate/ Adipate	-----	---	VCRP PCPC		no	no	no	no	no	X	no	
Glyceryl Heptanoate	26402-24-4	---	---		no	no	no	no	no	X	no	
Glyceryl Hydrogenated Rapeseedate	-----	---	---		X	no	no	no	no	X	no	
Glyceryl Hydrogenated Rosinate FCC	-----	2004	VCRP PCPC		X	no	no	no	no	X	no	
Glyceryl Hydrogenated Soyate	-----	2004	---		X	no	no	no	no	X	no	
Glyceryl Hydroxystearate	1323-42-8	2004	VCRP PCPC		X	no	preR	no	no	X	no	
Glyceryl Isopalmitate	-----	2004	---		X	no	no	no	no	X	no	
Glyceryl Isostearate	61332-02-3 66085-00-5	2004	VCRP PCPC		X	no	preR	no	no	X	no	
Glyceryl Isotridecanoate/Stearate/Adipate	-----	2004	VCRP		no	no	no	no	no	X	no	
Glyceryl Lanolate	-----	2004	VCRP		no	no	no	no	no	X	no	
Glyceryl Laurate	142-18-7 27215-38-9 37318-95-9	2004	VCRP PCPC		X	no	X (142-18-7)	no	no	X	no	
Glyceryl Laurate SE	-----	2004	---		no	no	no	no	no	X	no	
Glyceryl Laurate/Oleate	-----	2004	---		X	no	preR	no	no	X	no	
Glyceryl Linoleate	2277-28-3 26545-74-4 37348-65-5	2004	VCRP PCPC		X	no	preR	no	no	X	X	
Glyceryl Linolenate	18465-99-1 56554-41-7	2004	VCRP PCPC		X	no	preR	no	no	X	no	

	CAS No.	PrevRev	in Use	NTIS	FDA/CFR	NTP	ECHA	HPVIS	IUCLID/SIDS	EU	NICNAS	Web
Glyceryl Montanate	68476-38-0 71035-02-4	2004	---		no	no	preR	no	no	X	no	
Glyceryl Oleate	111-03-5 161403-66-3 25496-72-4 37220-82-9 68424-61-3	1986; RR not open 2004	VCRP PCPC		X	no	preR	no	X (glycerides)	X	no	
Glyceryl Oleate SE	-----	2004	---		no	no	no	no	no	X	no	
Glyceryl Oleate/Elaidate	-----	2004	VCRP		no	no	no	no	no	X	no	
Glyceryl Olivat	-----	---	---		no	no	no	no	no	X	LaurOliv	
Glyceryl Palmitate	26657-96-5 542-44-9	2004	VCRP		X	no	preR	no	no	X	no	
Glyceryl Palmitate/Stearate	68002-71-1	2004	---		X	no	X	no	no	X	no	
FCC												
Glyceryl Palmitoleate	-----	2004	---		X	no	no	no	no	X	no	
Glyceryl Pentadecanoate	122636-37-7	2004	---		no	no	no	no	no	X	no	
Glyceryl Ricinoleate	1323-38-2 141-08-2 5086-52-2	1998 2007	VCRP PCPC		X	no	preR	no	no	X	no	
Glyceryl Ricinoleate SE	---	2007	PCPC		no	no	no	no	no	X	no	
Glyceryl Rosinate	8050-31-5	2004	VCRP PCPC		X	no	X	X	no	X	no	
Glyceryl Stearate/Malate	-----	2004	PCPC		no	no	no	no	no	X	no	
Glyceryl Tallowate	-----	2004	---		no	no	no	no	no	X	no	
Glyceryl Undecylenate	123759-97-7 62285-15-8	2004	VCRP PCPC		no	no	preR	no	no	X	no	

X – indicates data were available

PubMed (August 4, 2015):

All CAS No.: 11099-07-3 OR 111-03-5 OR 11139-88-1 OR 122636-37-7 OR 123759-97-7 OR 123-94-4 OR 1323-38-2 OR 1323-42-8 OR 141-08-2 OR 142-18-7 OR 161403-66-3 OR 18465-99-1 OR 2277-28-3 OR 25496-72-4 OR 26402-22-2 OR 26402-24-4 OR 26402-26-6 OR 26446-35-5 OR 26545-74-4 OR 26657-96-5 OR 26699-71-8 OR 27215-38-9 OR 28063-42-5 OR 30208-87-8 OR 30233-64-8 OR 31566-31-1 OR 37220-82-9 OR 37318-95-9 OR 37348-65-5 OR 5086-52-2 OR 50906-68-8 OR 542-44-9 OR 56554-41-7 OR 61332-02-3 OR 61789-05-7 OR 62285-15-8 OR 66085-00-5 OR 68002-71-1 OR 68424-61-3 OR 68476-38-0 OR 6916-74-1 OR 71035-02-4 OR 77538-19-3 OR 8050-31-5 OR 85666-92-8

Glyceryl Stearate: ("1980"[Date - Completion] : "3000"[Date - Completion]) AND ((123-94-4[EC/RN Number]) OR 11099-07-3[EC/RN Number]) OR 31566-31-1) OR (85666-92-8 [EC/RN Number]) OR (GLYCERYL AND STEARATE) OR (glycerol AND stearate)))) – 289/3 useful

2004 Report Ingredients – by name: GLYCERYL AND (ADIPATE OR ALGINATE OR BEHENATE OR CAPRATE OR CAPRYLATE OR (CAPRATE AND CAPRYLATE) OR CITRATE OR COCOATE OR ELAIDATE OR ERUCATE OR ROSINATE OR (HYDROGENATED AND SOYATE) OR HYDROXYSTEARATE OR ISOPALMITATE OR ISOSTEARATE OR ISOTRIDECANOATE OR LACTATE OR LANOLATE OR LAURATE OR LINOLEATE OR LINOLENATE OR MONTANATE OR PALMITATE OR PALMITOLEATE OR PENTADECANOATE OR RICINOLEATE OR ROSINATE OR TALLOWATE OR UNDECYLENATE) – 331 hits/7 useful

2004 Report Ingredients: (("2000"[Date - Completion] : "3000"[Date - Completion]) AND (((26699-71-8[EC/RN Number]) OR (30208-87-8[EC/RN Number]) OR (50906-68-8[EC/RN Number]) OR (6916-74-1[EC/RN Number]) OR (77538-19-3[EC/RN Number]) OR (30233-64-8[EC/RN Number]) OR (11139-88-1[EC/RN Number]) OR (26402-22-2[EC/RN Number]) OR (26402-26-6[EC/RN Number]) OR (61789-05-7[EC/RN Number]) OR (28063-42-5[EC/RN Number]) OR (1323-42-8[EC/RN Number]) OR (61332-02-3[EC/RN Number]) OR (66085-00-5[EC/RN Number]) OR (142-18-7[EC/RN Number]) OR (27215-38-9[EC/RN Number]) OR (37318-95-9[EC/RN Number]) OR (2277-28-3[EC/RN Number]) OR (26545-74-4[EC/RN Number]) OR (37348-65-5[EC/RN Number]) OR (18465-99-1[EC/RN Number]) OR (56554-41-7[EC/RN Number]) OR (68476-38-0[EC/RN Number]) OR (71035-02-4[EC/RN Number]) OR (26657-96-5[EC/RN Number]) OR (542-44-9[EC/RN Number]) OR (68002-71-1[EC/RN Number]) OR (122636-37-7[EC/RN Number]) OR (8050-31-5[EC/RN Number]) OR (123759-97-7[EC/RN Number]) OR (62285-15-8[EC/RN Number]))) – 119 hits/2 useful

Glycerol Oleate ("1984"[Date - Completion] : "3000"[Date - Completion]) AND ((111-03-5[EC/RN Number] OR 161403-66-3[EC/RN Number] OR 25496-72-4[EC/RN Number] OR 37220-82-9[EC/RN Number] OR 68424-61-3[EC/RN Number]) OR ((Glycerol OR Glyceryl) AND oleate)) – 1306 hits/9 useful

Glycerol Ricinoleate: ("2005"[Date - Completion] : "3000"[Date - Completion]) AND ((1323-38-2[EC/RN Number]) OR 141-08-2[EC/RN Number]) OR (5086-52-2[EC/RN Number]) OR ((GLYCERYL OR GLYCEROL) AND RICINOLEATE)) – 16 hits/1 useful

Not Previously Reviewed:

26446-35-5[EC/RN Number] OR (GLYCERYL AND ACETATE) – 103 hits/1 useful

GLYCERYL AND COCOATE AND CITRATE AND LACTATE – 1 hit (CIR report)

GLYCERYL AND (COCOATE OR CITRATE OR LACTATE) – 81 hits/0 useful

(GLYCERYL AND ETHYLHEXANOATE) OR (GLYCERYL AND RAPESEEDATE) OR (GLYCERYL AND OLIVATE) – 2 hits/0 useful

(GLYCERYL AND HEPTANOATE) OR 26402-24-4[EC/RN Number] – 2 hits/0 useful

SciFinder (Aug 5, 2015) – KMP file created

Glyceryl monoesters – 31 hits/1 additional

Glyceryl esters – 84 hits/0 useful

Amended Safety Assessment of Monoglyceryl Monoesters as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: August 28, 2015
Panel Meeting Date: September 21-22, 2015

The 2015 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/Writer and Bart Heldreth, Ph.D., Chemist.

INTRODUCTION

In 1982, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published the Final Report on the Safety Assessment of Glyceryl Stearate and Glyceryl Stearate SE; based on the data presented in that assessment, that Panel concluded that glyceryl stearate and glyceryl stearate SE are safe for topical application to humans.¹ In accordance with its Procedures, CIR evaluates the conclusions of previously-issued reports every 15 years to determine whether or not the conclusion should be reaffirmed. A re-review of glyceryl stearate has not been conducted; therefore, one is now being initiated.

Numerous additional monoglyceryl monoesters have also been previously reviewed by CIR. These monoglyceryl monoesters are structurally-constituted of the esterification products of glycerin and fatty acids. Additionally, almost all of these ingredients are skin conditioning agents.² Therefore, because of the structural and functional similarities, the following are the monoglyceryl monoesters proposed to be included, and the existing conclusions:

- Glyceryl Oleate – reviewed in 1986, and found to be safe as a cosmetic ingredient in the present practices of use and concentration;³ a re-review was conducted in 2004, and the conclusion was reaffirmed
- Glyceryl Ricinoleate - first reviewed in 1988, and at that time the Panel concluded the data were insufficient to determine safety;⁴ in 2007, it was reviewed as part of a larger group of ingredients and found safe as a cosmetic ingredient in the practices of use and concentrations.⁵
- Glyceryl Ricinoleate SE - also reviewed as part of a larger group of ingredients in 2007, and found safe as a cosmetic ingredient in the practices of use and concentrations.⁵
- Glyceryl Monoesters – in 2004, the following glyceryl monoesters were determined to be safe as cosmetic ingredients in the present practices of use and concentration:⁶

Glyceryl Adipate
 Glyceryl Alginate
 Glyceryl Arachidate
 Glyceryl Behenate
 Glyceryl Caprate
 Glyceryl Caprylate
 Glyceryl Caprylate/Caprate
 Glyceryl Citrate/Lactate/Linoleate/Oleate
 Glyceryl Cocoate
 Glyceryl Erucate
 Glyceryl Hydrogenated Rosinate
 Glyceryl Hydrogenated Soyate
 Glyceryl Hydroxystearate
 Glyceryl Isopalmitate
 Glyceryl Isostearate
 Glyceryl Isotridecanoate/Stearate/Adipate
 Glyceryl Lanolate

Glyceryl Laurate
 Glyceryl Laurate SE
 Glyceryl Laurate/Oleate
 Glyceryl Linoleate
 Glyceryl Linolenate
 Glyceryl Montanate
 Glyceryl Oleate
 Glyceryl Oleate SE
 Glyceryl Oleate/Elaidate
 Glyceryl Palmitate
 Glyceryl Palmitate/Stearate
 Glyceryl Palmitoleate
 Glyceryl Pentadecanoate
 Glyceryl Rosinate
 Glyceryl Stearate/Maleate
 Glyceryl Tallowate
 Glyceryl Undecylenate

Please note: Glyceryl arachidonate was also included in the 2004 safety assessment of glyceryl monoesters; however, the data were insufficient to support the safety of this ingredient, and therefore glyceryl arachidonate is not part of the current re-review.

Furthermore, there are several monoglyceryl monoesters included in the *International Cosmetic Ingredient Dictionary* that have not yet been reviewed. It is proposed that these 8 ingredients also be included as part of this safety assessment:

Glyceryl Acetate
 Glyceryl Cocoate/Citrate/Lactate
 Glyceryl Ethylhexanoate
 Glyceryl Ethylhexanoate/Stearate/Adipate

Glyceryl Heptanoate
 Glyceryl Hydrogenated Rapeseedate
 Glyceryl Oliviate
 Glyceryl Stearate/Malate

Additional note: In 2004, the *International Cosmetic Ingredient Dictionary* included the name glyceryl stearate/maleate as an ingredient. That ingredient was subsequently included in the 2004 assessment of glyceryl monoester. However, that was an error and glyceryl stearate/maleate is not a cosmetic ingredient. Glyceryl stearate/malate is an ingredient, and will be included in the re-review. (The Panel published a safety assessment on malic acid in 2001; the Panel concluded malic acid was safe for use as a pH adjuster in cosmetic formulations, and the data were insufficient to determine the safety for any other functions.)⁷

An alphabetical listing of the 45 monoglyceryl monoesters that are proposed for inclusion in one safety assessment is provided in Table 1, and these ingredients are defined in Table 2.

Excerpts from the summaries of the reports on the previously reviewed monoglyceryl monoesters are disseminated throughout the text of this re-review document, as appropriate, and are *identified by italicized text*. (This information is not included in the tables or the summary section.)

As stated earlier, these monoesters all share a glycerin core. The Panel evaluated the safety of glycerin as used in cosmetics in 2014, concluding that glycerin is safe in cosmetics in the present practices of use and concentration described in the safety assessment.⁸ Many of the fatty acid components of these monoesters have also been reviewed by CIR. A listing of those that have been reviewed, and the associated conclusions, are provided in Table 3.^{5,7,9-19} (The full reports can be found on the CIR website: <http://www.cir-safety.org/ingredients>)

CIR will be concurrently reviewing the safety of Polyglyceryl Fatty Acid Esters. Originally, it was proposed to the Panel that the polyglyceryl fatty acid esters be included in this re-review. After further consideration, two separate reports were prepared. (The safety assessment of the Polyglyceryl Fatty Acid Esters is scheduled for review at the December meeting.)

Finally, much of the new data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.²⁰⁻²³ Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

The monoglyceryl monoesters are structurally constituted of the esterification products of one equivalent of glycerin and one equivalent of a fatty acid. These ingredients vary only in the identity of those fatty acids (e.g., variable length, branching, and unsaturation of those acid residues). The definitions and idealized structures of the monoglyceryl monoesters are provided in Table 2.

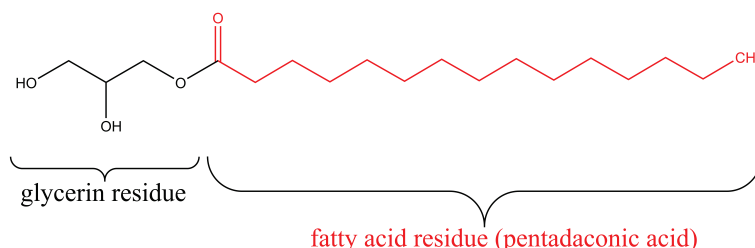


Figure 1. Glyceryl Pentadecanoate, a monoglyceryl monoester

Physical and Chemical Properties

Please refer to the original reports on the previously reviewed monoglyceryl monoesters.

Method of Manufacture

Glyceryl Oleate SE

The self-emulsifying grade of glyceryl oleate can be formulated by mixing glyceryl oleate with 5% of an anionic surfactant.²⁴

Glyceryl Monoesters – general

*Industrial monoglycerides can be prepared by the direct esterification of glycerol with a fatty acid, yielding mixtures of mono-, di-, and tri- glycerides, depending on the molar ratio of the reactants.*²⁵

Glyceryl Oleate

Glyceryl oleate is manufactured by the partial hydrolysis of corresponding tri- and diglycerides, by esterification of glycerol with oleic acid, or by glycerolysis of common fats and oils.³ The glycerolysis of fats and oils, a transesterification reaction, is a common commercial method for the preparation of monoglycerides.

Natural Occurrence

Glyceryl acetate may be a natural component of tobacco or a product of pyrolysis (in tobacco smoke).²⁶

Impurities/Constituents

Glyceryl Monoesters – general

According to one source, glyceryl monoesters are not pure monoesters, but are mostly mixtures with mono-, di-, and triesters in a ratio of approximately 4:4:2, respectively.²⁵ Another source indicates that the guaranteed purity of commercial and conventional monoglyceride (glyceryl monoester) is a minimum of 90%, meaning that impurities account for a maximum of 10%

of the composition. The results of impurities analyses of 14 glyceryl monoesters indicated that only one, glyceryl palmitate/stearate, contained (mono)glycerol diester at a concentration of 1.2%.

Glyceryl Stearate and Glyceryl Stearate SE

Glyceryl stearate and glyceryl stearate SE may contain mono-, di-, and triglyceride impurities and fatty acid impurities.¹

UV Absorption

Glyceryl Ricinoleate

Glyceryl ricinoleate absorb UV light, with a maximum absorbance at 270 nm.⁵

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the U.S. Food and Drug Administration (FDA) and from the cosmetics industry in determining the expected cosmetic use. The data received from the FDA are those collected from manufacturers on the use of individual ingredients in cosmetics by product category in its Voluntary Cosmetic Registration Program (VCRP). Data from the cosmetic industry are submitted in response to a survey of maximum use concentration by product category conducted by the Personal Care Products Council (Council).

Based on information from the VCRP and that received from the Council, 25 of the 45 ingredients included in this safety assessment are in use.²⁷⁻²⁹ Of those, glyceryl stearate has the highest frequency of use; according to the 2015 VCRP data, glyceryl stearate is reported to be used in 5153 formulations, and 4229 of those uses are in leave-on formulations. Glyceryl stearate SE has the next highest frequency of use, with 1420 reported uses²⁷ (Table 4).

The results of the concentration of use survey conducted by the Council in 2014 indicate that for the monoglyceryl monoesters in this group, glyceryl stearate has the highest maximum use concentration in leave-on formulations (17% in a deodorant), and glyceryl ricinoleate has the second highest maximum use concentration in leave-on formulations (15.2% in lipstick).^{28,29} Overall, glyceryl rosinatate is reported to have the greatest maximum reported used concentration, i.e., 96% in a depilatory (Table 4).

Most of the in-use ingredients have been reviewed previously by the Panel. For the majority of these ingredients, the frequency of use has increased but the concentration of use has remained the same or decreased. For example, in 1976 glyceryl stearate was reported to be used in 1371 cosmetic formulations at concentrations up to 50%;¹ currently, it is reported to be used in 5153 formulations at a maximum concentration of 18.9%. Additionally, for those ingredients that now have a higher concentration of use than what was reported historically, that increase has been relatively small. However, glyceryl rosinatate and glyceryl hydrogenated rosinatate are exceptions. The maximum concentration of use of glyceryl rosinatate has increased from 12% in 1999⁶ to 96% in 2014. The primary reason for this increase is that glyceryl rosinatate is now reported to be used at maximum concentrations of 72-96% in depilatories; yet, the next greatest concentration of use of glyceryl rosinatate is 8% in mascara, which is a decrease from the 12% concentration of use in mascara reported in 1999. Glyceryl hydrogenated rosinatate was not reported to be used in 1998, but now has 29 uses, with maximum use concentrations of 10% in leave-on products (lipstick) and 76.8% in rinse-off products (depilatories).

The 20 monoglyceryl monoesters not currently reported to be in use in use, according to the VCRP and industry survey, are listed in Table 5.

Several of the monoglyceryl monoesters are used in products that can be ingested, used near the eye, or come in contact with mucous membranes. Glyceryl ricinoleate is used at 11.6% in eyeliner and at 15.2% in lipstick (possible ingestion and mucous membrane exposure). (In the 2007 review of glyceryl ricinoleate, the use in lipstick was known, but a concentration of use was not reported.⁵)

Additionally, some of the monoglyceryl monoesters are used in cosmetic sprays and could possibly be inhaled; for example, glyceryl stearate is reported to be used at a maximum concentration of 14% in perfumes. 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 <10 µm compared with pump sprays.^{30,31} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{32,33} Some of the ingredients are used in spray deodorants; for example, glyceryl cocoate is used at a maximum concentration of 2% in a pump spray deodorant formulation. 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.³² 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.

All of the monoglyceryl monoesters named in the report are listed in the European Union inventory of cosmetic ingredients.³⁴

Non-Cosmetic

According to the FDA, many of the monoglyceryl monoesters are direct food substances affirmed as generally recognized as safe (GRAS) for human and/or animal use, are permitted as direct food additives, or are permitted as indirect food additives. The food additive status of the monoglyceryl monoesters is provided in Table 6.

Glyceryl Acetate

Glyceryl acetate is used as a gelatinizing agent for explosives, in leather tanning, and as a solvent for basic dyes.²⁶ It may be an additive for one or more types of tobacco products.

Glyceryl Monoesters - general

*Glyceryl monoesters have been approved by the FDA for use as direct or indirect food additives.*²⁵

Glyceryl Oleate

Glyceryl oleate has numerous applications in the pharmaceutical field.²⁴ Examples of these applications include emulsifier, solubilizer, absorption enhancer, oral drug delivery system, and vaginal drug delivery system.

Monoglycerides of edible fats or oils are considered GRAS and indirect food additives for human consumption by the FDA.³ Glyceryl oleate can be used as a prior-sanctioned food ingredient and as a direct and indirect food additive. The pharmaceutical industry uses glyceryl oleate as an inert carrier compound and to enhance intestinal drug absorption.

Glyceryl Ricinoleate

*Glyceryl ricinoleate is listed by the FDA as an inactive ingredient in drug preparations.*⁴

Glyceryl Stearate

Glyceryl stearate is widely used in foods as a surfactant, emulsifier, and thickener. Glyceryl stearate is an antistalant and dough conditioner in breads and is also used in pharmaceutical bases. Glyceryl stearate has been granted regulatory status (by the FDA) as GRAS ingredient, an indirect food additive, a direct food additive, and as an over-the counter (OTC) substance¹.

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Oral

Glyceryl Rosinate

Four groups of Fischer 344 rats were orally administered glycerol ester of wood rosin; the labeled compound was prepared using 1,3-¹⁴C glycerol.²³ One group of 8 females was fed a diet containing 14,000 ppm unlabeled ester for 18 hours, and two groups of 8 males were fed a diet containing 14,000 ppm unlabeled ester for 20 hours or 10 days, respectively; 5 rats from each of the 3 group was administered a single dose of 200 mg/kg bw ¹⁴C glycerol ester of wood rosin by gavage after completion of dietary administration. The animals were then placed in metabolism cages, and expired CO₂, urine, and feces were collected from each animal at 0-12 h, 12-24 h, and subsequent 24-h intervals through 120 h after dosing. The animals were then killed.

Less than 1% (males) to 2% (females) of the administered radioactivity was recovered in either expired CO₂, urine or the cage rinses with 120 h of administration; the majority of the radioactivity was excreted in the feces. Small traces of radioactivity were detectable in the carcasses; this trace material was most likely residual radioactivity in the gastrointestinal tract. No metabolites were specifically identified; however, analysis of fecal extracts following dosing indicate that little hydrolysis occurred, and results were similar with 1-day and 10-day dietary administration.

In the fourth group, jugular vein cannulas were implanted in 9 male rats and the following day, 6 of these rats were also implanted with biliary cannulas. The 6 rats implanted with 2 cannulas were then dosed by gavage with 200 mg/kg bw ¹⁴C glycerol ester of wood rosin. Excreted bile was collected continuously, and samples were obtained at 4, 8, 12, and 24 h after dosing, and blood samples were obtained from the jugular cannula at the same time intervals. The animals were killed 24 h after dosing. Low levels of radioactivity were absorbed by the rats following dosing, and the radioactive species excreted in bile appeared to be a hydrolyzed product of the administered test substance; no intact test substance was present. Radioactivity was excreted in bile within 4 h after dosing and was detectable in all samples collected for 24 h post dose. The total amount of radioactivity excreted in bile during the 24-h collection period ranged from 1.6-2.9% of the dose. Radioactivity content in the liver only accounted for 0.1-0.2% of the administered dose.

Glyceryl Monoesters – general

*Glyceryl monoesters (monoglycerides) are metabolized to free fatty acids and glycerol, both of which are available for the resynthesis of triglycerides.*²⁵

Glyceryl Ricinoleate

*Upon ingestion, glyceryl ricinoleate is absorbed into the intestinal mucosa.*⁴

Penetration Enhancement

Monoglyceryl monoesters can act as penetration enhancers. Several studies demonstrating this behavior are summarized in Table 7.³⁵⁻³⁹

Glyceryl Laurate

*Glyceryl Laurate enhanced the penetration of drugs through cadaverous skin and hairless rat skin in vitro.*²⁵

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Single dose (acute) toxicity studies are summarized in Table 8.

The dermal LD₅₀ of glyceryl rosinate is >10 g/kg bw in rabbits in a 24-h patch test.²³ In oral studies, the LD₅₀ of glyceryl behenate and glyceryl hydrogenated rosin is >2 g/kg, of glyceryl stearate is >5 g/kg, and of glyceryl rosinate is >10 g/kg.^{20,21,23}

Dermal

Glyceryl Citrate/Lactate/Linoleate/Oleate

*In an acute dermal toxicity study in rats, 2000 mg/kg glyceryl citrate/lactate/linoleate/oleate did not induce toxicity in rats that received a single oral dose of 2000 mg/kg.*²⁵

Oral

Glyceryl Citrate/Lactate/Linoleate/Oleate

*Glyceryl citrate/lactate/linoleate/oleate did not induce toxicity in rats that received a single oral dose of 2000 mg/kg.*²⁵

Glyceryl Isostearate

*Glyceryl isostearate did not induce toxicity in rats that received a single oral dose of 2000 mg/kg.*²⁵

Glyceryl Laurate

*An LD₅₀ of >20,000 mg/kg was reported for rats dosed orally with glyceryl laurate.*²⁵

Glyceryl Oleate

*Oral administration of a single 13 ml/kg dose of a sunscreen formulation containing 5% glyceryl oleate to rats produced no signs of toxicity and no lethality.*³

Glyceryl Ricinoleate

*Acute oral toxicity tests indicated that glyceryl ricinoleate has an LD₅₀ greater than 25.0 ml/kg in mice and that products containing 5.6% glyceryl ricinoleate were not toxic when ingested.*⁴

Glyceryl Rosinate

*Undiluted, purified ester gum-2-octyldodecyl myristate (contains 50% glyceryl rosinate and 50% octyldodecyl myristate) was not toxic (LD₅₀ > 5 g/kg) when administered orally to fasted Wistar albino rats (five males, five females).*²⁵ *None of the animals died.*

Glyceryl Stearate and Glyceryl Stearate SE

*In acute oral toxicity studies in rats, glyceryl stearate and glyceryl stearate/SE were nontoxic or mildly toxic.*¹

Repeated Dose Toxicity

Repeated dose toxicity studies are summarized in Table 9.

In a 90-day dietary study, the no-observable adverse effect level (NOAEL) for glyceryl hydrogenated rosinate in rats was 10,000 ppm. For glyceryl rosinate, the NOAEL for rats was 1% in one 90-day study, and 2500 mg/kg bw/day in another. In a 28-day study of glycerides, C8-18 and C18-unsatd. mono- and di-, acetates in rats, the NOAEL was 1000 mg/kg bw/day.^{20,23}

Intravaginal dosing with 5% glyceryl oleate for 6 mos in monkeys did not induce vaginal inflammation or mucosal lesions in cervical vaginal tissues.⁴⁰

Animal

Dermal

Glyceryl Stearate

*In subchronic and chronic dermal toxicity tests, 4-5% glyceryl stearate was nontoxic to rabbits but did cause moderate irritation (slight to moderate erythema, edema, atonia, desquamation, and/or fissuring).*¹

Oral

Glyceryl Laurate

*No test substance-related gross or microscopic changes were observed in albino rats fed a mixture of mono-, di-, and triglycerides containing 40% to 45% glyceryl laurate for two.*²⁵

years.

Glyceryl Stearate

*In chronic studies, 15-25% glyceryl stearate in the diet of rats for three consecutive generations had no adverse effects.*¹ *Rats fed a diet containing 25% glyceryl stearate for two years developed renal calcifications.*

Inhalation

Glyceryl Laurate

*A no-effect level of 280 mg/m³ was reported for glyceryl laurate in a short-term inhalation toxicity study involving rats.*²⁵ *Rats were subjected to 14 1-hour exposures during a 3-week period. Neither gross nor microscopic lesions were noted in rats fed 25% Glyceryl laurate in another short-term (10 weeks) study.*

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Glyceryl Oleate

A reproduction/developmental toxicity screening test was conducted in male and female Sprague-Dawley rats for glyceryl oleate.²¹ Both males and females were dosed by gavage with 0, 100, 300, or 1000 mg/kg bw/day glyceryl oleate in corn oil once daily for 14 days prior to mating; the males were dosed for an additional 28 days, and dosing of the females continued until day 4 of lactation. The groups were comprised of 12 females for the control and 3 test groups, 7 males in the control and high dose groups, and 12 males in the low- and mid-dose groups. A satellite group of 5 males and 5 females were dosed for 42 days, with a 14-day post-dosing observation period. The NOAELs for systemic toxicity (males and females), fertility (males and females), and development (F₁ generation) were 1000 mg/kg bw/day. No effects related to the administration of the test-article were observed in parental animals or offspring.

For Read-Across

In the 28-day oral toxicity study with 0, 100, 300 and 1000 mg/kg/day glycerides, C8-18 and C18-unsatd. mono- and di-, acetates in polyethylene glycol described in Table 9 (Repeated Dose Toxicity Studies), an additional 10 female Wistar Han rats were included in each group to assess reproduction and developmental toxicity.²⁰ After a minimum of 14 days of dosing, females of the reproduction study group were cohabitated with a male from the same treatment group. The test females were dosed for a total of 41-49 days, i.e. during those 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation. No treatment-related effects were observed, and the NOAEL for parental fertility was 1000 mg/kg bw/day.

Glyceryl Hydrogenated Rosinate and Glyceryl Rosinate

*Following the administration of hexane extracts of Pinus ponderosa needles to mice by stomach tube, increased embryonic resorptions were observed.*²⁵ *Glyceryl rosinate and glyceryl hydrogenated rosinate are esters of glycerin and acids derived from rosin, and rosin is obtained from trees of various species of Pinus.*

GENOTOXICITY

Genotoxicity studies are summarized in Table 10.

Glyceryl acetate was not mutagenic in an Ames test ($\leq 10,000$ $\mu\text{g}/\text{plate}$) or chromosomal aberration assay (≤ 5000 $\mu\text{g}/\text{plate}$) with or without metabolic activation; in a sister chromatid exchange assay, it was not genotoxic with metabolic activation, but without activation, a dose-dependent increase was observed in 2 trials, and a doubling of sister chromatid exchanges (SCEs) was produced with 5000 $\mu\text{g}/\text{ml}$.^{41,42} Glyceryl laurate was not mutagenic in an Ames test (≤ 5000 $\mu\text{g}/\text{plate}$), and glyceryl rosinate was not mutagenic in an Ames test (≤ 500 $\mu\text{g}/\text{plate}$), mammalian chromosome assay (≤ 507 $\mu\text{g}/\text{ml}$), or unscheduled DNA synthesis test (≤ 102 $\mu\text{g}/\text{ml}$).^{22,43} Glycerides, C16-18 and C18-hydroxy mono- and di- (up to 10,000 mg/kg bw) was not genotoxic in a mouse micronucleus test.²⁰

In Vitro

Glyceryl Citrate/Lactate/Linoleate/Oleate

*In Ames plate incorporation and preincubation mutagenicity tests, glyceryl citrate!lactate!linoleate/oleate was not mutagenic (with or without metabolic activation) to the following Salmonella typhimurium strains: TA 98, TA 100, TA 1535, and TA 1537.*²⁵

Glyceryl Hydrogenated Rosinate and Glyceryl Rosinate

In studies on the mutagenicity of resin acids, only neoabietic acid (component of rosin) was mutagenic in the Ames/Salmonella assay. glyceryl rosin ate and glyceryl hydrogenated rosin ate are esters of glycerin and acids derived from rosin, which is composed of diterpene resin acids.²⁵

CARCINOGENICITY

Oral

Glyceryl Oleate

Glyceryl oleate administration was associated with development of a few brain tumors (3 tumors in 63 mice) in a two-generation study in mice of the T.M. strain whose feed was supplemented with 50-100 mg/mouse per day glyceryl oleate.³ Digestive tract tumors were found in T.M. strain mice fed 200 mg/mouse per day glyceryl oleate (feed supplement) for four-seven generations and were considered due to free fatty acid impurities. The Expert Panel found the results of these studies equivocal.

Glyceryl Ricinoleate

Glyceryl ricinoleate was not a tumor promoter in a study involving groups of ten mice.⁵ However, the test substance induced slight epidermal hyperplasia in groups of three mice following the application of each to a small area of skin in the interscapular region.

Glyceryl Stearate

Glyceryl stearate, fed to mice in doses of 50-100 mg/day or 1.5% in the diet until they died, did not induce significant brain or gastric tumor formation, respectively. Five percent glyceryl stearate did not promote the carcinogenicity of 9,10-dimethylbenz(a)anthracene (DMBA) in mouse skin.¹

IRRITATION AND SENSITIZATION

Dermal Irritation/Sensitization

Dermal irritation and sensitization studies are summarized in Table 11.

Undiluted glyceryl behenate, and glyceryl hydrogenated rosin ate, and glyceryl rosin ate were not irritating to rabbit skin. Glyceryl hydrogenated rosin ate (challenge at up to 50%), glyceryl rosin ate (challenge at 100%), and glyceride, C16-18 and C18 mono- and dihydroxy (25% at challenge) were not sensitizers in guinea pigs.^{20,21,23}

In clinical testing, 5% glyceryl stearate was not irritating and glyceryl behenate (applied neat), glyceryl hydrogenated rosin ate, and glyceryl rosin ate were not sensitizers in human repeated insult patch tests (HRIPTs).^{21,23,44}

Non-Human

Glyceryl Citrate/Lactate/Linoleate/Oleate

Neither erythema nor edema was observed in rabbits after semi-occlusive patches containing heated glyceryl citrate/lactate/linoleate/oleate (single application) were applied to intact skin. In another study, glyceryl citrate/lactate/linoleate/oleate (single application) induced clearly circumscribed erythema and very mild edema when applied to intact skin of rabbits.²⁵ All reactions had cleared by day 10 post application.

The sensitization potential of glyceryl citrate/lactate/linoleate/oleate in 20 guinea pigs was evaluated using the Buehler method.²⁵ Following the dermal application of undiluted test substance during induction and challenge phases, no evidence of irritation or sensitization was observed.

Glyceryl Isostearate

Overall, glyceryl isostearate was classified as nonirritating to the skin of rabbits in a study in which single, semi-occlusive patch applications were made to intact skin.²⁵ The most severe reaction (moderate irritation) did not clear until day 5 post removal. Glyceryl isostearate was also classified as nonirritating to the skin of rabbits in another study in which single occlusive patch applications were made to intact and abraded skin sites.

Glyceryl isostearate was also evaluated in the maximization test.²⁵ After induction, ten guinea pigs were challenged with 50% glyceryl isostearate in polyethylene glycol (PEG) and microcrystalline cellulose (MCC). Two additional challenges were also conducted. The first challenge yielded one and two positive reactions (all slight reactions) at 24 and 48 h, respectively. These results were confirmed by reactions observed after the third challenge.

Glyceryl Laurate

Undiluted glyceryl laurate induced minor erythema and edema when applied (occlusive patches, single application) to intact skin of rabbits.²⁵ In another study, single occlusive patch applications of 20% glyceryl laurate emulsion to abraded and intact skin caused moderate skin irritation in rabbits.

The skin sensitization potential of glyceryl laurate was evaluated in the maximization test.²⁵ Guinea pigs were subjected to four sensitizing injections of 2% glyceryl laurate and then challenged with intradermal injections of 0.8% glyceryl laurate and topical applications of 25% glyceryl laurate. No positive reactions were observed. In another maximization test, skin sensitization was induced in 2 of 10 guinea pigs challenged with a 10% dilution of 20% glyceryl laurate emulsion. When a second challenge was initiated 7 days after the first, positive reactions were observed in five animals. Positive reactions were also observed in four animals challenged with a 5% dilution of 20% glyceryl laurate emulsion. Because positive reactions were also noted in the control group after the first and second challenge, the results were attributed to skin irritation (but not sensitization) effects of the test substance.

Glyceryl Oleate

Undiluted and 50% in corn oil concentrations of glyceryl oleate used in dermal irritation studies with rabbits were found to be minimally irritating.³ A volume of 0.5 ml of a sunscreen formulation containing 5% glyceryl oleate produced erythema and slight edema in rabbits.

Daily applications of 2.0 ml/kg of a 25.0% corn oil solution of a formulation containing glyceryl oleate for 20 days produced severe dermal irritation in rabbits.³ In another 4-week dermal toxicity/phototoxicity study, product formulations containing varying concentrations of two sunscreen ingredients produced slight, reversible dermal irritation. Each sunscreen ingredient contained 5% glyceryl oleate.

Glyceryl Ricinoleate

Glyceryl ricinoleate, when evaluated by a Draize skin test, was a mild irritant to rabbits.⁴ In a primary skin irritation test in rabbits, glyceryl ricinoleate was classified as a nonirritant. When rabbits were tested with products containing 5.6% glyceryl ricinoleate in a single-insult occlusive patch test, the products had either no (four of five tests) or mild (one of five tests) irritation potentials.

Glyceryl Rosinate

A primary irritation index (PII) of 3.40 (potential for severe irritation-warning label may be considered) was reported in an occlusive patch test evaluating the skin irritation potential of undiluted, purified ester gum-2-octyldodecyl myristate (contains 50% glyceryl rosinate and 50% octyldodecyl myristate) in rabbits.²⁵ Follicular hyperkeratosis (comedone formation) was not observed in another study in which the same undiluted test substance was applied to the ears of rabbits.

Glyceryl Stearate and Glyceryl Stearate SE

Glyceryl stearate and glyceryl stearate/SE at concentrations of up to 100% were reported to be mildly irritating or non-irritating to the skin of rabbits.¹ In seven guinea pig sensitization studies, it was concluded that neither glyceryl stearate nor glyceryl stearate/SE was capable of inducing sensitization.

Human

Glyceryl Caprylate

Glyceryl caprylate (15%) did not induce skin irritation or sensitization in a repeated insult patch test (RIPT) involving 63 healthy subjects, 58 of whom completed the study.²⁵

Glyceryl Hydrogenated Rosinate

Neither skin irritation nor sensitization was observed in any of the 51 subjects patch tested (semi-occlusive patches) with a material consisting of 20% hydrogenated purified ester gum-2-octyldodecyl myristate and 80% white petrolatum (a.k.a. hydrogenated PEGMOD [20]).²⁵ (Because hydrogenated purified ester gum-2-octyldodecyl myristate is a trade mixture consisting of 50% hydrogenated glyceryl rosinate and 50% octyldodecyl myristate, the effective concentration of hydrogenated glyceryl rosinate in the test material is 10%.) The subjects were challenged at a new test site, but not at the original site.

Glyceryl Laurate

Glyceryl laurate was tested at a concentration of 50% w/v, in liquid paraffin, in a RIPT (Finn chambers) involving 91 healthy human subjects.²⁵ Glyceryl laurate induced mild, erythematous reactions during induction in most of the subjects and questionable reactions in seven subjects during the challenge phase. Reactions ranged from mild to moderate erythema (score = 2) during induction and challenge phases.

The skin irritation and sensitization potential of glyceryl laurate was evaluated in a second RIPT (Finn chambers) using 107 healthy subjects, 93 of whom completed the study.²⁵ Glyceryl laurate was tested at a concentration of 25% in liquid paraffin oil. Glyceryl laurate induced moderate erythema (score = 2) in eight subjects during induction and in one subject during the challenge phase. It was considered a sensitizer.

Glyceryl Linoleate

Glyceryl laurate was tested at a concentration of 50% w/v, in liquid paraffin, in a RIPT (Finn chambers) involving 91 healthy human subjects.²⁵ Glyceryl Linoleate did not induce skin irritation or sensitization in the 74 subjects who completed the study.

Glyceryl Myristate

The skin irritation and sensitization potential of glyceryl myristate was evaluated in a RIPT (Finn chambers) using 107 healthy subjects, 93 of whom completed the study.²⁵ It was tested at a concentration of 50% in paraffin oil. Glyceryl myristate did not induce irritation or sensitization.

Glyceryl Oleate

Two aqueous glyceryl oleate preparations (15% and 30% concentrations) and a fragrance preparation containing 19.0% glyceryl oleate were negative for cutaneous irritation when tested on human skin using single insult occlusive patch tests.³

Two sunscreen formulations containing 5% glyceryl oleate were considered mild compounds and caused no irritation in a cumulative occlusive patch test using human subjects.³

No signs of irritation or sensitization were observed in humans after repeated insult patch testing of a 15% aqueous glyceryl oleate preparation and a sunscreen formulation containing 5% glyceryl oleate.³ A few subjects involved in simultaneous photoallergy and phototoxicity tests had slight, transient erythematous responses. No positive reactions were observed at any irradiated site during induction and challenge phases of the photoallergy test.

The skin irritation and sensitization potential of glyceryl oleate was evaluated in a RIPT (Finn chambers) using 107 healthy subjects, 93 of whom completed the study.²⁵ Glyceryl oleate were tested at a concentration of 50% in paraffin oil. Glyceryl oleate did not induce irritation or sensitization.

Glyceryl Rosinate

Skin irritation was not observed in 12 healthy volunteers patch tested (occlusive patches) with a lipstick containing 1.0% glyceryl rosinate.²⁵ Neither skin irritation nor sensitization was observed in 78 healthy volunteers patch tested (occlusive patches) with the same product in a repeated insult patch test.

The contact sensitization potential of three product formulations containing glyceryl rosinate was evaluated in three maximization assays (healthy human subjects), respectively.²⁵ Results were negative for the following three study groups: foundation containing 4.0% glyceryl rosinate (25 subjects), blush containing 2.0% glyceryl rosinate (27 subjects), and lip gloss containing 2.0% glyceryl rosinate (27 subjects).

Skin irritation and sensitization were observed in one of 49 subjects patch tested (RIPT, semi-occlusive patches) with a material consisting of 20% purified ester gum-2-octyldodecyl myristate and 80% white petrolatum (a.k.a. PEGMODWP-20).²⁵ (Because purified ester gum-2-octyldodecyl myristate is a trade mixture consisting of 50% glyceryl rosinate and 50% octyldodecyl myristate, the effective concentration of glyceryl rosinate in the test material is 10%.) The challenge reaction was observed at the original test site, but not at the new site. It was concluded that the positive reaction observed was unique to that individual.

Glyceryl Stearate

Single and repeated insult patch tests used to evaluate human skin irritation and sensitization potential of glyceryl stearate and glyceryl stearate/SE showed both ingredients to be nonsensitizing and nonirritating.¹

Allergenicity

Non-Human

Glyceryl Rosinate

The reaction of rosin with glycerol to form two esterification products (glyceryl triabietate [GTA] and glycerol esterified tall oil rosin [TORG]), in effect, reduced the allergenicity of rosin.²⁵ GTA results from the esterification of glycerol with abietic acid, the major component of rosin.²⁵ The incidence of positive challenge reactions in 15 guinea pigs tested was as follows: 1 (8.3% GTA), 2 (10% TORG), 3 (0.93% and 2.8% GTA), and 9 (20% gum rosin). Glyceryl diabietate and glyceryl monoabietate induced either the same incidence or a higher incidence of sensitization in other experiments (similar test groups) in the same study.

Human

Glyceryl Ricinoleate

In human single-insult occlusive patch tests, no indication of skin irritation potential was observed in the two products tested (each contained 5.6% glyceryl ricinoleate).⁴

Glyceryl Rosinate

Data on 12 patients suspected of having gum rosin allergy indicated that sensitization to Portuguese gum rosin exhibited a dose-response relationship (0.001% to 20%).²⁵ In the same study, the incidence of positive reactions to Portuguese gum rosin in a second group of 12 patients with gum rosin allergy was summarized as follows: 0.001% gum rosin (0 to 1 patient), 0.01% gum rosin (2 to 3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients), and 10% gum rosin (10 to 12 patients). These data were based on patch tests with serial dilutions of Portuguese gum rosin in petrolatum.

The esterification of rosin with glycerol, in effect, reduced the allergenicity of rosin in dermatitis patients.²⁵ Five of eight patients had positive reactions to 10% tall oil rosin in petrolatum, whereas four of eight patients had positive reactions to 20% glycerol-esterified tall oil rosin in petrolatum. Additionally, seven of eight patients had positive reactions to 5% Portuguese gum rosin in petrolatum and three of eight patients had positive reactions to 20% glycerol-esterified gum rosin in petrolatum.

Glyceryl-1-monoabietate was identified as a contact allergen in another study evaluating the allergenicity of rosin and its esterification products.²⁵ Abietic acid (esterified to form glyceryl-1-monoabietate) is a main component of rosin, and, furthermore, clinical data indicate that it is easily oxidized to form contact allergens (e.g., 15-hydroperoxyabietic acid and its methyl ester). It is also important to note that oxidation products of abietic acid and dehydroabietic acid (also a main component of rosin) that can be formed during storage have been found to be allergenic.

Phototoxicity

Glyceryl Isostearate

No evidence of significant cutaneous reactions, with or without UV irradiation, was found when the phototoxicity and photoallergenicity potential of glyceryl isostearate was evaluated using 20 guinea pigs.²⁵

Glyceryl Rosinate

Phototoxicity was not induced in a group of 10 healthy volunteers tested with a lipstick containing 1.0% glyceryl rosinate. Patches were not applied to test sites.²⁵ Similarly, photoallergenicity was not induced in a group of 26 healthy volunteers patch tested (occlusive patches) with the same product in a repeat insult patch test.

Glyceryl Stearate

Products containing 2% glyceryl stearate were non-phototoxic and non-photoallergic.¹

Ocular Irritation

Ocular irritation studies are summarized in Table 12.

Undiluted glyceryl behenate and glyceryl palmitate/stearate were non-irritating to rabbit eyes, and undiluted glyceryl rosinate was slight irritating.^{20,21,23}

Glyceryl Citrate/Lactate/Linoleate/Oleate

Glyceryl citrate/lactate/linoleate/oleate was not classified as ocular irritants in rabbits.²⁵

Glyceryl Isostearate

Glyceryl isostearate was not classified as ocular irritants in rabbits.²⁵

Glyceryl Laurate

Glyceryl laurate was not classified as ocular irritants in rabbits.²⁵

Glyceryl Oleate

Minimal to moderate eye irritation was produced by undiluted glyceryl oleate, 50% glyceryl oleate in corn oil, and a fragrance preparation containing 19.0% glyceryl oleate when administered to rabbits.³ A formulation containing 5% glyceryl oleate administered at a 0.1 ml dose to rabbit eyes induced slight conjunctivitis.

Glyceryl Ricinoleate

Glyceryl ricinoleate was nonirritating to rabbit eyes in a primary eye irritation test, and in a Draize test, it was mildly irritating to rabbit eyes from which it was not rinsed but nonirritating to rabbit eyes from which it had been rinsed 2 and 4 sec after instillation.⁴ Various products containing glyceryl ricinoleate were tested for irritation potential in rabbit eyes. Of eight tests, two products demonstrated no irritation potential, five products had a minimal irritation potential, and one product had a mild irritation potential.

Glyceryl Rosinate

Undiluted, purified ester gum-2-octyldodecyl myristate (contains 50% glyceryl rosinate and 50% octyldodecyl myristate) was not irritating to the eyes of rabbits.²⁵

Glyceryl Stearate

In primary eye irritation studies, glyceryl stearate and glyceryl stearate/SE at concentrations up to 100% were mildly irritating or non-irritating when instilled in the eyes of rabbits.¹

Case Reports

Case reports of reactions to use of formulations containing several of the monoglyceryl monoesters are described in Table 13.⁴⁵⁻⁴⁹

Glyceryl Isostearate

Two case reports indicated skin reactions to two cosmetic products containing glyceryl isostearate, as well as positive patch test reactions to this ingredient.²⁵

SUMMARY

In 1982, the Panel concluded that glyceryl stearate and glyceryl stearate SE are safe for topical application to humans. Since that time, the Panel has issued final reports on other monoglyceryl monoesters, finding them all safe as used in cosmetic products; an additional 8 monoglyceryl monoesters that are cosmetic ingredients and have not been reviewed by the Panel have also been identified. This safety assessment is a compilation of these 45 monoglyceryl monoesters, and these ingredients are similar because they are all constituted of the esterification products of glycerin and fatty acids. Most of the monoglyceryl monoesters included in this safety assessment are reported to function as skin conditioning agents.

Twenty-five of the 45 ingredients included in this safety assessment are in use, and glyceryl stearate has the highest frequency of use, 5153 formulations. Glyceryl stearate also has the highest maximum use concentration in leave-on formulations (17% in a deodorant), and glyceryl ricinoleate has the second highest maximum use concentration in leave-on formulations (15.2% in lipstick); overall, glyceryl rosinatate is reported to have the greatest maximum reported used concentration (96% in a depilatory). Most of the in-use ingredients have been reviewed previously by the Panel; for the majority of these ingredients, the frequency of use has increased but the concentration of use has remained the same or decreased.

According to the FDA, many of the monoglyceryl monoesters are direct food substances affirmed as GRAS for human and/or animal use, are permitted as direct food additives, or are permitted as indirect food additives. Monoglyceryl monoesters can act as penetration enhancers.

In rats fed a diet containing radiolabeled glycerol ester of wood rosin, most of the radioactivity was excreted in the feces, primarily unchanged; results were similar with 1-day and 10-day dietary administration. In rats dosed by gavage, low levels of radioactivity were absorbed by the rats following dosing, and the radioactive species excreted in bile appeared to be a hydrolyzed product of the administered test substance; no intact test substance was present. Radioactivity was excreted in bile within 4 h after dosing and was detectable in all samples collected for 24 h post dose. The total amount of radioactivity excreted in bile during the 24-h collection period ranged from 1.6-2.9% of the dose.

In a 24-h patch test, the dermal LD₅₀s of glyceryl rosinatate and of glycerides, C16-18 and C18-hydroxy mono- and di-are >10 and >2 g/kg bw in rabbits, respectively. In oral studies, the LD₅₀ of glyceryl behenate and glyceryl hydrogenated rosin is >2 g/kg, of glyceryl stearate is >5 g/kg, and of glyceryl rosinatate is >10 g/kg. In a 90-day dietary study, NOAEL for glyceryl hydrogenated rosinatate in rats was 10,000 ppm. For glyceryl rosinatate, the NOAEL for rats was 1% in one 90 day study, and 2500 mg/kg bw/day in another. In a 28-day study of glycerides, C8-18 and C18-unsatd. mono- and di-, acetates in rats, the NOAEL was 1000 mg/kg bw/day.

Intravaginal dosing with 5% glyceryl oleate for 6 mos in monkeys did not induce vaginal inflammation or mucosal lesions in cervical vaginal tissues.

Glyceryl oleate was not a reproductive or developmental toxin in rats. The NOAELs for systemic toxicity (males and females), fertility (males and females), and development (F₁ generation) were 1000 mg/kg bw/day. No effects related to the administration of the test-article were observed in parental animals or offspring. In a reproductive and developmental toxicity study in which rats were dosed with 0, 100, 300 and 1000 mg/kg/day glycerides, C8-18 and C18-unsatd. mono- and di-, acetates in polyethylene glycol, no treatment-related effects were observed, and the NOAEL for parental fertility was 1000 mg/kg bw/day.

Glyceryl acetate was not mutagenic in an Ames test (≤10,000 µg/plate) or chromosomal aberration assay (≤5000 µg/plate) with or without metabolic activation; in a sister chromatid exchange assay, it was not genotoxic with metabolic activation, but without activation, a dose-dependent increase was observed in 2 trials, and a doubling of sister chromatid exchanges (SCEs) was produced with 5000 µg/ml. Glyceryl laurate was not mutagenic in an Ames test (≤5000 µg/plate), and glyceryl rosinatate was not mutagenic in an Ames test (≤500 µg/plate), mammalian chromosome assay (≤507 µg/ml), or unscheduled DNA synthesis test (≤102 µg/ml). Glycerides, C16-18 and C18-hydroxy mono- and di- (up to 10,000 mg/kg bw) was not genotoxic in a mouse micronucleus test

Undiluted glyceryl behenate, and glyceryl hydrogenated rosinat, and glyceryl rosinat were not irritating to rabbit skin. Glyceryl hydrogenated rosinat (challenge at up to 50%), glyceryl rosinat (challenge at 100%), and glyceride, C16-18 and C18 mono- and dihydroxy (25% at challenge) were not sensitizers in guinea pigs. In clinical testing, 5% glyceryl stearate was not irritating and glyceryl behenate (applied neat), glyceryl hydrogenated rosinat, and glyceryl rosinat were not sensitizers in HRIPTs. Case reports of reactions to use of formulations containing several of the monoglyceryl monoesters have been described.

Undiluted glyceryl behenate and glyceryl palmitate/stearate were non-irritating to rabbit eyes, and undiluted glyceryl rosinat was slight irritating.

TABLES

Table 1. Monoglyceryl Monoesters

Glyceryl Acetate*	Glyceryl Laurate
Glyceryl Adipate	Glyceryl Laurate SE
Glyceryl Alginate	Glyceryl Laurate/Oleate
Glyceryl Arachidate	Glyceryl Linoleate
Glyceryl Behenate	Glyceryl Linolenate
Glyceryl Caprate	Glyceryl Montanate
Glyceryl Caprylate	Glyceryl Oleate
Glyceryl Caprylate/Caprate	Glyceryl Oleate SE
Glyceryl Citrate/Lactate/Linoleate/Oleate	Glyceryl Oleate/Elaidate
Glyceryl Cocoate	Glyceryl Olivat*
Glyceryl Cocoate/Citrate/Lactate*	Glyceryl Palmitate
Glyceryl Erucate	Glyceryl Palmitate/Stearate
Glyceryl Ethylhexanoate*	Glyceryl Palmitoleate
Glyceryl Ethylhexanoate/Stearate/Adipate*	Glyceryl Pentadecanoate
Glyceryl Heptanoate*	Glyceryl Ricinoleate
Glyceryl Hydrogenated Rapeseedate*	Glyceryl Ricinoleate SE
Glyceryl Hydrogenated Rosinate	Glyceryl Rosinate
Glyceryl Hydrogenated Soyate	Glyceryl Stearate
Glyceryl Hydroxystearate	Glyceryl Stearate SE
Glyceryl Isopalmitate	Glyceryl Stearate/Malate*
Glyceryl Isostearate	Glyceryl Tallowate
Glyceryl Isotridecanoate/Stearate/ Adipate	Glyceryl Undecylenate
Glyceryl Lanolate	

*not previously reviewed by CIR

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. (2; CIR Staff)

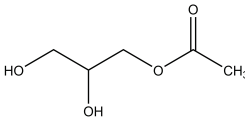
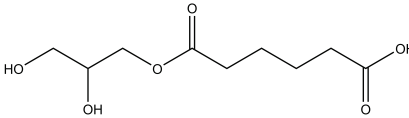
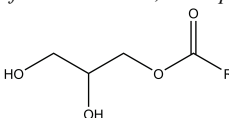
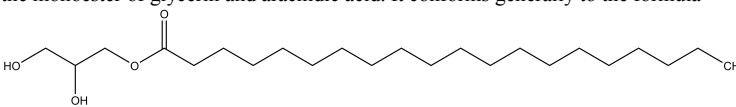
Ingredient CAS No.	Definition & Structure	Function(s)
Glyceryl Acetate 26446-35-5	the ester of acetic acid and glycerin 	skin conditioning agent - misc
Glyceryl Adipate 26699-71-8	the ester of glycerin and adipic acid that conforms to the formula: 	skin conditioning agent - emollient
Glyceryl Alginate	the ester of glycerin and alginic acid <i>(Alginic acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.)</i>  wherein RC(O)- represents the residue of alginic acid	skin conditioning agent - emollient; viscosity increasing agent – aq.
Glyceryl Arachidate 30208-87-8 50906-68-8	the monoester of glycerin and arachidic acid. It conforms generally to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent; viscosity increasing agent –non-aq

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. (2; CIR Staff)

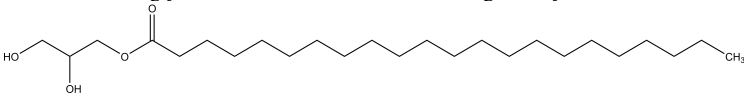
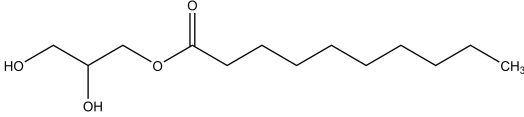
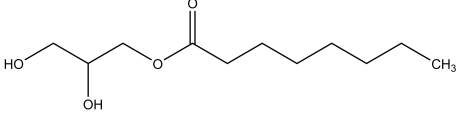
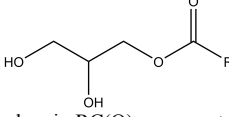
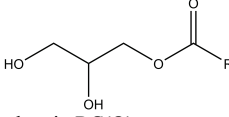
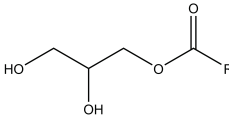
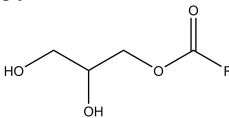
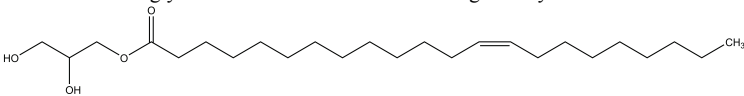
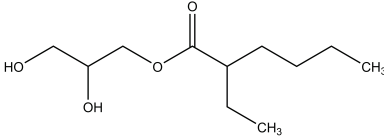
Ingredient CAS No.	Definition & Structure	Function(s)
Glyceryl Behenate 6916-74-1 77538-19-3 30233-64-8	the monoester of glycerin and behenic acid. It conforms generally to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Caprate 11139-88-1 26402-22-2	the monoester of glycerin and capric acid. It conforms to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Caprylate 26402-26-6	the monoester of glycerin and caprylic acid. It conforms to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Caprylate/Caprate	a monoester of glycerin esterified with a mixture of caprylic and capric acids.  wherein RC(O)- represents the residue of caprylic or capric acid	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Citrate/Lactate/Linoleate/Oleate	glycerin esterified with a blend of citric, lactic, linoleic and oleic acids  wherein RC(O)- represents the residue of citric, lactic, linoleic, or oleic acid	skin-conditioning agent - emollient
Glyceryl Cocoate 61789-05-7	the monoester of glycerin and coconut fatty acids. It conforms generally to the formula:  where RC(O)- represents the fatty acids derived from coconut oil	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Cocoate/Citrate/Lactate	glycerin esterified with a blend of coconut, citric and lactic acids  wherein RC(O)- represents the residue of coconut, citric, or lactic acid	skin-conditioning agent - emollient
Glyceryl Erucate 28063-42-5	the monoester of glycerin and erucic acid. It conforms generally to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Ethylhexanoate	the ester of glycerin and ethylhexanoic acid that conforms to the formula 	skin-conditioning agent - emollient

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. (2; CIR Staff)

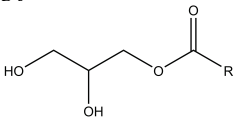
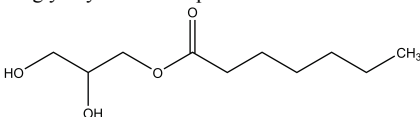
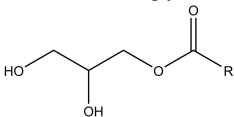
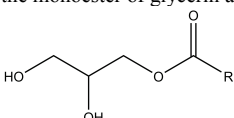
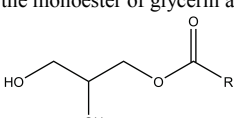
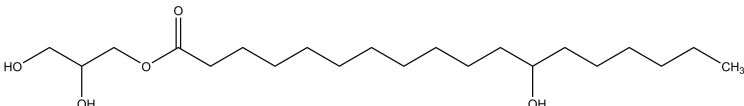
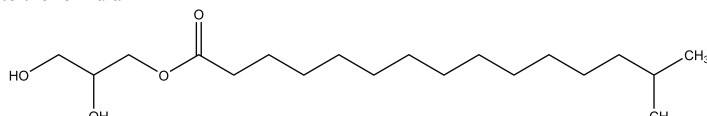
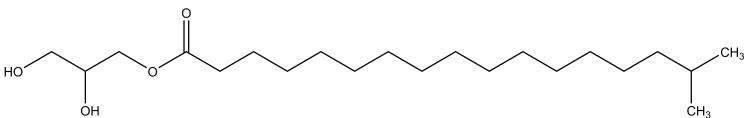
Ingredient CAS No.	Definition & Structure	Function(s)
Glyceryl Ethylhexanoate/Stearate/Adipate	glycerin esterified with a blend of 2-ethylhexanoic acid, stearic acid and adipic acid  wherein RC(O)- represents the residue of 2-ethylhexanoic, stearic, or adipic acid	skin-conditioning agent - occlusive
Glyceryl Heptanoate 26402-24-4	the glyceryl ester of heptanoic acid that conforms to the formula: 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Hydrogenated Rapeseedate	the monoester of glycerin and the fatty acids derived from hydrogenated rapeseed oil  wherein RC(O)- represents the residue of the fatty acids derived from hydrogenated rapeseed oil	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Hydrogenated Rosinate	the monoester of glycerin and hydrogenated mixed long chain acids derived from rosin  wherein RC(O)- represents the residue of the hydrogenated mixed long chain acids derived from rosin	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Hydrogenated Soyate	the monoester of glycerin and hydrogenated mixed long chain acids derived from soy  wherein RC(O)- represents the residue of the hydrogenated mixed long chain acids derived from soy	skin-conditioning agent - emollient
Glyceryl Hydroxystearate 1323-42-8	the monoester of glycerin and hydroxystearic acid. It conforms generally to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Isopalmitate	the monoester of glycerin and a branched chain 16 carbon aliphatic acid. It conforms to the formula  one example of an “iso”	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Isostearate 61332-02-3 66085-00-5	the monoester of glycerin and isostearic acid. It conforms generally to the formula  one example of an “iso”	skin-conditioning agent - emollient; surfactant – emulsifying agent

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. (2; CIR Staff)

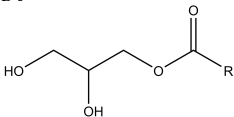
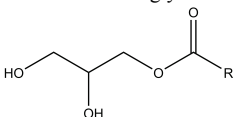
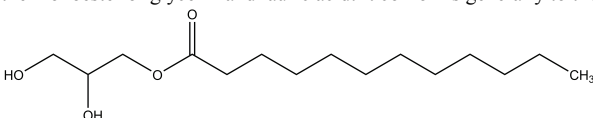
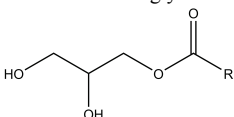
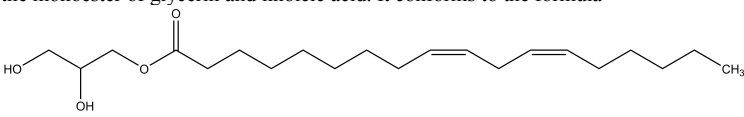
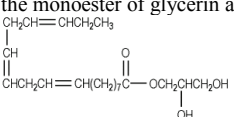
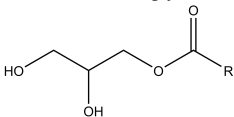
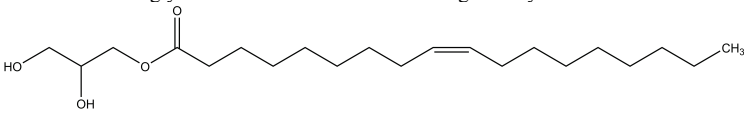
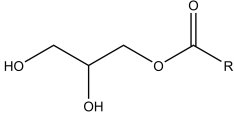
Ingredient CAS No.	Definition & Structure	Function(s)
Glyceryl Isotridecanoate/Stearate/Adipate	glycerin esterified with a blend of isotridecanoic acid, stearic acid and adipic acid  wherein RC(O)- represents the residue of isotridecanoic, stearic, or adipic acid	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Lanolate	the monoester of glycerin and lanolin acid  wherein RC(O)- represents the residue of lanolin acid	hair conditioning agent; skin-conditioning agent - emollient; surfactant - emulsifying agent
Glyceryl Laurate 142-18-7 27215-38-9 37318-95-9	the monoester of glycerin and lauric acid. It conforms generally to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Laurate SE	a self-emulsifying grade of Glyceryl Laurate that contains some sodium and/or potassium laurate	surfactant – emulsifying agent
Glyceryl Laurate/Oleate	the monoester of glycerin esterified with a blend of lauric and oleic acids  wherein RC(O)- represents the residue of lauric or oleic acid	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Linoleate 2277-28-3 26545-74-4 37348-65-5	the monoester of glycerin and linoleic acid. It conforms to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Linolenate 18465-99-1 56554-41-7	the monoester of glycerin and linolenic acid. It conforms to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Montanate 68476-38-0 71035-02-4	the monoester of glycerin and montan acid wax  wherein RC(O)- represents the residue of montan acid wax	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Oleate 111-03-5 161403-66-3 25496-72-4 37220-82-9 68424-61-3	the monoester of glycerin and oleic acid. It conforms generally to the formula 	fragrance ingredient; skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Oleate SE	a self-emulsifying grade of Glyceryl Oleate that contains some sodium and/or potassium oleate	surfactant – emulsifying agent
Glyceryl Oleate/Elaidate	a mixture of monoglycerides of oleic and elaidic acids  wherein RC(O)- represents the residue of elaidic or oleic acid	skin-conditioning agent - emollient; surfactant – emulsifying agent

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. (2; CIR Staff)

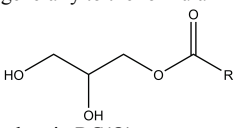
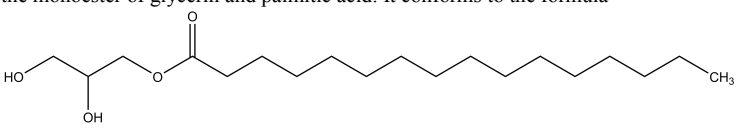
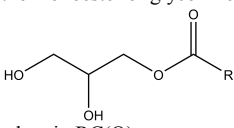
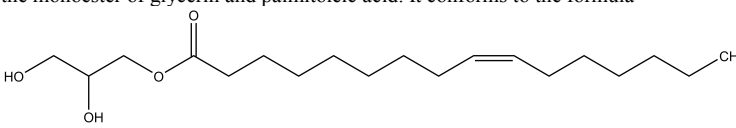
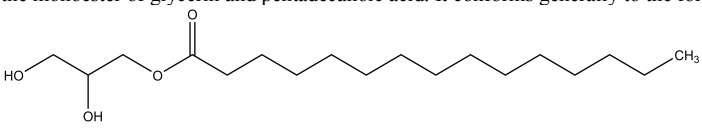
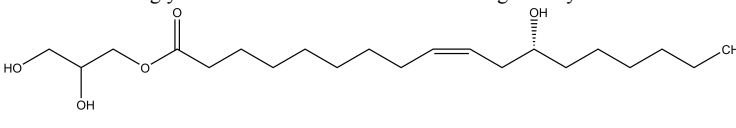
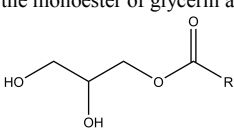
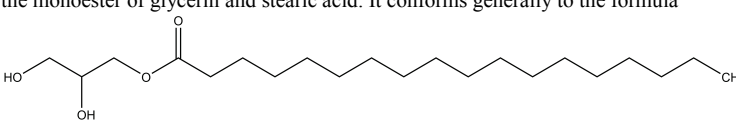
Ingredient CAS No.	Definition & Structure	Function(s)
Glyceryl Olivat	the monoester of glycerin and the fatty acids derived from olive oil. It conforms generally to the formula  wherein RC(O)- represents the fatty acids derived from olive oil	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Palmitate 26657-96-5 542-44-9	the monoester of glycerin and palmitic acid. It conforms to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Palmitate/Stearate 68002-71-1	the monoester of glycerin esterified with a blend of palmitic and stearic acids  wherein RC(O)- represents the residue of palmitic or stearic acid	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Palmitoleate	the monoester of glycerin and palmitoleic acid. It conforms to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Pentadecanoate 122636-37-7	the monoester of glycerin and pentadecanoic acid. It conforms generally to the formula 	surfactant – emulsifying agent
Glyceryl Ricinoleate 1323-38-2 141-08-2 5086-52-2	the monoester of glycerin and ricinoleic acid. It conforms generally to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Ricinoleate SE	a self-emulsifying grade of glyceryl ricinoleate containing sodium and/or potassium stearate.	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Rosinate 8050-31-5	the monoester of glycerin and mixed long chain acids derived from rosin  wherein RC(O)- represents the residue of mixed long chain acids derived from rosin	depilating agent; fragrance ingredient; skin-conditioning agent - emollient; surfactant - emulsifying agent
Glyceryl Stearate 11099-07-3 123-94-4 31566-31-1 85666-92-8	the monoester of glycerin and stearic acid. It conforms generally to the formula 	fragrance ingredient; skin-conditioning agent – emollient; surfactant - emulsifying agent
Glyceryl Stearate SE 11099-07-3 85666-92-8	a self-emulsifying grade of glyceryl stearate that contains some sodium and/or potassium stearate	surfactant - emulsifying agent

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. (2; CIR Staff)

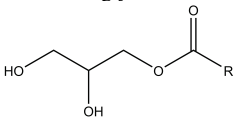
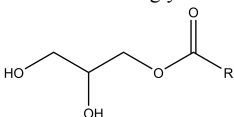
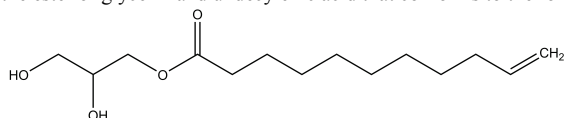
Ingredient CAS No.	Definition & Structure	Function(s)
Glyceryl Stearate/Malate	the ester of glycerin esterified with a blend of stearic and malic acids  wherein RC(O)- represents the residue of stearic or malic acid	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Tallowate	the monoester of glycerin and tallow fatty acids. It conforms generally to the formula  wherein RC(O)- represents the residue of the fatty acids derived from tallow	skin-conditioning agent - emollient; surfactant – emulsifying agent
Glyceryl Undecylenate 123759-97-7 62285-15-8	the ester of glycerin and undecylenic acid that conforms to the formula 	skin-conditioning agent - emollient; surfactant – emulsifying agent

Table 3. Components Previously Reviewed

Component	Conclusion	Reference
Glycerin	safe in cosmetics in the present practices of use and concentration (was used in 15,654 formulations, 10,046 of which were leave-ons; the maximum use concentrations were 79.2% in leave-on products, 99.4% in rinse-off products, and 47.9% in products diluted for the bath)	8
Acetic Acid	safe in the present practices of use and concentration	9
Adipic Acid	safe in the present practices of use and concentration	10
Alginic Acid	safe in the present practices of use and concentration	11
Citric Acid	safe in the present practices of use and concentration	12
Coconut Acid	safe for use in cosmetic products	13
Hydrogenated Rapeseed Oil	safe in the present practices of use and concentration	14
Hydrogenated Soybean Oil	safe in the present practices of use and concentration	14
Hydroxystearic Acid	safe as a cosmetic ingredient in the present practices of use	15
Isostearic Acid	safe as a cosmetic ingredient in the present practices of use	16
Lactic Acid	safe for use in cosmetic products at concentrations ≤10%, at final formulation pH ≥3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations ≤30%, at final formulation pH ≥3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection	17
Lanolin Acid	safe for topical application to humans in the present practice of use and concentration	18
Lauric Acid	safe in the present practices of use and concentration	19
Malic Acid	safe for use as a pH adjuster in cosmetic formulations; data are insufficient to determine the safety for any other functions	9
Oleic Acid	safe in the present practices of use and concentration	19
Olea Europaea (Olive) Fruit Oil	safe in the present practices of use and concentration	14
Palmitic Acid	safe in the present practices of use and concentration	19
Ricinoleic Acid	safe in the present practices of use and concentration	5
Stearic Acid	safe in the present practices of use and concentration	19

Table 4. Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Glyceryl Alginate				Glyceryl Behenate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	NR	1	NR	0.5	90	NR	0.27-2.5	2-5
Duration of Use								
Leave-On	NR	1	NR	0.5	81	NR	0.3-2.5	2-5
Rinse-Off	NR	NR	NR	NR	9	NR	0.27	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	20	NR	0.3-1.5	2
Incidental Ingestion	NR	NR	NR	NR	7	NR	NR	NR
Incidental Inhalation-Spray	NR	1 ^a	NR	0.5 ^b	22 ^a , 13 ^b	NR	0.48 ^a	5 ^a
Incidental Inhalation-Powder	NR	NR	NR	0.5 ^b	13 ^b	NR	0.45-2 ^c	NR
Dermal Contact	NR	1	NR	0.5	65	NR	0.3-2.5	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	5
Hair - Non-Coloring	NR	NR	NR	NR	3	NR	0.48	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	2	NR	0.27	NR
Mucous Membrane	NR	NR	NR	NR	7	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Glyceryl Caprate				Glyceryl Caprylate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	57	NR	1	NR	190	NR	0.001-1.5	NR
Duration of Use								
Leave-On	46	NR	1	NR	177	NR	0.001-1.5	NR
Rinse-Off	11	NR	NR	NR	13	NR	0.01-1.5	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	4	NR	NR	NR	29	NR	0.03-1	NR
Incidental Ingestion	7	NR	NR	NR	20	NR	0.3-1	NR
Incidental Inhalation-Spray	7 ^a , 8 ^b	NR	1	NR	33 ^a , 37 ^b	NR	1 ^a	NR
Incidental Inhalation-Powder	8 ^b , 1 ^c	NR	NR	NR	16; 37 ^b	NR	0.98; 0.001-1 ^c	NR
Dermal Contact	50	NR	NR	NR	161	NR	0.001-1.5	NR
Deodorant (underarm)	5 ^a	NR	pump spray: 1	NR	2 ^a	NR	1.5	NR
Hair - Non-Coloring	NR	NR	NR	NR	6	NR	0.01-1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	NR	NR	NR	20	NR	0.3-1	NR
Baby Products	1	NR	NR	NR	NR	NR	NR	NR
	Glyceryl Caprylate/Caprate				Glyceryl Citrate/Lactate/Linoleate/Oleate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	2	1	NR	2	NR	NR	0.0004-0.004	NR
Duration of Use								
Leave-On	1	1	NR	NR	NR	NR	NR	NR
Rinse-Off	1	NR	NR	NR	NR	NR	0.0004-0.004	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1	NR	NR	2 ^b	NR	NR	0.0004	NR
Incidental Inhalation-Powder	NR	NR	NR	2 ^b	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	2	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	NR	NR	0.0004-0.004	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 4. Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Glyceryl Cocoate				Glyceryl Erucate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	14	1	1-2	0.3-5	NR	NR	NR	0.5
Duration of Use								
Leave-On	11	NR	2	0.3-2	NR	NR	NR	0.5
Rinse-Off	3	1	1-2	1-5	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	1	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.3-2	NR	NR	NR	NR
Incidental Inhalation-Spray	10 ^b	NR	NR	NR	NR	NR	NR	0.5
Incidental Inhalation-Powder	10 ^b	NR	NR	NR	NR	NR	NR	0.5 ^b
Dermal Contact	11	1	2	1-5	NR	NR	NR	0.5
Deodorant (underarm)	NR	NR	2 (pump spray)	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	NR	1	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	0.3-4	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Glyceryl Ethylhexanoate/Stearate/Adipate				Glyceryl Hydrogenated Rosinate			
	2015 ²⁷		2014 ^{28,29}		2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	39		0.6-3		29	NR	3-76.8	NR
Duration of Use								
Leave-On	38		0.6-3		22	NR	3-10	NR
Rinse-Off	1		NR		7	NR	65-76.8	NR
Diluted for (Bath) Use	NR		NR		NR	NR	NR	NR
Exposure Type								
Eye Area	21		0.8-3		14	NR	3-4.8	NR
Incidental Ingestion	1		NR		6	NR	4-10	NR
Incidental Inhalation-Spray	1 ^a		NR		1 ^a	NR	6.5 ^a	NR
Incidental Inhalation-Powder	4		1-1.4		NR	NR	NR	NR
Dermal Contact	37		0.8-3		9	NR	65-76.8	NR
Deodorant (underarm)	NR		NR		NR	NR	NR	NR
Hair - Non-Coloring	1		NR		NR	NR	6.5	NR
Hair-Coloring	NR		NR		NR	NR	NR	NR
Nail	NR		NR		NR	NR	NR	NR
Mucous Membrane	1		NR		6	NR	4-10	NR
Baby Products	NR		NR		NR	NR	NR	NR
	Glyceryl Hydroxystearate				Glyceryl Isostearate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	14	32	0.5-2	0.8-2	104	53	0.3-2	0.3-6
Duration of Use								
Leave-On	14	22	0.5-2	0.8-2	14	53	0.8-2	0.5-6
Rinse-Off	NR	10	NR	NR	90	NR	0.3-1.5	0.3-3
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	1
Exposure Type								
Eye Area	10	NR	1-2	2	4	23	NR	0.5-2
Incidental Ingestion	4 ^a	1	NR	NR	1	NR	NR	NR
Incidental Inhalation-Spray	NR	10 ^a ; 8 ^b	NR	0.8 ^a ; 2 ^b	5a	3 ^a ; 1 ^b	NR	3 ^a ; 2 ^b
Incidental Inhalation-Powder	NR	8 ^b	0.5-0.9 ^c	2 ^b	NR	1; 1 ^b	0.8-1 ^c	2 ^b
Dermal Contact	13	31	0.5-0.9	0.8-2	14	53	0.8-2	0.3-6
Deodorant (underarm)	NR	NR	0.9 (not spray)	2 ^a	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	1	NR	0.3	NR
Hair-Coloring	NR	NR	NR	NR	78	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	2	NR	NR	1	NR	NR	1
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 4. Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Glyceryl Isotridecanoate/Stearate/Adipate				Glyceryl Lanolate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	1	NR	NR	NR	1	3	NR	NR
Duration of Use								
Leave-On	1	NR	NR	NR	1	3	NR	NR
Rinse-Off	NR	NR	NR	NR	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1 ^a	NR	NR	NR	1 ^a	1 ^a , 2 ^b	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	2 ^b	NR	NR
Dermal Contact	1	NR	NR	NR	1	3	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Glyceryl Laurate				Glyceryl Linoleate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	210	29	0.000065-4.5	0.1-4	87	17	0.000055-4.6	0.7-1
Duration of Use								
Leave-On	101	12	0.000065-0.5	0.4-4	70	13	0.000055-4.6	0.7-1
Rinse-Off	106	17	0.000065-4.5	0.1-4	17	4	NR	0.7-1
Diluted for (Bath) Use	3	NR	1	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	9	3	0.000065-0.48	0.1	8	1	2.5	NR
Incidental Ingestion	8	NR	NR	NR	1	3	0.056-2.5	0.7
Incidental Inhalation-Spray	1; 24 ^a ; 10 ^b	1; 5 ^a	0.2 ^a	1; 0.4 ^a	1; 16 ^a ; 30 ^b	1; 2 ^a ; 2 ^b	0.000055-0.0002 ^a	1 ^b
Incidental Inhalation-Powder	1; 10 ^b ; 3c	NR	0.1-0.5 ^c	NR	30 ^b ; 2 ^c	1	0.003-0.75 ^b	1 ^b
Dermal Contact	176	20	0.000065-4.5	NR	64	14	0.0002-2.5	0.7-1
Deodorant (underarm)	15 ^a	4 ^a	NR	0.1-4	NR	NR	NR	NR
Hair - Non-Coloring	26	9	0.088-1.5	0.3-2	17	NR	0.000055	NR
Hair-Coloring	NR	NR	NR	NR	1	NR	NR	NR
Nail	NR	NR	NR	NR	4	NR	0.019-4.6	NR
Mucous Membrane	72	7	0.000065-4.5	0.3	2	3	NR	0.7
Baby Products	6	NR	NR	NR	2	NR	NR	NR
	Glyceryl Linolenate				Glyceryl Oleate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	2002 ⁵⁰	2014 ^{28,29}	2004 ⁵⁰
Totals*	70	10	0.00045-0.4	0.7-1	663	112	0.0001-3	0.00002-5
Duration of Use								
Leave-On	55	9	0.00045-0.4	0.7-1	231	92	0.0001-3	0.00002-3
Rinse-Off	15	1	NR	0.7-1	411	19	0.1-2.7	0.02-5
Diluted for (Bath) Use	NR	NR	NR	NR	21	1	NR	0.2-3
Exposure Type								
Eye Area	7	1	0.2	NR	87	7	0.0075-2.3	0.008-0.01
Incidental Ingestion	1	3	0.046-0.2	0.7	34	18	0.0001-0.075	0.01-0.3
Incidental Inhalation-Spray	1; 12 ^a ; 20 ^b	2 ^a ; 2 ^b	0.00045 ^a	1 ^b	2; 48 ^a ; 22 ^b	1; 27 ^a ; 20 ^b	1.4; 0.0092 ^a	0.0003; 0.00002-0.5 ^a ; 0.1-2 ^b
Incidental Inhalation-Powder	20 ^b ; 2 ^c	2 ^b	NR	1 ^b	7; 22 ^b ; 2 ^c	2; 20 ^b	0.0028-3 ^c	0.01-3; 0.1-2 ^b
Dermal Contact	47	7	0.09-0.2	0.7-1	493	73	0.0075-3	0.00002-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	0.1-2.7	NR
Hair - Non-Coloring	17	NR	0.00045	NR	118	21	0.0092-2.7	0.08-0.2
Hair-Coloring	1	NR	NR	NR	5	NR	2	0.02
Nail	4	NR	0.001-0.4	NR	NR	NR	0.015	NR
Mucous Membrane	2	NR	0.046-0.2	0.7	262	19	0.0001-2.4	0.01-5
Baby Products	2	NR	NR	NR	13	2	NR	0.01-3

Table 4. Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Glyceryl Oleate/Elaidate				Glyceryl Palmitate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶
Totals*	4	NR	NR	0.3-2	4	NR	NR	NR
Duration of Use								
Leave-On	2	NR	NR	0.3-2	3	NR	NR	NR
Rinse-Off	2	NR	NR	NR	1	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2 ^a	NR	NR	2 ^a , 2 ^b	3 ^b	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	2 ^b	3 ^b	NR	NR	NR
Dermal Contact	2	NR	NR	0.3-2	4	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Glyceryl Ricinoleate				Glyceryl Ricinoleate SE			
	2015 ²⁷	2002 ⁵	2014 ^{28,29}	2004 ⁵	2015 ²⁷	2002 ⁵	2014 ^{28,29}	2004 ⁵
Totals*	42	16	1.5-15.2	2-12	NR	NR	6.8	NR
Duration of Use								
Leave-On	40	15	1.5-15.2	2-12	NR	NR	6.8	NR
Rinse-Off	2	1	NR	NR	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	10	7	1.5-11.6	2-12	NR	NR	6.8	NR
Incidental Ingestion	16	5	11.9-15.2	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	6 ^a	1 ^a , 2 ^b	NR	12 ^a	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	2 ^b	NR	NR	NR	NR	NR	NR
Dermal Contact	26	11	1.5-12.6	2-12	NR	NR	6.8	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	N	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	18	5	11.9-15.2	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Glyceryl Rosinate				Glyceryl Stearate			
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶	2015 ²⁷	1976 ¹	2014 ^{28,29}	1976 ¹
Totals*	50	4	0.018-96	0.06-12	5153	1371	0.0002-18.9	0.1-50
Duration of Use								
Leave-On	36	3	0.018-8	0.06-12	4229	1086	0.0002-17	0.1-50
Rinse-Off	14	1	2.6-96	3	914	284	0.006-18.9	0.1-25
Diluted for (Bath) Use	NR	NR	NR	NR	10	1	1-10	0.1-1
Exposure Type								
Eye Area	6	2	0.3-8	12	566	115	0.014-9	0.1-50
Incidental Ingestion	20	NR	0.48-0.5	6	30	NR	0.0002-3	NR
Incidental Inhalation-Spray	2 ^a	NR	NR	NR	17; 1705 ^a , 1380 ^b	5; 308 ^a , 212 ^b	2-14; 0.5-4.8 ^a , 2.3-6 ^b	0.1-25; 0.1-25 ^{a,b}
Incidental Inhalation-Powder	1	NR	NR	NR	20; 1380 ^b , 28 ^c	137; 212 ^b , 11 ^c	0.05-3; 2.3-6 ^b , 0.0083-10 ^c	0.1-25
Dermal Contact	23	2	0.018-96	0.6-10	4346	1167	0.0083-18.9	0.1-25; 0.1-25 ^b
Deodorant (underarm)	NR	NR	NR	NR	42 ^a	NR	0.25-17	NR
Hair - Non-Coloring	1	NR	2.6	NR	318	97	0.15-4.8	0.1-25
Hair-Coloring	2	NR	NR	3	200	29	0.9-7	0.1-10
Nail	NR	NR	NR	NR	11	15	0.006-6	1-50
Mucous Membrane	20	NR	0.48-0.5	0.4-6	182	36	0.0002-18	0.1-25
Baby Products	NR	NR	NR	NR	33	11	1.8	0.1-5

Table 4. Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses	Max Conc of Use (%)	
	Glyceryl Stearate SE				Glyceryl Stearate/Malate		
	2015 ²⁷	1976 ¹	2014 ^{28,29}	1976 ¹	2015 ²⁷	2014 ^{28,29}	
Totals*	1420	217	0.001-10	0.1-25	NR	0.25	
Duration of Use							
Leave-On	944	196	0.001-10	0.1-25	NR	0.25	
Rinse-Off	476	21	0.5-6	0.1-25	NR	NR	
Diluted for (Bath) Use	NR	NR	6	NR	NR	NR	
Exposure Type							
Eye Area	59	40	0.2-5	0.1-5	NR	0.25	
Incidental Ingestion	1	NR	NR	NR	NR	NR	
Incidental Inhalation-Spray	1; 565 ^a ; 253 ^b	1; 36 ^a ; 24 ^b	3; 0.001-3 ^a ; 2-3.9 ^b	1-5; 0.1-25 ^{a,b}	NR	NR	
Incidental Inhalation-Powder	253 ^b ; 3 ^c	24 ^b	2-3.9 ^b ; 0.2-10 ^c	0.1-25 ^b	NR	NR	
Dermal Contact	1013	205	0.2-10	0.1-25	NR	0.25	
Deodorant (underarm)	1 ^a	NR	NR	NR	NR	NR	
Hair - Non-Coloring	45	7	0.001-4	1-25	NR	NR	
Hair-Coloring	340	NR	3-6	NR	NR	NR	
Nail	1	NR	NR	NR	NR	NR	
Mucous Membrane	22	2	3-6	10-25	NR	NR	
Baby Products	3	NR	NR	NR	NR	NR	
	Glyceryl Undecylenate						
	2015 ²⁷	1998 ⁶	2014 ^{28,29}	1999 ⁶			
Totals*	17	2	1	NR			
Duration of Use							
Leave-On	15	2	1	NR			
Rinse-Off	2	NR	1	NR			
Diluted for (Bath) Use	NR	NR	NR	NR			
Exposure Type							
Eye Area	2	NR	NR	NR			
Incidental Ingestion	NR	NR	NR	NR			
Incidental Inhalation-Spray	7 ^a ; 6 ^b	2 ^a	NR	NR			
Incidental Inhalation-Powder	6 ^b	NR	NR	NR			
Dermal Contact	14	2	1	NR			
Deodorant (underarm)	NR	NR	NR	NR			
Hair - Non-Coloring	2	NR	NR	NR			
Hair-Coloring	NR	NR	NR	NR			
Nail	NR	NR	NR	NR			
Mucous Membrane	NR	NR	NR	NR			
Baby Products	NR	NR	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.

^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 – no reported use

Table 5. Ingredients Currently Not Reported to be Used

Glyceryl Acetate
 Glyceryl Adipate
 Glyceryl Alginate (was in use in 1998)
 Glyceryl Arachidate
 Glyceryl Cocoate/Citrate/Lactate
 Glyceryl Erucate (was in use in 1998)
 Glyceryl Ethylhexanoate
 Glyceryl Heptanoate
 Glyceryl Hydrogenated Rapeseedate
 Glyceryl Hydrogenated Soyate

Glyceryl Isopalmitate
 Glyceryl Laurate SE
 Glyceryl Laurate/Oleate
 Glyceryl Montanate
 Glyceryl Oleate SE
 Glyceryl Olivatate
 Glyceryl Palmitate/Stearate
 Glyceryl Palmitoleate
 Glyceryl Pentadecanoate
 Glyceryl Tallowate

Table 6. Food Additive Status

Ingredient	CFR Citation
GRAS Ingredients for Human Use	
Glyceryl Behenate	21CFR184.1328
Glyceryl Laurate	21CFR184.1505
Glyceryl Linoleate	21CFR184.1505
Glyceryl Oleate	21CFR184.1323
Glyceryl Palmitate	21CFR184.1324
Glyceryl Palmitate/Stearate	21CFR184.1329
Glyceryl Stearate	21CFR184.1324
GRAS Ingredients for Animal Use	
Glyceryl Caprate	21CFR582.4505
Glyceryl Caprylate/Caprate	21CFR582.4505
Glyceryl Laurate	21CFR582.4505
Glyceryl Laurate/Oleate	21CFR582.4505
Glyceryl Palmitate/Stearate	21CFR582.4505
Glyceryl Stearate	21CFR582.4505
	21CFR582.1324
Direct Food Additives	
Glyceryl Hydrogenated Rapeseedate	21CFR172.736
Glyceryl Hydrogenated Rosinate	21CFR172.615
Glyceryl Hydrogenated Soyate	21CFR172.736
Glyceryl Rosinate	21CFR172.615; 21CFR172.735
Prior-Sanctioned Food Ingredients	
Glycerol Oleate	21CFR181.27
Indirect Food Additives	
Glyceryl Acetate	21CFR177.1200
Glyceryl Behenate	21CFR175.105; 21CFR176.210
Glyceryl Caprate	21CFR175.105; 21CFR176.180; 21CFR177.2800
Glyceryl Caprylate	21CFR175.105; 21CFR176.210
Glyceryl Caprylate/Caprate	21CFR175.105; 21CFR176.210; 21CFR177.2800
Glyceryl Cocoate	21CFR175.105; 21CFR176.210; 21CFR177.2800
Glyceryl Erucate	21CFR175.105
Glyceryl Hydrogenated Rosinate	21CFR178.3130
Glyceryl Hydroxystearate	21CFR175.105; 21CFR176.170; 21CFR176.200; 21CFR177.1200; 21CFR177.2800
Glyceryl Isopalmitate	21CFR175.105
Glyceryl Isostearate	21CFR175.105
Glyceryl Laurate	21CFR175.105; 21CFR176.210; 21CFR177.2800
Glyceryl Laurate/Oleate	21CFR175.105; 21CFR176.210; 21CFR177.2800
Glyceryl Linoleate	21CFR175.105
Glyceryl Linolenate	21CFR175.105
Glyceryl Oleate	21CFR175.105; 21CFR175.300; 21CFR175.320; 21CFR176.210; 21CFR177.2800
Glyceryl Palmitate	21CFR175.105
Glyceryl Palmitate/Stearate	21CFR175.105; 21CFR176.210; 21CFR177.2800
Glyceryl Palmitoleate	21CFR175.105
Glyceryl Ricinoleate	21CFR175.105; 21CFR176.170; 21CFR176.210; 21CFR178.3130
Glyceryl Rosinate	21CFR175.105; 21CFR175.300; 21CFR178.3120
Glyceryl Stearate	21CFR175.105; 21CFR175.210; 21CFR175.300; 21CFR176.200; 21CFR176.210; 21CFR176.210

Table 7. Penetration Enhancement

Ingredient	Test Compound	Test System	Results	Reference
Glyceryl Caprylate/Caprate	5-fluorouracil	human abdominal skin samples ability to enhance skin penetration was determined in vitro by measuring skin permeability coefficients	10-fold increase in penetration, as compared to the buffer control (statistically significant)	³⁵
Glyceryl Isostearate	5-fluorouracil	human abdominal skin samples (same protocol as above)	did not enhance penetration	³⁵
Glyceryl Oleate 77.5% in a hexagonal gel phase	vitamin K, 2.5%	porcine ear skin in Franz diffusion cells was compared to vaseline as a vehicle	2.2-fold increase to the stratum corneum (9 h); 3- and 2-fold increase to the epidermis + dermis after 3 and 12 h, respectively	³⁶
15% in a nanodispersion of a hexagonal phase			2.7-fold increase to the stratum corneum (9 h); 3- and 3.7-fold increase to the epidermis + dermis after 3 and 12 h, respectively	
Glyceryl Oleate 1:2 with PEG-40 hydrogenated castor oil 3:2 with PEG-40 stearate	lidocaine, 2.5%	hairless mouse skin in Franz diffusion cells	statistically significant increase in penetration	³⁷
Glyceryl Oleate, 5-20% in a propylene glycol solution	cisplatin, 0.05%	porcine ear skin in Franz diffusion cells; full thickness skin and tape-stripped skin (stratum corneum removed) was used	greater penetration than with above mixture did not act as a real penetration enhancer, but increased drug partition to the receptor solution, thereby improving transdermal penetration only a small enhancement was observed in skin without the stratum corneum as compared to intact skin	³⁸
Glyceryl Oleate, 0.1-30% in propylene glycol	5-aminolevulinic acid, 5%	full-thickness hairless mouse skin in diffusion cells	significantly increased in vitro skin permeation/retention	³⁹
5-20% in propylene glycol		4-h application to dorsal area of hairless mice	concentration-dependent increase in photoporphyrin IX (conversion product of test substance)	

Table 8. Single Dose (Acute) Toxicity Studies

Ingredient	Animals/Group	Concentration/Dose/Vehicle	Procedure	LD ₅₀ /Results	Reference
DERMAL					
Glyceryl Rosinate	4 male NZW rabbits	5 g/kg bw, in water	24-h patch; it was not stated whether it was occlusive	>5 g/kg bw no irritation observed	²³
Glyceryl Rosinate	5 male NZW rabbits	10 g/kg bw, in water	24-h occlusive patch	>10 g/kg bw no irritation observed	²³
Glycerides, C16-18 and C18-hydroxy mono- and di-	5 Wistar rats	2 g/kg bw, neat	24-h occlusive patch	>2 g/kg bw no irritation observed	²⁰
ORAL					
Glyceryl Behenate	5 female Swiss mice	2 g/kg bw, neat	by gavage	>2 g/kg bw	²¹
glycerol ester of partially hydrogenated gum rosin	5 male Sprague-Dawley rats	2 g/kg bw in olive oil	by gavage	>2 g/kg bw	²³
glycerol ester of partially hydrogenated gum rosin	5 male Sprague-Dawley rats	2 g/kg bw, neat	by gavage	>2 g/kg bw	²³
Glyceryl Rosinate	Sprague-Dawley rats, 5/sex	2 g/kg bw in vaselin oil	by gavage	>2 g/kg	²³
Glyceryl Rosinate	10 male Sprague-Dawley rats	5 g/kg of a 10% w/v suspension in corn oil	by gavage	>5 g/kg; urinary and fecal staining, soft stool and decreased motor activity were observed for the first 48 h	³¹
Glyceryl Rosinate	10 rats	5 g/kg of a 10% w/v suspension in corn oil	by gavage	>5 g/kg; urinary and fecal staining, soft stool, piloerection, and decreased motor activity were observed for 1 wk, most notably for 24 h	³²
Glyceryl Rosinate	male Hilltop-Wistar albino rats; 3 (low dose) or 10 (high dose)	5 or 10 g/kg in 0.25% agar and 0.10% Tween 80	by gavage	>10 g/kg	²³
Glyceryl Stearate	5 female NMRI mice/sex	40 ml/kg bw; vehicle not stated	OECD guideline 401; given orally (details not provided)	>5 g/kg bw	²⁰
Glyceryl Stearate	5 male NMRI mice	not given	OECD guideline 401 (details not provided)	>5 g/kg bw	²⁰

Abbreviations: OECD – Organisation for Economic Co-operation and Development

Table 9. Repeated Dose Toxicity Studies

Ingredient	Animals/Group	Study Duration	Dose/Concentration	Procedure	Results	Reference
ORAL						
Glyceryl Hydrogenated Rosinate	Sprague-Dawley rats, 20/sex in low dose group; 25/sex in all other groups	90 days	mixed with corn oil (50:50); 2000, 5000, and 10,000 ppm in feed	dietary study; 5 control, mid- and high-dose animals/sex were killed at 30 days	NOAEL – 10,000 ppm no signs of toxicity	23
Glyceryl Rosinate	Sprague-Dawley rats, 10/sex	28 days	30% in 70% corn oil, given at 0.2% and 1.0%	dietary study	NOEL – 1% no effect on mortality, morbidity, clinical signs, food consumption, or body weight gain; no gross or microscopic lesions	23
Glyceryl Rosinate	Sprague-Dawley rats, 15/sex	90 days	0.2, 1, and 5% in corn oil	dietary study	NOAEL – 1% decreased food consumption during the initial weeks of dosing in males and females, increased liver weights in females, and increased relative liver-to-body weight in males in the high dose group	23
Glyceryl Rosinate	Fischer 344 rats, 20/sex/group	90 days	625, 1250, and 2500 mg/kg/day	dietary study	NOAEL – 2500 mg/kg/day no toxic effects	23
Glycerides, C8-18 and C18-unsatd. mono- and di-, acetates	10 male and 5 female Wistar Han rats - recovery group with an additional 5 males and females in the control and high dose group	28 days	0, 100, 300 and 1000 mg/kg/day; on polyethylene glycol	by gavage	NOAEL – 1000 mg/kg bw/day no clinical signs of toxicity; no toxicologically-relevant changes in hematology, clinical chemistry, organ weights, or gross or microscopic lesions	20
MUCOUS MEMBRANE EXPOSURE						
Glycerol Oleate	12 female rhesus macaque monkeys	6 mos	5% dissolved in K-Y warming gel	intravaginal administration of 1 ml of gel containing 50 mg test article; administration was 2x/day for first 8 wks; after a 3-wk non-treatment period, dosing was 1x/day for 11 wks	no vaginal inflammation or mucosal lesions in cervical vaginal tissues	40

Abbreviations: NOAEL - no-observable adverse effect level; NOEL – no-observed effect level

Table 10. Genotoxicity studies

Test Article	Concentration/Vehicle	Test System	Procedure	Results	Reference
IN VITRO					
Glyceryl Acetate	100-10,000 µg/plate	<i>S. typhimurium</i> TA100, TA1535, TA1537, or TA98	Ames test	not mutagenic	41
Glyceryl Acetate (89% pure)	500-5000 µg/ml in deionized water	CHO cells	chromosomal aberration assay, with or without metabolic	not mutagenic	42
Glyceryl Acetate (89% pure)	501-5010 µg/ml, with metabolic activation 1500-5010 µg/ml, without metabolic activation vehicle - deionized water	CHO cells	SCE assay	not genotoxic with metabolic activation positive results without metabolic activation; a dose-dependent increase was observed in 2 trials, and a doubling of SCEs was produced with 5000 µg/ml	42
Glyceryl Laurate	6.25-5000 µg/plate in Tween 80/bidistilled water (0.1 ml/plate)	<i>S. typhimurium</i> TA 1535, TA 1537, TA 1538, TA 98 and TA 100	Ames test, with and without metabolic activation (OECD Guideline 471)	negative positive controls gave expected results	22
Glyceryl Rosinate	2.5-500 µg/plate (vehicle not specified)	<i>S. typhimurium</i> TA 1535, TA 1537, TA 1538, TA 98 and TA 100	Ames test, with and without metabolic activation (OECD Guideline 471)	negative positive controls gave expected results	45
Glyceryl Rosinate	50.7-507 µg/ml	CHO cells	mammalian chromosome aberration test, with (2 h incubation) and without (7.3 h incubation) metabolic activation (OECD Guideline 473)	not genotoxic positive controls gave expected results	43
Glyceryl Rosinate	5.08-102 µg/ml	rat hepatocyte primary cell cultures	UDS test (OECD Guideline 482)	not genotoxic positive controls gave expected results	43
Acetic and fatty acid esters of glycerol	0.61-78 µg/plate (all <i>S. typhimurium</i> strains, without activation) 10-313 µg/plate (all <i>S. typhimurium</i> strains, with activation) 313-5000 µg/plate (<i>E. coli</i> , with and without activation) vehicle - acetone	<i>S. typhimurium</i> TA 1535, TA 1537, TA 98 and TA 100; <i>E. coli</i> WP2 uvr A	Ames test, with and without metabolic activation (OECD Guideline 471)	negative positive controls gave expected results	22
Glyceride, C14-18 and C16-22 unsaturated, mono- and di-	8-5000 µg/plate in Tween 80/bidistilled water	<i>S. typhimurium</i> TA 1535, TA 1537, TA1538, TA 98 and TA 100	Ames test, with and without metabolic activation (OECD Guideline 471)	negative positive controls gave expected results	20
Glycerides, C8-18 and C18-unsatd. mono- and di-, acetates	6 h, with and without metabolic activation: 0.02, 0.39, 0.078 0.156 mg/ml 24 and 48 h without activation: 0.078, 0.156, 0.313, 0.625, 1.25, 2.5, 5.0 mg/mL vehicle: acetone	Chinese hamster lung fibroblasts	mammalian chromosome aberration test (OECD Guideline 473)	negative positive controls gave expected results	20
IN VIVO					
Glycerides, C16-18 and C18-hydroxy mono- and di-	1000, 5000,(24 h analysis) or 10,000 (24, 48, and 72 h analysis) mg/kg bw	7 male and female CFW 1 mice	micronucleus test; animals were dosed with a single 20 ml/kg bw by gavage	negative positive controls gave expected results	20

Abbreviations: CHO – Chinese hamster ovary; DMSO – dimethyl sulfoxide; OECD – Organisation for Economic Co-operation and Development; SCE – sister chromatid exchange; UDS – unscheduled DNA synthesis

Table 11. Dermal irritation and sensitization

Test Article	Concentration/Dose	# per Group	Procedure	Results	Reference
DERMAL IRRITATION					
NON-HUMAN					
Glyceryl Behenate	neat	3 male NZW rabbits	4-h semi-occlusive patch applied to shaved and abraded skin; 0.5 ml applied; animals were observed for up to 7 days	not irritating slight erythema was observed in 1 animal at 24 h; no edema was observed	21
glycerol ester of partially hydrogenated gum rosin	neat	NZW rabbits, 2 males and 1 female	4-h occlusive patch applied to intact skin; 0.5 g applied; animals were observed for up to 72 h	not irritating no erythema or edema	23
Glyceryl Rosinate	no vehicle, but moistened with distilled water	3 NZW rabbits	4-h semi-occlusive patch applied to intact skin; 0.5 g applied; animals were observed for up to 72 h	not irritating no erythema or edema	23
Glyceryl Rosinate	neat	3 NZW rabbits	4-h semi-occlusive patch applied to intact and abraded skin; 0.5 g applied; animals were observed for up to 72 h	not a primary irritant; at most, a minimal irritant mean primary cutaneous irritation score was 0.6 slight to well-defined erythema was observed in damaged skin; slight erythema in intact skin	23
Glyceryl Rosinate	neat	3 NZW rabbits	4-h semi-occlusive; 0.5 g applied to intact and abraded skin; animals were observed for up to 72 h	not a primary irritant; at most, a minimal irritant mean primary cutaneous irritation score was 0.3 slight to well-defined erythema was observed in damaged skin; slight erythema in intact skin	23
Glyceryl Rosinate	no vehicle, but moistened with distilled water	NZW rabbits, 2 males and 1 female	24-h occlusive patch applied to intact skin; 0.5 g applied; animals were observed for up to 72 h	not irritating no erythema or edema	23
Glyceryl Stearate	75% in vaseline	3 NZW rabbits	4-h semi-occlusive patch; 0.5 ml applied; animals were observed for 72 h	no irritating no erythema or edema	20
HUMAN					
Glyceryl Stearate	5% emulsion in a mineral oil/water mixture (50:50)	20 subjects	a 12 mm Finn chamber containing 50 µl of the test article was applied for 48 h to the volar forearm of each subject using adhesive tape; the test sites were evaluated 24 h after patch removal on a scale of 0-3; TEWL) was measured using an evaporimeter	no difference in erythema between treated and control sites; the median value for clinical erythema was 0 at the glyceryl stearate-treated site (with 5% of the observations having a score >1, i.e., slight erythema, spotty or diffuse) and 0.5 at the control site (with 10% of the observations having a score >1) no significant effect on TEWL when compared to the control	44
Glyceryl Stearate	5% emulsion in a mineral oil/water mixture (50:50)	27 subjects	SLS (15% for 7 h) was used prior to application of the test article; 17-h patches were then applied to the SLS-treated skin	no difference in the erythema between treated and control site; with application to irritated skin, the median value for clinical erythema was 1 both at the glyceryl stearate-treated site and control site; 22% of the observations at the test site and 15% of the observations at the control site had a score >1 no significant effect on TEWL	44

Table 11. Dermal irritation and sensitization

Test Article	Concentration/Dose	# per Group	Procedure	Results	Reference
SENSITIZATION					
NON-HUMAN					
glycerol ester of partially hydrogenated gum rosin	10% in corn oil 25% in petroleum jelly	5 male and 5 female Hartley guinea pigs	GPMT <u>intradermal induction</u> : 3 pairs of intradermal injections: 1) FCA with an equal volume of water; 2) test article (10%) in vehicle; 3) test article (10%) in a 50:50 mixture of FCA and vehicle <u>topical induction</u> : 6 days after intradermal induction, the test site was pre-treated with 10% SLS; a 48-h occlusive patch (25% test article) was applied the next day <u>challenge</u> : topical challenge with 24-h occlusive patches (25% test article) was performed after a 2-wk non-treatment period	not an irritant or a sensitizer	23
glycerol ester of partially hydrogenated gum rosin	neat for induction 25% and 50% in in paraffin oil for challenge	female Hartley guinea pigs	as above	not an irritant or a sensitizer	23
Glyceryl Rosinate	intradermal induction: 7.5% topical induction: 83.3% topical challenge: 83.3% and 41.65% in a coconut oil product	20 female Dunkin-Hartley guinea pigs	GPMT <u>intradermal induction</u> : 3 pairs of intradermal injections: 1) FCA with an equal volume of water; 2) test article in vehicle; 3) test article in a 50:50 mixture of FCA and vehicle <u>topical induction</u> : 6 days after intradermal induction, the test site was pre-treated with SLS; a 48-h occlusive patch was applied the next day <u>challenge</u> : topical challenge with 48-h occlusive patches was performed after a 2-wk non-treatment period	not a sensitizer slight to well defined erythema was observed during the first 48 h in both control and test article-treated animals challenged at 83.3%; all animals appeared normal after 72 hour	23
Glyceryl Rosinate	induction: 100% challenge: 6.25% and 12.5% in paraffin oil	15 female Dunkin-Hartley guinea pigs	GPMT <u>induction</u> : on day 0, test animals received 2 injections of FCA, the skin was abraded, and a 498-h semi-occlusive patch was applied; on day 7, a second 48-h semi-occlusive patch was applied <u>challenge</u> : topical challenge with 24-h semi-occlusive patches was performed after a 2-wk non-treatment period	not an irritant or a sensitizer	23
Glyceride, C16-18 and C18 Mono- and Dihydroxy	induction: 50% in paraffin oil challenge: 25% in vaseline	20 female Pirbright white guinea pigs	<u>induction</u> : 1 intradermal (day 0) and 1 occlusive 48-h epicutaneous (day 7) exposure, with FCA <u>challenge</u> : 24 h occlusive patch applied 14 days after second induction exposure	not a sensitizer	20
HUMAN					
Glyceryl Behenate	applied neat	93 subjects	HRIPT; 0.2 g applied with an occlusive patch 9 24-h patches induction patches were applied (3x/wk for 3 wks); the challenge patch was applied to a previously untreated site after a 2-wk non-treatment period	not a sensitizer	21

Table 11. Dermal irritation and sensitization

Test Article	Concentration/Dose	# per Group	Procedure	Results	Reference
glycerol ester of partially hydrogenated gum rosin	not stated, assumed neat	202 subjects	HRIPT <u>induction</u> : 24-h occlusive patches were applied 3x/wk for 3 wks <u>challenge</u> : patches were applied to the original site and a previously untreated site after a 2-wk non-treatment period	not an irritant or a sensitizer	23
Glyceryl Rosinate	not stated	25 male and 25 female subjects	HRIPT <u>induction</u> : patches were applied every other day, for a total of 15 applications <u>challenge</u> : 24-h patch was applied after a 2-wk non-treatment period	not an irritant or a sensitizer	23
Glyceryl Rosinate	not stated	100 male and 100 female subjects	Schwartz patch test 5 day exposure for induction; challenge after a 6-wk non-treatment period, a 48-h patch was applied	not an irritant or a sensitizer	23

Abbreviations: FCA – Freund’s Complete Adjuvant; GPMT – guinea pig maximization test; HRIPT – human repeated insult patch test; ME – microemulsion; NZW – New Zealand White; OECD – Organisation for Economic Co-operation and Development; TEWL – transepidermal water loss

Table 12. Ocular irritation studies

Test Article	Concentration	#/Animals/Grp	Method	Results	Reference
NON-HUMAN					
Glyceryl Behenate	undiluted	3 male NZW rabbits	single instillation; 0.1 ml eyes were not rinsed	not irritating; slight lacrimation in all animals at 1 h and 1 animal at 24 h; no other ocular effects were observed	²¹
Glyceryl Palmitate/Stearate	undiluted	6 NZW rabbits	single instillation; 0.1 ml eyes were not rinsed	not irritating	²⁰
Glyceryl Rosinate	undiluted	6 NZW rabbits	single instillation; 100 mg	slightly irritating; mild irritation (of the conjunctiva) was observed in 4 rabbits at 24-h	²³
Glyceryl Rosinate	undiluted	6 NZW rabbits	single instillation; 100 mg	slightly irritating; slight signs of irritation to the cornea, iris, and the conjunctiva; conjunctival irritation did not fully reverse in 2 animals within 72 h	²³

Abbreviations: NZW – New Zealand White; OECD – Organisation for Economic Co-operation and Development

Table 13. Case Reports

Ingredient	Case History	Patch Testing	Reference
Glyceryl Caprylate	female with a history of facial eczema for several years that occurred after application of a skin care cream; the cream was composed of 90% glyceryl caprylate, 6% glyceryl dicaprylate, 4% free glycerol, and <0.1% glyceryl tricaprylate	- a 24-h occlusive patch test with several allergen series and the patient's products resulted in positive reactions to several compounds at 72 h - a subsequent ROAT with the patient's own products, applied 2x/day for 1 wk, resulted in a distinct reaction (erythema and vesicles) with the product containing 90% glyceryl caprylate - additional patch testing with 5% glyceryl caprylate in pet gave a +++ reaction - further patch testing with 0.1 and 1.0% glyceryl caprylate (in pet) produced a + and +++ reaction, respectively - no reactions were observed in 3 control subjects patched tested with 5% in pet	⁴⁵
Glyceryl Hydrogenated Rosinate	female with severe bullous eruption on the wrist and hand following repeated application of a medicated patch	- patch testing with a standard series, the patch, and constituents of the patch, including 20% glyceryl hydrogenated rosinatate in pet resulted in a strong positive reaction (+++) to the patch and to glyceryl hydrogenated rosinatate on days 2 and 4 - no reactions were observed in 5 control subjects	⁴⁶
Glyceryl Isostearate	female with a history of persistent itchy and scaly erythema on the lips that appeared after using 5 different lipsticks	- patient had positive patch test reactions to all 5 lipsticks and 4 ingredients from 2 of the formulations, including 1% glyceryl isostearate in pet. - no reactions were observed in 3 control subjects patched tested with the same ingredients	⁴⁷
Glyceryl Rosinate	female with history of venous eczematous ulcerations on both legs, with recurrent eczematous dermatitis presented with an ulcer after application of medicated wound dressings; patient had sensitivities to multiple compounds	- positive patch test (+) to a medicated patch and 20% glyceryl rosinatate in pet.	⁴⁸
Glyceryl Stearate	female with dermatitis of the arms due to a body lotion that was originally used for months without an effect	- patch testing with the lotion had positive (+) results - subsequent testing with ingredients of the lotion resulted in positive reaction to 20% glyceryl stearate in pet (?+ at 48 h; + at 72 h) - no reactions were observed in 20 control subjects	⁴⁹

Abbreviations: pet – petrolatum; ROAT - repeated open application test

REFERENCES

1. Elder RL (ed). Final report on the safety assessment of glyceryl stearate and glyceryl stearate/SE. *J Am Coll Toxicol.* 1982;1(4):169-192. <http://www.cir-safety.org/ingredients>.
2. Nikitakis J and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 15 ed. Washington, DC: Personal Care Products Council, 2014.
3. Elder RL (ed). Final report on the safety assessment of glyceryl oleate. *J Am Coll Toxicol.* 1986;5(5):391-413. <http://www.cir-safety.org/ingredients>.
4. Elder RL (ed). Final report on the the safety assessment of glyceryl ricinoleate. *J Am Coll Toxicol.* 1988;7(6):721-739. <http://www.cir-safety.org/ingredients>.
5. Andersen FA (ed). Final Report on the Safety Assessment of Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate. *Int J Toxicol.* 2007;26(Suppl 3):31-77. <http://www.cir-safety.org/ingredients>.
6. Andersen FA (ed). Final Report of the Amended Safety Assessment of Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, G lyceryl Isostearates, G lyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl Isotridecanoate/Stearate/ Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Eiaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate. *Int J Toxicol.* 2004;23(Suppl 2):55-94.
7. Andersen FA (ed). Final report on the safety assesment of malic acid and sodium malate. *Int J Toxicol.* 2001;20(Suppl 1):47-55. <http://www.cir-safety.org/ingredients>.
8. Becker LC, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, and Gill LJ. Safety assessment of glycerin as used in cosmetics. 2015. <http://www.cir-safety.org/ingredients>. Date Accessed 8-23-2015. Available on the CIR website.
9. Heldreth BA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Final report of the Cosmetic Ingredient Review Expert Panel on the safety assessment of methyl acetate. *Int J Toxicol.* 2012;31(Suppl 1):112S-136S. <http://www.cir-safety.org/ingredients>.
10. Fiume MM, Heldreth BA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Final report of the Cosmetic Ingredient Review Expert Panel on the safety assessment of dicarboxylic acids, salts, and esters. *Int J Toxicol.* 2012;31(Suppl 1):5S-76S. <http://www.cir-safety.org/ingredients>.
11. Johnson WJ Jr, Heldreth BA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, and Gill LJ. 2015. Safety assessment of polysaccharide gums as used in cosmetics (Tentative report issued by the CIR Expert Panel). Available on the CIR website. Tentative report expected to be made final at the Sept 2015 CIR Expert Panel meeting.
12. Fiume MM, Heldreth BA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Safety assessment of citric acid, inorganic citrate salts, and alkyl citrate esters as used in cosmetics. *Int J Toxicol.* 2014;33(Suppl 2):16S-46S. <http://www.cir-safety.org/ingredients>.
13. Burnett CL, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Final report on the safety assessment of *Cocos nucifera* (coconut) oil and related ingredients. *Int J Toxicol.* 2011;30(Suppl 1):5S-16S. <http://www.cir-safety.org/ingredients>.
14. Burnett CL, Fiume MM, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. 2011. Final report on the safety assesement of plant-dervied fatty acid oils as used in cosmetics. Available on the CIR website.

15. Andersen FA (ed). Amended final report on the safety assessment of hydroxystearic acid. *Int J Toxicol*. 1999;18(Suppl 1):1-10. <http://www.cir-safety.org/ingredients>.
16. Elder RL (ed). Final report on the safety assessment of isostearic acid. *J Am Coll Toxicol*. 1983;2(7):61-74. <http://www.cir-safety.org/ingredients>.
17. Andersen FA (ed). Final report on the safety assessment of glycolic acid, ammonium, calcium, potassium, and sodium glycolates, methyl, ethyl, propyl, and butyl glycolates, and lactic acid, ammonium, calcium, potassium, sodium, and TEA-lactates, methyl, ethyl, isopropyl, and butyl lactates, and lauryl, myristyl, and cetyl lactates. *Int J Toxicol*. 1998;17(Suppl 1):1-241. <http://www.cir-safety.org/ingredients>.
18. Elder RL (ed). Final report of the safety assessment for acetylated lanolin alcohol and related compounds. *J Environ Pathol Toxicol*. 1980;4(4):63-92. <http://www.cir-safety.org/ingredients>.
19. Elder RL (ed). Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. *J Am Coll Toxicol*. 1987;6(3):321-401. <http://www.cir-safety.org/ingredients>.
20. European Chemical Agency (ECHA). Stearic acid, monoester with glycerol (CAS No. 31566-31-1; glyceryl stearate). [http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7f326e-20f4-1eb1-e044-00144f67d249/DISS-9c7f326e-20f4-1eb1-e044-00144f67d249.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7f326e-20f4-1eb1-e044-00144f67d249/DISS-9c7f326e-20f4-1eb1-e044-00144f67d249_DISS-9c7f326e-20f4-1eb1-e044-00144f67d249.html). Last Updated 2013. Date Accessed 7-23-2015.
21. European Chemical Agency (ECHA). Docosanoic acid, ester with 1,2,3-propanetriol (77538-19-3; glyceryl behenate). [http://apps.echa.europa.eu/registered/data/dossiers/DISS-dcee0b84-aa0b-5bf9-e044-00144f67d031/DISS-dcee0b84-aa0b-5bf9-e044-00144f67d031.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-dcee0b84-aa0b-5bf9-e044-00144f67d031/DISS-dcee0b84-aa0b-5bf9-e044-00144f67d031_DISS-dcee0b84-aa0b-5bf9-e044-00144f67d031.html). Last Updated 2013. Date Accessed 7-23-2015.
22. European Chemical Agency (ECHA). 2,3-Dihydroxypropyl laurate (CAS No. 142-18-7; glyceryl laurate). [http://apps.echa.europa.eu/registered/data/dossiers/DISS-dffb4072-e286-47ae-e044-00144f67d031/DISS-dffb4072-e286-47ae-e044-00144f67d031.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-dffb4072-e286-47ae-e044-00144f67d031/DISS-dffb4072-e286-47ae-e044-00144f67d031_DISS-dffb4072-e286-47ae-e044-00144f67d031.html). Last Updated 2015. Date Accessed 7-27-2015.
23. European Chemical Agency (ECHA). Resin acids and Rosin acids, esters with glycerol (CAS No. 8050-31-5). [http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d6cc4e-2e09-6585-e044-00144f67d031/DISS-97d6cc4e-2e09-6585-e044-00144f67d031.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d6cc4e-2e09-6585-e044-00144f67d031/DISS-97d6cc4e-2e09-6585-e044-00144f67d031_DISS-97d6cc4e-2e09-6585-e044-00144f67d031.html). Last Updated 2015. Date Accessed 8-30-2015.
24. Ganem-Quintanar A, Quinianar-Guerrero D, and Buri P. Monoolein: A review of the pharmaceutical applications. *Drug Development and Industrial Pharmacy*. 2000;26(8):809-820.
25. Andersen FA (ed). Final Report of the Amended Safety Assessment of Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate. *Int J Toxicol*. 2004;23(Suppl 2):55-94. <http://www.cir-safety.org/ingredients>.
26. National Toxicology Program (NTP). Testing status of Acetin - 10780 - J (glyceryl acetate). <http://ntp.niehs.nih.gov/testing/status/agents/ts-10780-j.html>. Last Updated 2015. Date Accessed 7-23-2015.
27. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. 2015.
28. Personal Care Products Council. 4-29-2014. Concentration of Use by FDA Product Category: Glyceryl Monoesters. Unpublished data submitted Aug 7, 2015 by the Personal Care Products Council.
29. Personal Care Products Council. 1-6-2015. Concentration of Use by FDA Product Category: Glyceryl Esters (mixed). Unpublished data submitted by Personal Care Products Council. 1 pages.

30. Johnsen MA. The influence of particle size. *Spray Technol Marketing*. 2004;14(11):24-27.
31. Rothe H. Special Aspects of Cosmetic Spray Evaluation. 9-26-2011. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, D.C.
32. Bremmer HJ, Prud'homme de Lodder LCH, and Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. Report No. RIVM 320104001/2006. pp. 1-77.
33. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.
34. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. <http://ec.europa.eu/consumers/cosmetics/cosing/>. Last Updated 2015. Date Accessed 8-7-2015.
35. Cornwell PA, Tubek J, van Gompel HAHP, Little CJ, and Wiechers JW. Glyceryl monocaprylate/caprate as a moderate skin penetration enhancer. *International Journal of Pharmaceutics*. 1998;171(2):243-255.
36. Lopes LB, Speretta FF, and Bentley MV. Enhancement of skin penetration of vitamin K using monoolein-based liquid crystalline systems. *Eur J Pharm Sci*. 2007;32(3):209-215.
37. Sintov AC and Shapiro L. New microemulsion vehicle facilitates percutaneous penetration in vitro and cutaneous drug bioavailability in vivo. *J Control Release*. 3-5-2004;95(2):173-183.
38. Simonetti LDD, Gelfuso GM, Barbosa JCR, and Lopez RFV. Assessment of the percutaneous penetration of cisplatin: The effect of monoolein and the drug skin penetration pathway. *Eur J Pharm Biopharm*. 2009;73(1):90-94.
39. Steluti R, De Rosa FS, Collett J, Tedesco AC, and Bentley MV. Topical glycerol monooleate/propylene glycol formulations enhance 5-aminolevulinic acid in vitro skin delivery and in vivo protoporphyrin IX accumulation in hairless mouse skin. *Eur J Pharm Biopharm*. 2005;60(3):439-444.
40. Schlievert PM, Strandberg KL, Brosnahan AJ, Peterson ML, Pambuccian SE, Nephew KR, Brunner KG, Schultz-Darken NJ, and Haase AT. Glyceryl monolaurate does not alter rhesus macaque (*Macaca mulatta*) vaginal lactobacilli and is safe for chronic use. *Antimicrob Agents Chemother*. 2008;52(12):4448-4454.
41. Haworth S, Lawlor T, Mortelmans K, Speck W, and Zeiger E. Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen*. 1983;Suppl 1:1-142.
42. Loveday KS, Lugo MH, Resnick MA, Anderson BE, and Zeiger E. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro: II. Results with 20 chemicals. *Environ Mol Mutagen*. 1989;13(1):60-94.
43. Environmental Protection Agency (EPA). Detailed chemical results for Resin acids and Rosin acids, esters with glycerol; CAS No. 8050-31-5. <http://ofimpub.epa.gov/opptphv/quicksearch/display?pChem=100024>. Last Updated 2015. Date Accessed 7-30-2015.
44. Bárány E, Lindberg M, and Lodén M. Unexpected skin barrier influence from nonionic emulsifiers. *Int J Pharm*. 2-15-2000;195(1-2):189-195.
45. Herbert VG, Spiro JM, Reich K, Steinkraus V, Karimi J, Martin V, and Breuer K. Glyceryl (mono)caprylate - a new contact allergen. *Contact Dermatitis*. 2013;69(6):383-385.
46. Foti C, Bonamonte D, Conserva A, Casulli C, and Angelini G. Allergic contact dermatitis to glyceryl-hydrogenated rosinates in a topical plaster. *Contact Dermatitis*. 2006;55(2):120-121.
47. Inui S, Azukizawa H, and Katayama I. Recurrent contact cheilitis because of glyceryl isostearate, diisostearyl maleate, oleyl alcohol, and Lithol Rubine BCA in lipsticks. *Contact Dermatitis*. 2009;60(4):231-232.
48. Pereira TM, Flour M, and Goossens A. Allergic contact dermatitis from modified colophonium in wound dressings. *Contact Dermatitis*. 2007;56(1):5-9.
49. de Groot AC, van der Meeren HL, and Weyland JW. Cosmetic allergy from stearic acid and glyceryl stearate. *Contact Dermatitis*. 1988;19(1):77-78.

50. Andersen FA (ed). Re-review document on glyceryl oleate. 2004. <http://www.cir-safety.org/ingredients>. Available on the CIR website.
51. Biodynamics, Inc. Acute oral toxicity study in rats with Zonester[®] 85 DB-3012 in Sprague-Dawley male albino rats. 1979. [http://yosemite.epa.gov/oppts/epatscat8.nsf/by+Service/A27D3331EFBEB88B8525704B004F707A/\\$File/88000000139.pdf](http://yosemite.epa.gov/oppts/epatscat8.nsf/by+Service/A27D3331EFBEB88B8525704B004F707A/$File/88000000139.pdf). Date Accessed 8-22-2015. Report No. 5787-79. pdf pages 7-18.
52. Biodynamics, Inc. Acute oral toxicity study in rats with Zonester[®] 85 NF-7015. 1979. [http://yosemite.epa.gov/oppts/epatscat8.nsf/by+Service/A27D3331EFBEB88B8525704B004F707A/\\$File/88000000139.pdf](http://yosemite.epa.gov/oppts/epatscat8.nsf/by+Service/A27D3331EFBEB88B8525704B004F707A/$File/88000000139.pdf). Date Accessed 8-22-2015. Report No. 5788-79. pdf pages 18-21.

Final Report on the Safety Assessment of Glyceryl Stearate and Glyceryl Stearate/SE

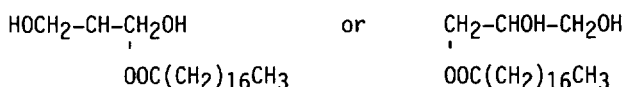
Glyceryl Stearate and Glyceryl Stearate/SE are the esterification products of glycerine and stearic acid, and are used in cosmetic formulations as emollients, emulsifiers, and stabilizers. In acute oral toxicity studies in rats, both ingredients were slightly toxic. Glyceryl Stearate in the diet of rats for three consecutive generations had no adverse effects. Five percent Glyceryl Stearate did not promote the carcinogenicity of DMBA in mouse skin. In subchronic and chronic dermal toxicity tests, Glyceryl Stearate was non-toxic to rabbits but did cause moderate irritation. Primary eye irritation studies, at concentrations up to 100%, were mildly irritating or nonirritating to rabbits. Single and Repeated Insult Patch Tests showed both ingredients to be nonsensitizing and nonirritating. Products containing 2% Glyceryl Stearate were nonphototoxic and nonphotoallergenic. On the basis of the available data, it is concluded that Glyceryl Stearate and Glyceryl Stearate/SE are safe for topical application to humans in the present practices of use and concentration.

CHEMISTRY

Description and Preparation

Glyceryl Stearate

GLYCERYL Stearate is the esterification product of glycerol and stearic acid. The monoglyceride can conform to either of the following structures:^(1,2)



Glyceryl Stearate is prepared commercially by high temperature esterification of stearic acid and glycerol or by transesterification of an appropriate triglyceride with glycerine.⁽³⁾ Verkade and Van der Lee⁽⁴⁾ mixed anhydrous glycerol with the methyl ester of stearic acid in a solution of 1% sulfuric acid and sodium sulfate and added magnesium oxide to form the Glyceryl Stearate product. Bertoni et al.⁽⁵⁾ reported a similar preparation, although he used a sodium methoxide catalyst and a pyridine solvent. Veikhertz⁽⁶⁾ reacted stearic acid with anhydrous glycerol for 40 h at 200°C and extracted the Glyceryl Stearate in cold water. Cressey⁽²⁾ reported a method in which stearic acid triglyceride is hydrolyzed in the presence of an alkaline catalyst. Lichnerova⁽⁷⁾ prepared the 1-monoester by first reacting glycerol with acetone to form isopropylidene glycerol. With the hydroxy groups protected in the 2nd and 3rd positions, the one free primary alcohol group was esterified with the chloride salt of stearic acid. The resulting stearic ester was then partially hydrolyzed, resulting in the desired 1-glyceryl stearate.

In addition to these methods, Glyceryl Stearate can be extracted commercially from sea buckthorn, whale oil, and shark liver oil.⁽⁸⁻¹⁰⁾

COSMETIC INGREDIENT REVIEW

Glyceryl Stearate/Self-Emulsifying

Glyceryl Stearate/Self-Emulsifying is the esterification product of glycerol and an excess of stearic acid; the excess stearic acid is reacted with potassium hydroxide to produce an emulsifying soap. Glyceryl Stearate/SE is prepared by the controlled high-temperature esterification of glycerol and excess stearic acid or by partial saponification of a triglyceride. The excess stearic acid is neutralized with potassium hydroxide to yield a product which contains potassium stearate.⁽³⁾

Properties

Glyceryl Stearate is a white or cream-colored wax-like solid with a faint odor and an agreeable fatty taste. It is soluble in alcohol, petroleum ether, benzene, acetone, and mineral oil but insoluble in water. Glyceryl Stearate is characterized by "plastic" flow at temperatures between 20° and 50°C.^(3,7,11,12) The chemical and physical properties of Glyceryl Stearate are summarized in Table 1.

Glyceryl Stearate has a polymorphic crystalline structure with three modifications: a low melting α form and two higher melting forms, β and β' . The α form is the first to separate when molten glyceryl stearate is cooled. The α form changes rapidly into the more stable β form, which in turn slowly changes into the most stable β' form.^(13,14) Lichnerova⁽⁷⁾ reported a fourth, sub- α form which lacks a defined melting point and readily passes into the α form. The transformation of the sub- α form to the α form was reversible; this is an exception to the rule of irreversible crystalline transformation.

Glyceryl Stearate/SE is a white to cream-colored wax-like solid.⁽³⁾ Its physical and chemical properties are summarized in Table 2.

Reactivity

Glyceryl Stearate undergoes reactions typical of fatty acid esters including glycerolysis, hydrolysis, transesterification, and enzymatic cleavage.^(2,15,16) Under favorable conditions, Glyceryl Stearate can also autoxidize.⁽¹⁷⁾ Glyceryl Stearate undergoes hydrolysis in aqueous media.⁽¹⁸⁾

Analytical Methods

Glyceryl Stearate is frequently determined by chromatographic analyses. These include gas chromatography, reversed-phase partition chromatography, thin-layer chromatography, high-performance liquid chromatography, and absorption chromatography.⁽¹⁹⁻²⁷⁾ Glyceryl Stearate can be analyzed directly or converted, prior to gas chromatographic analysis, to a trimethyl silyl ether derivative.⁽²⁷⁾ Glyceryl Stearate can also be added to acetyl nitrate in silicic acid and the nitrate derivative then separated by chromatographic methods.

Other analytical methods include x-ray diffraction, differential thermal analysis, periodimetry, periodic oxidation, electron spin resonance, and infrared spectroscopy.^(2,13,14,33-36) Forman and Grady⁽³⁷⁾ identified Glyceryl Stearate from other compounds in pharmaceutical creams by a method of channel-type inclusion in urea.

Impurities

Both Glyceryl Stearate and Glyceryl Stearate/SE contain such reaction impurities as glycerol, stearic acid, and water.⁽³⁾ Commercial Glyceryl Stearate and Glyceryl Stearate/SE may contain glyceryl distearate (42-44%), glyceryl tristearate (20-23%), free glycerol (3-5%) and small quantities of soap (if an alkaline catalyst is used in its preparation).⁽²⁾ Certain preparations of Glyceryl Stearate and Glyceryl Stearate/SE also contain mono-, di-, and triesters of palmitic, oleic, and myristic acids, as well as unreacted fatty acids. The amount of these ester impurities is varied by the manufacturer to modify product stability and emulsification. Molecularly distilled Glyceryl Stearate contains over 90% of the monoester.⁽³⁸⁾

ASSESSMENT: GLYCERYL STEARATE AND GLYCERYL STEARATE/SE

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF GLYCERYL STEARATE.^a

<i>Property</i>	<i>Value</i>
Molecular weight	358.57
Melting point	
α -form	74 °C
β -form	81 °C
β' -form	79 °C
Commercial	56°–58 °C
Boiling point	238°–240 °C
Density (g/cm ³)	0.9841
Specific gravity (25°C)	0.97
Refractive index	1.400
pH (3%)	9.309
Acid value ^b	1.5–3.0
Iodine value	0.5–4.0
Saponification value	160–177
Fatty free acids	< 5%
Monoglycerides	40–50%
Glycerol	1.0–8.0%
Water	1.0% (max.)

^aData from Refs. 3, 6, 12, 28–30.^bThe acid value of Glyceryl Stearate increases as the compound ages.⁽³¹⁾**Additives**

Both Glyceryl Stearate and Glyceryl Stearate/SE may contain 200 ppm butylated hydroxytoluene (BHT), which is added by the manufacturer as a preservative.⁽³⁾ BHT is a Generally Recognized as Safe (GRAS) substance for which regulations have been issued under the Food, Drug and Cosmetic Act.⁽³⁹⁾ Its use in food as a GRAS food additive is limited to 0.02%.

TABLE 2. PHYSICAL AND CHEMICAL PROPERTIES OF GLYCERYL STEARATE/SE.^a

<i>Property</i>	<i>Value</i>
Melting range	50°–78 °C
Acid value	10–22 (max.)
Saponification value	138–170
Combustion residue	0.1% (max.)
Free glycerine	6–10%
Iodine value	3–6% (max.)
Isobutane soluble material	85.7%
Free fatty acids	76.0%
Combined glycerol	12.7%
Monoglycerides	30–45%
Potassium Stearate	5–12%
Water	1% (max.)
Ionic character	Nonionic/Anionic

^aData from Refs. 3, 32.

COSMETIC INGREDIENT REVIEW

USE

Cosmetic Use

Purpose of Use

Glyceryl Stearate and Glyceryl Stearate/SE are widely used in cosmetics. When applied to skin, they produce a waxy, occlusive, water-soluble film, which makes it useful for hand lotions and creams. The viscosity of any emulsion that contains Glyceryl Stearate is directly proportional to the amount of Glyceryl Stearate present; Glyceryl Stearate is used to regulate the thixotropic index and viscosity of a cosmetic. Products that contain up to 3% Glyceryl Stearate are lotions, whereas those containing 10% Glyceryl Stearate are creams. Excessive skin defatting caused by the sulfates and sulfonates in detergent cleansing creams can be avoided by the presence of Glyceryl Stearate. Glyceryl Stearate base is used to stabilize a product, decrease water evaporation, make the product freeze-resistant, and keep it from forming surface crusts. Glyceryl Stearate also reduces the greasiness of oils used in certain cosmetic preparations. Glyceryl Stearate is used in cosmetic products as an opacifier, auxiliary oil/water emulsifier, acid stabilizer, and nonionic surfactant. ^(11,31,38,40-50)

Glyceryl Stearate/SE is used as an emulsifier and viscosity regulator. It needs no other auxiliary emulsifier to form a stable emulsion unlike Glyceryl Stearate, which requires such surfactants as soap to yield a stable preparation. ⁽³¹⁾

Scope and Extent of Use in Cosmetics

According to the industry's voluntary submissions to the Food and Drug Administration (FDA) in 1976, Glyceryl Stearate and Glyceryl Stearate/SE are used in over 1200 and over 200 cosmetic formulations, respectively, in concentrations of ≥ 0.1 -50%. Table 3 summarizes the product formulation data for the two ingredients. ⁽⁵¹⁾

TABLE 3. PRODUCT FORMULATION DATA.^a

<i>Ingredient/Cosmetic Product Type</i>	<i>Concentration (percent)</i>	<i>No. of product formulations</i>
<i>Glyceryl Stearate</i>		
Lotions, oils, powders, and creams	>0.1-5	11
Other bath preparations	>0.1-1	1
Eyeline	>0.1-5	32
Eyeshadow	>0.1-10	28
Eye makeup remover	>1-5	2
Mascara	>25-50	1
	>10-25	7
	>5-10	12
	>1-5	24
	>0.1-1	2
Other eye makeup preparations	>1-10	7
Perfumes	>1-25	4
	≤ 0.1	1
Powders	>0.1-25	129
Sachets	>0.1-10	16
Hair conditioners	>0.1-25	65
Permanent waves	>1-5	1
	>0.1-1	1
Rinses	>1-5	9
	>0.1-1	4
Shampoos	>5-10	3
	>1-5	4
	>0.1-1	1

ASSESSMENT: GLYCERYL STEARATE AND GLYCERYL STEARATE/SE

TABLE 3. (Continued).

<i>Ingredient/Cosmetic Product Type</i>	<i>Concentration (percent)</i>	<i>No. of product formulations</i>
Tonics and dressings	> 1-5	6
	> 1-10	3
Hair dyes	> 5-10	2
Rinses	≤ 0.1	24
Bleaches	> 1-5	1
Shampoos (coloring)	> 1-5	1
	≤ 0.1	1
Blushers	> 1-5	7
	> 0.1-1	5
	≤ 0.1	3
Face powders	> 0.1-1	2
	≤ 0.1	6
Foundations	> 1-5	89
	> 0.1-1	13
	≤ 0.1	5
Leg and body paints	> 1-5	15
Makeup bases	> 5-10	1
	> 1-5	36
	> 0.1-1	8
Rouges	> 1-5	2
	> 0.1-1	1
Skin care preparations (cleansing)	> 10-25	7
	> 5-10	6
	> 1-5	64
	> 0.1-1	27
	≤ 0.1	2
Depilatories	> 1-5	2
Face, body, and hand	> 10-25	4
	> 5-10	15
	> 1-5	151
	> 0.1-1	42
Hormone	> 1-5	2
	> 0.1-1	1
Moisturizing	> 10-25	2
	> 5-10	16
	> 1-5	183
	> 0.1-1	49
Night	> 10-25	1
	> 5-10	6
	> 1-5	35
	> 0.1-1	3
Mud packs	> 10-25	2
	> 5-10	9
	> 1-5	5
Skin lighteners	> 10-25	4
	> 5-10	1
	> 1-5	2
Skin fresheners	> 1-5	1
	> 0.1-1	1
Fixatives	> 1-5	1
	> 0.1-1	1
Other makeup preparations (not eye)	> 1-5	4
	> 0.1-1	6

COSMETIC INGREDIENT REVIEW

TABLE 3. (Continued).

<i>Ingredient/Cosmetic Product Type</i>	<i>Concentration (percent)</i>	<i>No. of product formulations</i>
Cuticle softeners	> 10-25	1
	> 5-10	2
	> 1-5	5
Nail creams and lotions	> 25-50	1
	> 10-25	1
	> 1-5	5
Bath soaps and detergents	> 1-5	2
	≤ 0.1	1
Douches	> 10-25	3
	> 5-10	6
	> 1-5	7
	> 0.1-1	1
Other personal cleanliness products	> 10-25	2
	> 5-10	6
	> 1-5	5
	> 0.1-1	2
Aftershave lotions	> 0.1-1	2
Shaving cream	> 1-5	3
	> 0.1-1	2
Other shaving preparations	> 1-5	1
Wrinkle removers	> 1-5	2
Other skin care preparations	> 10-25	2
	> 5-10	1
	> 1-5	16
	> 0.1-1	4
Suntan and sunscreen products (gels, creams, and liquids)	> 5-10	9
	> 1-5	23
	> 0.1-1	4
Indoor tanning	> 1-5	2
<i>Glyceryl Stearate/SE</i>		
Eyeliners	> 0.1-1	32
Eyeshadows	> 1-5	2
Eye lotion	> 1-5	1
Mascara	> 1-5	1
Other eye makeup preparations	> 0.1-1	4
Sachets	> 1-5	14
	> 0.1-1	1
Other fragrance preparations	> 1-5	1
Hair conditioners	> 10-25	1
	> 5-10	1
	> 1-5	1
Hair straighteners	> 5-10	4
Blushers	≤ 0.1	1
Foundations	> 1-5	13
	> 0.1-1	1
Makeup bases	> 1-5	1
	> 0.1-1	54
Other personal cleanliness products	> 10-25	2
Aftershave lotions	> 5-10	1
Skin care preparations (face, body, and hand)	> 10-25	3
	> 5-10	5
	> 1-5	15
	≤ 0.1	1

ASSESSMENT: GLYCERYL STEARATE AND GLYCERYL STEARATE/SE

TABLE 3. (Continued).

<i>Ingredient/Cosmetic Product Type</i>	<i>Concentration (percent)</i>	<i>No. of product formulations</i>
Hormone	> 5-10	1
Moisturizing	≤ 0.1-25	32
Night	> 1-5	2
	> 0.1-1	1
Skin lighteners	> 1-5	3
Skin fresheners	> 0.1-5	1
Other skin care preparations	> 10-25	1
	> 1-5	2
	> 0.1-1	1
	≤ 0.1	1
Cleansing creams	> 5-10	2
	> 1-5	4
	> 0.1-1	3
	≤ 0.1	3

^aFrom Ref. 51.

Non-Cosmetic Use

Glyceryl Stearate is used in food as a surfactant, emulsifier, flavor dispersant, antistalant, antisticking, and thickening agent. It is most widely used in bread for its emulsifying and surfactant properties; in baking products it serves as an antistalant and dough conditioner. ^(2,11,52-63)

Glyceryl Stearate is a GRAS substance regulated by the Food, Drug and Cosmetic Act. ⁽³⁹⁾ Its concentration in food ranges from 0.01 to 2.0%; the possible average daily intake, based on the types of food consumed, is about 15 mg/kg for persons aged two or older and 150 mg/kg for infants. These estimates are considered to be maximum possible intakes; more realistically, a person is likely to ingest approximately 63 mg (or approximately 1 mg/kg) of Glyceryl Stearate daily. ⁽⁶⁴⁾

Glyceryl Stearate is also approved as a specific indirect food additive, under regulation of the Food, Drug and Cosmetic Act. There are no specific limitations on the use in food of Glyceryl Stearate as a surface lubricant and as a defoamer in coatings intended for use in food production, packaging, treating, transporting, or holding (21 CFR 176.200, 21 CFR 175.300).

Glyceryl Stearate is used in pharmaceutical preparations as a solidifier and controlled release agent. It is used in suppositories as a lipophile and as an agent to prevent sedimentation of dispersed solids. ⁽⁶⁵⁻⁷³⁾ Glyceryl Stearate is used as a base in over-the-counter (OTC) topical analgesics (44 CFR 69771). Table 4 lists the non-cosmetic uses of Glyceryl Stearate.

BIOLOGICAL PROPERTIES

Bactericidal Properties

Glyceryl Stearate (1.50 µg/ml) did not inhibit growth of gram-positive bacteria. ⁽⁷⁴⁾ Weddeburn ⁽⁷⁵⁾ observed that in cosmetic preparations containing a preservative, and Glyceryl Stearate as a surfactant, the preservative's efficiency was reduced as the surfactant preservative ratio increased. He suggested that such nonionic surfactants as Glyceryl Stearate allow microorganisms to become resistant to preservatives.

Absorption, Metabolism, and Excretion

When ingested, monoglycerides are readily absorbed through the duodenal mucosa and converted to triglycerides. However, ingestion of 25 g of Glyceryl Stearate by human subjects caused no ap-

COSMETIC INGREDIENT REVIEW

TABLE 4. NON-COSMETIC USE OF GLYCERYL MONOSTEARATE AS DRUG-RELEASE AGENT, SURFACTANT, AND EMULSIFIER.

<i>Drug Released/In</i>	<i>Surfactant in</i>	<i>Emulsifier in</i>
Aminophenazone/Suppositories ^(67,79-81)	Tablets ⁽⁸²⁾	Salves ⁽⁸³⁾
Azophen/Suppositories ^(84,85)	Macaroni ⁽⁸⁶⁻⁹⁰⁾	Liquid milk replacers ^(52,91,92)
Salicylate/Suppositories ⁽⁹³⁻⁹⁶⁾	Bread ^(97,98)	Ice cream ^(99,100)
Salicylate/Ointments ^(38,101)	Cakes ⁽¹⁰²⁾	Ointments ^(103,104)
Oxytetracycline/Ointments ⁽¹⁰⁵⁾	Dehydrated potatoes ⁽¹⁰⁶⁾	Dental lotions ⁽¹⁰⁷⁾
Sulfathiazole + Ephedrine/Ointments ⁽¹⁰⁸⁾	Coconut oil ⁽¹⁰⁹⁾	Cakes ^(110,111)
Sulfanilamide/Tablets ⁽¹¹²⁾	Frying oils ⁽¹¹³⁾	Bread ⁽¹¹⁴⁾
Sulfosalicylate/PVC Tablets Matrix ^(115,116)	White petroleum ⁽¹¹⁷⁾	Pasta ^(118,119)
Bromophenylamine Maleax/— ⁽¹²⁰⁾	—	Margarine ⁽¹²¹⁾
Ethyl Aminobenzoate/Dental Lotions ⁽¹²²⁾	—	Starch paste ⁽¹²³⁾
Phenindion/Capsules ⁽¹²⁴⁾	—	Peanut butter ⁽¹²⁵⁾
Isoprenaline/Tablets ⁽¹²⁶⁾	—	Food (general) ^(127,128)
Morphine-Naltrexone/Tablets ⁽¹²⁹⁾	—	—
Acetylsalicylic Acid/Tablets ^(130,131)	—	—

parent change in serum triglyceride concentrations. Only a slight increase occurred after ingestion of 50 g. Since stearic acid is a solid fat at body temperature, it may not be readily absorbed in the intestine.⁽⁷⁶⁾

The effects of Glyceryl Stearate on kidney tissue and splenic enzymes have been studied. Gall⁽⁷⁷⁾ reported that a solution of 0.5 mg/ml Glyceryl Stearate had no deleterious effect on monkey kidney tissue cultures. Blonder et al.⁽⁷⁸⁾ observed that Glyceryl Stearate did not inhibit glucocerebrosidase activity in vitro.

Animal Toxicology

Oral Toxicity

Acute

Various high doses of Glyceryl Stearate and Glyceryl Stearate/SE at concentrations greater than those used in cosmetics, were practically nontoxic when administered to rats by gavage (Table 5).

Chronic

When incorporated in the diet of rats at concentrations of 15–25% for three consecutive generations, Glyceryl Stearate had no adverse effects on body weight, growth, and reproduction. In a simultaneous study, rats which consumed a diet containing 25% Glyceryl Stearate daily for two years developed renal calcifications and their liver weight increased.⁽¹⁰⁾

Dermal Toxicity

Primary irritation

The Draize method (or a modification of it), the Federal Hazardous Substances Labeling Act (FHSLA) method, and the Department of Transportation (DOT) method were used to evaluate the potential skin irritancy of Glyceryl Stearate and Glyceryl Stearate/SE. These two substances were reported to be nonirritating or mildly irritating even when they were tested at 100 percent concentrations. The highest reported Primary Irritation Index (PII) was 1.80 out of a possible 4.00 (Table 6).

Subchronic toxicity

Glyceryl Stearate (4–5%) was applied at 2 ml/kg/day five days a week for four weeks to the clipped abraded dorsal skin of six white rabbits. Comparison of mean body weights, clinical signs, hematological results, and gross pathology results showed no significant differences between

TABLE 5. ACUTE ORAL TOXICITY.

<i>Compound</i>	<i>Conc. (Percent)</i>	<i>No. of animals/Species</i>	<i>Dose</i>	<i>LD50</i>	<i>Comments^c</i>	<i>Ref.</i>
GS ^a	33.3 in PGDD ^d	10 rats	10 g/kg	> 10 g/kg	40% fatalities at 10 g/kg-mildly toxic/ practically nontoxic	132
GS	33.3 in PGDD	10 rats	10 g/kg	> 10 g/kg	Practically nontoxic	133
GS	33.3 in PGDD	10 rats	10 g/kg	> 10 g/kg	Practically nontoxic	134
GS	33.3 in corn oil	30 rats	1.0-32.0 g/kg	> 32.0 g/kg	Relatively harmless	135
GS	20.0 in corn oil	30 rats	2-64 ml/kg	> 64 ml/kg	Relatively harmless	135
GS (protective cream)	2 (active ingredient)	10 mice	15 ml/kg	> 15 ml/kg	Relatively harmless	136
GS	100	5 rats (per grp)	—	> 5.0 g/kg	Practically nontoxic	137
GS	100	5 rats (per grp)	—	> 5.0 g/kg	Practically nontoxic	137
GS/SE ^b	33.3 in corn oil	30 rats	1.0-32.0 g/kg	> 32 g/kg	Relatively harmless	138
GS/SE	33.3 in PGDD	10 rats	10 g/kg	> 10 g/kg	40% fatalities at 10 g/kg-mildly toxic/ practically nontoxic	139
GS/SE	25 in corn oil	15 rats	7.5 and 10 g/kg	> 10 g/kg	40% fatalities at 10 g/kg-mildly toxic/ practically nontoxic	140
GS/SE	25 in PGDD	10 rats	10 g/kg	> 10 g/kg	Practically nontoxic	141
GS/SE	100	5 rats (per grp)	—	> 5 g/kg	Practically nontoxic	137

^aGlyceryl Stearate.^bGlyceryl Stearate/SE.^cAccording to Hodge and Sterner.^dPropylene glycol dicaprylate-dicaprate.

TABLE 6. PRIMARY SKIN IRRITATION.

<i>Compound</i>	<i>Protocol</i>	<i>No. of rabbits</i>	<i>Conc. (Percent)</i>	<i>PII</i>	<i>Comments</i>	<i>Ref.</i>
GS ^a	FHSLA	6	50 in corn oil	0	Nonirritating	138
GS	FHSLA	6	100	0	Nonirritating	144
GS	DOT	6	100	0	Nonirritating	144
GS	Draize	6	100	0.208	Erythema only—mostly at 24 h—mildly irritating	134
GS	Draize	6	100	0.208	One rabbit only—erythema and edema (1 +) at 24 and 72 h—mildly irritating	133
GS	Draize (Mod)	2	100	0.625	Erythema and edema at 24 and 72 h—mildly irritating	132
GS	A ^c	9	100	0.039 ^d	Minimally irritating	145
GS	A	9	20 in corn oil	0.039 ^d	Minimally irritating	145
GS	Draize	3	3.0 in mineral oil	0.5	Erythema at 24 h only—mildly irritating	146
GS	A	9	50 in corn oil	0.72 ^d	Mildly irritating	145
GS	A	9	50 in corn oil	0.11	Mildly irritating	137
GS	A	9	100	1.8	Mildly irritating	148
GS	A	9	100	1.6	Mildly irritating	148
GS	A	9	100	1.6	Mildly irritating	148
GS	A	9	100	1.4	Mildly irritating	148
GS	A	9	100	1.2	Mildly irritating	148
GS	A	9	100	1.5	Mildly irritating	148
GS	A	9	100	1.4	Mildly irritating	148
GS	A	9	100	1.33	Mildly irritating	148
GS	A	9	100	0.33	Minimally irritating	148
GS	A	9	50 in corn oil	0.06	Minimally irritating	148
GS (Protective cream)	Draize	3	2.0 (active ingredient)	0.5	Erythema at 24 h only—mildly irritating	136

GS (First aid cream)	A	3	5.0 (active ingredient)	0.89	Mildly irritating	149
GS (Blemish stick)	A	9	13.8 (active ingredient)	0.89	Mildly irritating	150
GS (Suntan lotion)	A	9	2.0 (active ingredient)	0.5	Mildly irritating	136
GS/SE ^b	Draize	6	100	0	Nonirritating	141
GS/SE	Draize	6	100	0	Nonirritating	140
GS/SE	Draize	6	100	0.25	Mildly irritating	139
GS/SE	FHSLA	6	50 in corn oil	0	Nonirritating	144
GS/SE	FHSLA	6	50 in corn oil	0	Nonirritating	135
GS/SE	DOT	6	50 in corn oil	0	Nonirritating	135
GS/SE	Draize (Mod)	3	5.0 in water	0	Nonirritating	146
GS/SE	A	9	50 in corn oil	0.22 ^d	Mildly irritating	145
GS/SE	A	9	50 in corn oil	0.50	Mildly irritating	137
GS/SE	A	9	50 in corn oil	0.63	Mildly irritating	137
GS/SE	A	9	50 in corn oil	0.66	Mildly irritating	137
GS/SE	A	9	50 in corn oil	0.38	Mildly irritating	137
GS/SE	A	9	50 in corn oil	0	Nonirritating	137
GS/SE	A	9	50 in corn oil	0.17	Minimally irritating	137

^aGlyceryl Stearate.^bGlyceryl Stearate/SE.^c0.5 ml applied to clipped intact back of each animal under occlusive patch. Patch removed at 24 h. Site scored at 24 and 72 h.⁽¹⁴⁷⁾^dMaximum score (PII) = 4.

COSMETIC INGREDIENT REVIEW

Glyceryl Stearate-treated rabbits and untreated controls. Animals treated with the Glyceryl Stearate solution developed such moderate irritation as slight to moderate desquamation and slight to well-defined erythema in all animals and many cases of atonia and fissuring.⁽¹⁴²⁾

Chronic toxicity

A 4–5% solution of Glyceryl Stearate was applied at 2 ml/kg/day five days a week for 13 weeks to the clipped abraded dorsal skin of six white rabbits. Slight to moderate erythema, edema, atonia, and occasional fissuring occurred in all test animals. Dermatopathologic findings consisted of dermal inflammatory cell infiltrates, hyperkeratosis, and acanthosis. There were no changes in body weight, no gross toxic effects, no gross skin lesions, and no changes in organ weight attributable to the test material. It was concluded that the Glyceryl Stearate-solution was a moderate skin irritant.⁽¹⁴³⁾

Sensitization

The Landsteiner/Jacobs Method and the Kligman Maximization Procedure were used to determine the sensitizing potential of Glyceryl Stearate and Glyceryl Stearate/SE in guinea pigs. Glyceryl Stearate and Glyceryl Stearate/SE proved to be nonsensitizing (Table 7).

Eye Irritation

The Draize procedure or a modification of it was used to evaluate the potential eye irritancy of Glyceryl Stearate and Glyceryl Stearate/SE. The ingredient was instilled into one eye of each test rabbit. In four tests, some eyes were rinsed after the introduction of the test substance. Eye irritation was scored for a specified number of days after the ingredient was instilled. These studies indicate that Glyceryl Stearate and Glyceryl Stearate/SE are nonirritating to mildly irritating to the eye at concentrations up to 100%. The highest reported mean irritation score at any time was 7 (maximum score = 110) (Table 8).

Carcinogenicity

Glyceryl Stearate was fed to 53 mice at doses of 50–100 mg daily until the animals died. Three mice (5.6%) developed brain tumors on the upper surface of the frontal lobe, consisting mainly of differentiated nerve cells. Glyceryl Stearate (50–100 mg/day) plus cholesterol (4–5 mg/day) in the diet induced brain tumors in ten of 72 mice (13.8%). Of 80 mice fed 4–5 mg/day cholesterol alone, 20 developed brain tumors (25%) but none of the 188 control mice did.⁽¹⁵²⁾

A diet containing 1.5% Glyceryl Stearate was fed to mice daily until they died to determine if the ingredient induced gastric tumors. Two or 1.7% of the 115 mice developed forestomach papillomas. Two of the 195 control mice (1.0%) developed forestomach papillomas.⁽¹⁵³⁾

Saffiotti and Shubik⁽¹⁵⁴⁾ tested the tumor promoting activity of Glyceryl Stearate on the clipped dorsal skin of Swiss mice. One week after a single application of 9,10-dimethylbenz(a)anthracene (DMBA) (1–1.5% in mineral oil), 5% Glyceryl Stearate (in acetone) was applied to skin twice weekly. No tumors developed; slight epidermal hyperplasia at the site of application was noted.

Glyceryl Stearate, administered orally in doses of 2.5 or 10 mg/day for five days, was not an effective antitumor agent in mice implanted with one-day-old Erlich ascites carcinomas.⁽¹⁵⁵⁾

Clinical Assessment of Safety**Single Insult Patch Test (SIPT)**

Seven lots of Glyceryl Stearate were tested for irritation on panels of 20 subjects each. A single occlusive patch containing the undiluted test material was applied to each subject's skin and left in place for 24 h. Patches were then removed and the skin sites scored for irritation. Of the 140 patches applied, only six resulted in irritation (no score was greater than 2 in a maximum of 4). The results indicated that undiluted Glyceryl Stearate is, at worst, a mild irritant.⁽¹⁴⁸⁾

A blemish stick and a first aid cream containing 13.8% and 5.0% Glyceryl Stearate, respectively, were tested for potential skin irritancy using a SIPT. Each formulation was applied under occlusion to 20 subjects. The PII's for the blemish stick and first aid cream were 0.03 and 0.3, respectively (maximum score = 4.0), indicating mild irritation.^(150,159)

A modified Maibach Cumulative Irritancy Test was used to study a hair product containing

TABLE 7. SENSITIZATION.

<i>Compound</i>	<i>Dose/ Conc. (percent)</i>	<i>Method</i>	<i>No. of Guinea pigs</i>	<i>No. of Induction Phases/ Route/Time</i>	<i>Rest period</i>	<i>Challenge (site)</i>	<i>Comments</i>	<i>Ref.</i>
GS ^a	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	132
GS	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	133
GS	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	134
GS	5 ^c	Kligman Max.	10	6 applied to abraded skin; every other day	2 weeks	0.5 ml	Nonsensitizing	151
GS/SE ^b	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	141
GS/SE	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	140
GS/SE	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	139

^aGlyceryl Stearate^bGlyceryl Stearate/SE^cBooster of 75% GS in petrolatum (0.05 ml) applied occlusively for 48 h one week after last induction application.

TABLE 8. DRAIZE PRIMARY EYE IRRITATION.

Compound	No. of rabbits	Conc. (Percent)	Eye wash Y/N	Scores (Max = 110) Day						Comments	Ref.
				1 h	1	2	3	4	5		
GS ^a	9	100	Y	0	0	0	0	0	0	Nonirritating	156
GS	9	100	Y	0	0	0	0	0	0	Nonirritating	144
GS	6	100	N	—	0	0	0	—	—	Nonirritating	138
GS	3	3.0 in mineral oil	N	0	0	0	0	0	0	Nonirritating	157
GS	6	20 in corn oil	N	—	1	1	1	0	0	Minimally irritating	145
GS	6	100	N	—	2	1	0	0	0	Minimally irritating	148
GS	6	50 in corn oil	N	—	6	3	1	0	0	Mildly irritating	137
GS (Suntan lotion)	3	2.0 (active ingredient)	N	—	0	0	0	0	0	Nonirritating	136
GS (Blemish stick)	3	13.8 (active ingredient)	N	—	4	0	—	—	—	Minimally irritating	150
GS (First aid cream)	2	5.0 (active ingredient)	N	—	1	1	0	—	—	Minimally irritating	149
GS (Protective cream)	3	2.0 (active ingredient)	N	0	0	0	0	0	0	Nonirritating	136

GS/SE ^b	6	100	N	—	0	0	0	—	—	Nonirritating	158
GS/SE	9	50	Y	67	0	0	0	0	0	Minimally irritating	135
GS/SE	3	5.0 in water	N	0	0	0	0	0	0	Nonirritating	146
GS/SE	6	50 in corn oil	Y	—	1	1	0	0	0	Minimally irritating	137
GS/SE	6	50 in corn oil	N	—	1	1	0	0	0	Minimally irritating	137
GS/SE	6	50 in corn oil	N	—	1	1	0	0	0	Minimally irritating	137
GS	6	100	N	—	0	—	—	—	—	Nonirritating	137
GS	6	100	N	—	6	2	1	1	0	Slightly irritating	137
GS	6	100	N	—	5	2	1	0	—	Minimally irritating	137
GS	6	100	N	—	7	2	0	—	—	Slightly irritating	137
GS	6	100	N	—	4	2	1	—	0	Mildly irritating	137
GS	6	100	N	—	1	0	—	—	—	Nonirritating	137
GS	6	100	N	—	3	2	0	—	—	Mildly irritating	137
GS	6	100	N	—	2	2	0	—	—	Mildly irritating	148
GS	6	100	N	—	1	1	0	—	—	Minimally irritating	148
GS	6	100	N	—	2	1	0	—	—	Minimally irritating	148
GS	6	100	N	—	1	1	0	—	—	Minimally irritating	137
GS	6	50 in corn oil	N	—	2	0	—	—	—	Minimally irritating	137

^aGlyceryl Stearate^bGlyceryl Stearate/SE

Y = Yes

N = No

COSMETIC INGREDIENT REVIEW

12.5% Glyceryl Stearate on seven males and females. The test material was applied under occlusion to the back of each subject for 24 h; upon patch removal, sites were scored and a fresh patch applied. This procedure was repeated daily for 21 days. Although it produced minimal or definite erythema in five subjects, the product containing 12.5% Glyceryl Stearate was considered to be "essentially nonirritating," when compared to positive and negative control values.⁽¹⁶⁰⁾

Repeated Insult Patch Test (RIPT)

A RIPT was used on 61 subjects to evaluate the potential irritancy and sensitizing effect of 20% Glyceryl Stearate in a 10% mineral oil/10 percent petrolatum vehicle. Ten to fifteen 24-hour occlusive patches were applied for two to three weeks. After a 10- to 14-day rest, a challenge patch was applied to either the original or a virgin site; the sites were scored on patch removal. Twenty percent Glyceryl Stearate did not induce sensitization.⁽¹³⁷⁾

Patches containing 20% Glyceryl Stearate in petrolatum were applied daily for three days to the arms of 1206 subjects; the Chamber method was used. None of the subjects developed allergic reactions.⁽¹⁶¹⁾

A suntan lotion and a face cream, each containing 2.0% Glyceryl Stearate, were tested with a RIPT. Ten occlusive 24-hour patches containing the test substance were applied to one arm of each of 19 subjects for two weeks. Patch sites were scored 24 hours after each patch was removed, before a fresh patch was reapplied. Ten to 14 days after the removal of the tenth induction patch, 24-hour challenge patches were applied to each original site as well as to a virgin site. Sites were scored 24 and 48 h later. There were no reactions to either induction or challenge patches and it was concluded that the suntan lotion and the face cream are incapable of inducing significant irritation or sensitization.⁽¹⁶²⁾

A similar RIPT was used to evaluate a first aid cream containing 5.0% Glyceryl Stearate. Occlusive patches with the test product were applied for 24 h to subject's skin once daily for two to three weeks. After a 10- to 14-day rest, a single occlusive 24-hour challenge patch was applied. Thirty-one of the 52 subjects tested experienced minimal irritation to the induction patches but none had a sensitization reaction to the challenge patch.^(147,149)

The same first aid cream was tested for cumulative irritancy in a Maibach 21-day Cumulative Irritancy Test. Occlusive patches containing the test product were applied to the backs of nine subjects. The patches were removed 24 h later, the sites scored, and fresh patches reapplied to the site. This procedure was repeated until 21 patches had been applied. The cumulative irritation index for this formulation was calculated to be 48 (maximum score = 756).⁽¹⁴⁹⁾

Photoallergy and Phototoxicity

A suntan lotion and a face cream, each containing 2% Glyceryl Stearate, were tested for potential phototoxicity and photoallergenicity. For the phototoxicity test, 0.2 ml of the lotion was tested under occlusive patches to a tape-stripped area of each arm of the subject. The patches were removed 24 h later and the sites scored for irritation. The contact site of the left arm was designated as the nonirradiated control and that of the right arm was exposed to four FYBL black lights (maximum output = 360 nm) at a dose of 4400 $\mu\text{W}/\text{cm}^2$ for 15 min at a distance of 10–12 cm. Immediately after irradiation and after 24, 48, and 168 h, none of the ten subjects showed reactions, either at control or irradiated sites. It was concluded that the two formulations are nonphototoxic.⁽¹⁶²⁾

For the photoallergy test, the protocol was similar to that used above except that patches were applied and the sites irradiated every other day until ten patches had been applied. After a two-week rest, 24-hour challenge patches were applied to the original and to virgin sites. The treated sites were scored upon patch removal and then they were irradiated. Treated sites were again scored at 24, 48, and 72 h after irradiation. Occasional irritation occurred at various sites but both products were considered to be "incapable of producing significant photoallergy" in humans.⁽¹⁶²⁾

Other Clinical Experience

Rudzki et al.⁽¹⁶³⁾ added various emulsifiers to a base containing a known irritant to determine if the emulsifiers enhanced percutaneous absorption. Patches containing various concentrations of potassium dichromate in a white paraffin base were applied to the arms of 66 men and women. When 10% Glyceryl Stearate was added to each patch, subjects reacted to lower dichromate concen-

ASSESSMENT: GLYCERYL STEARATE AND GLYCERYL STEARATE/SE

trations. An in vitro study showed that 10% Glyceryl Stearate enhanced release of Cr(VI) from the white paraffin base.

Worker Experience

A chemical manufacturing company which has been producing Glyceryl Stearate and Glyceryl Stearate/SE for 14 years has no complaints of adverse reaction from any employee directly involved with the handling of these ingredients.⁽¹⁶⁴⁾

SUMMARY

Glyceryl Stearate and Glyceryl Stearate/SE are the esterification products of glycerine and stearic acid. Glyceryl Stearate/SE contains excess stearic acid reacted with potassium hydroxide to produce a self-emulsifying product. Both Glyceryl Stearate and Glyceryl Stearate/SE are white to cream-colored wax-like solids. Either ingredient may contain mono-, di-, and triglyceride impurities and fatty acid impurities.

Glyceryl Stearate and Glyceryl Stearate/SE are widely used in cosmetic formulations as emollients, auxiliary emulsifiers, viscosifiers, stabilizers, bases, and surfactants. Glyceryl Stearate is used in more than 1200 cosmetic formulations at concentrations of ≥ 0.1 –50%; Glyceryl Stearate/SE is used in over 200 cosmetic products at concentrations of ≥ 0.1 –50%.

Glyceryl Stearate is also widely used in foods as a surfactant, emulsifier, and thickener. Glyceryl Stearate is an antistalant and dough conditioner in breads and is also used in pharmaceutical bases. Glyceryl Stearate has been granted regulatory status as GRAS ingredient, an indirect food additive, a direct food additive, and as an OTC substance.

In acute oral toxicity studies in rats, Glyceryl Stearate and Glyceryl Stearate/SE were nontoxic or mildly toxic. In chronic studies, 15–25% Glyceryl Stearate in the diet of rats for three consecutive generations had no adverse effects. Rats fed a diet containing 25% Glyceryl Stearate for two years developed renal calcifications.

Glyceryl Stearate and Glyceryl Stearate/SE at concentrations of up to 100% were reported to be mildly irritating or nonirritating to the skin of rabbits. In subchronic and chronic dermal toxicity tests, 4–5% Glyceryl Stearate was nontoxic to rabbits but did cause moderate irritation (slight to moderate erythema, edema, atonia, desquamation, and/or fissuring). In seven guinea pig sensitization studies, it was concluded that neither Glyceryl Stearate nor Glyceryl Stearate/SE was capable of inducing sensitization.

In primary eye irritation studies, Glyceryl Stearate and Glyceryl Stearate/SE at concentrations up to 100% were mildly irritating or nonirritating when instilled in the eyes of rabbits.

Glyceryl Stearate, fed to mice in doses of 50–100 mg/day or 1.5% in the diet until they died, did not induce significant brain or gastric tumor formation, respectively. Five percent Glyceryl Stearate did not promote the carcinogenicity of DMBA in mouse skin.

Single and Repeated Insult Patch Tests used to evaluate human skin irritation and sensitization potential of Glyceryl Stearate and Glyceryl Stearate/SE showed both ingredients to be nonsensitizing and nonirritating. Products containing 2% Glyceryl Stearate were nonphototoxic and nonphotoallergic. Worker experience shows that Glyceryl Stearate and Glyceryl Stearate/SE are nonirritating to human skin.

DISCUSSION

Glyceryl Stearates are used in 1,400 cosmetic formulations to regulate their thixotropic indices and viscosity. The viscosity of the emulsions containing these compounds is directly proportional to the amount of Glyceryl Stearates present. Thus, products that contain up to 3% are lotions and those containing 10% are creams.

In food products, Glyceryl Stearates are used as antistalants, surfactants, emulsifiers, flavor dispersants, antisticking, and thickening agents. They are GRAS ingredients and have been approved as direct food additives by the Food, Drug and Cosmetic Act. The compounds have also

COSMETIC INGREDIENT REVIEW

been used in pharmaceutical preparations for about 40 years. In pharmaceuticals they are largely used as solidifiers and controlled release agents. They are also used in suppositories. It is not surprising, therefore, to find extensive literature on the preparation, usefulness, and safety of these ingredients. There are, in addition, numerous unpublished data on animal tests applicable to the assessment of the safety of these ingredients.

Glyceryl Stearates have been subjected to a number of chronic toxicity tests that show no adverse effects on reproduction in rats fed high levels in the diet through three generations,⁽¹⁰⁾ no tumor initiation^(152,153) and no tumor promotion in mice.⁽¹⁵⁴⁾

Clinical safety data are limited, but long clinical experience and abundant animal studies prove these compounds to be nonsensitizing, nonphototoxic and nonphotosensitizing. Human phototesting, single and repeated patch testing has been carried out on too few subjects, but none of the available data provides suspicion of risk associated with the use of Glyceryl Stearate and Glyceryl Stearate/SE as cosmetic ingredients. Furthermore, chemical manufacturing worker experience for 14 years has produced no adverse employee reactions.

CONCLUSION

On the basis of the available animal data and clinical experience presented in this report, the Panel concludes that Glyceryl Stearate and Glyceryl Stearate/SE are safe for topical application to humans in the present practices of use and concentration.

ACKNOWLEDGMENT

Mr. Kevin Fisher, Scientific Analyst and writer, prepared the literature review and technical analysis used by the Expert Panel in developing this report.

REFERENCES

1. ESTRIN, N.F. (ed.). (1977). *CTFA Cosmetic Ingredient Dictionary*, 2nd ed. Washington, DC: Cosmetic, Toiletry and Fragrance Assoc.
2. CRESSEY, S. (1957). Glyceryl monostearate in food. *Food Manuf.* **32**, 165-8, 175.
3. COSMETIC, TOILETRY and FRAGRANCE ASSOCIATION (CTFA). (1974). *CTFA Standards: Cosmetic Ingredient Descriptions*. Washington, DC.
4. VERKADE, P.E. and VAN DER LEE, J. (1936). The synthesis of glycerides with the help of trityl compounds. II. Diaciddiglycerides. *Rec. Trav. Chim.* **55**, 267-77.
5. BERTONI, M.H., RATSZTEOM DE GYMERYNG, F., and CATTANEO, P. (1963). Studies on monoglycerides. I. Preparation of pure monoglycerides of saturated fatty acids. *Methods of determination. Rev. Arg. Grasas Aceites* **(591)**, 3-12.
6. VEIKHERTZ, I. (1932). Preparation of glycerol mono- and distearates. *Khim. Farm. Prom.* 284-6.
7. LICHNEROVA, I. (1970). Properties of glycerol esters of higher fatty acids studied as auxiliary substances for rectal administration. *Acta Fac. Pharm.* **70(18)**, 117-67.
8. MAJOR, F. and PEARMAN, R.W. (1948). Shark liver oil from Trinidad. *Bull. Imperial Inst.* **(4691)**, 53-6.
9. MERAT, P. (1949). Hydrogenated whale oil. Its industrial uses. *Oleagineux* **4(4)**, 203-12.
10. SEGALAS, L. (1971). Use and toxicity of glyceryl monostearate in bakery products. *Afinidad* **28(288)**, 735-8.
11. HAWLEY, G.G. (ed.). (1971). *The Condensed Chemical Dictionary*, 8th ed. New York: Van Nostrand Reinhold.
12. WINDHOLZ, M. (ed.). (1976). *The Merck Index*, 9th ed. Rahway, NJ: Merck and Co.
13. CORNISH, R.M. (1968). Glyceryl monostearate. *J. Soc. Cosmet. Chem.* **19**, 109-17.
14. MALKIN, T. and EL SHURBAGY, M.R. (1936). X-ray and thermal examination of the glycerides. *J. Chem. Soc.* 1628-34.

*Available upon request: Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Ave., NW, Washington, DC 20005.

ASSESSMENT: GLYCERYL STEARATE AND GLYCERYL STEARATE/SE

15. MORRISON, R.T. and BOYD, R.N. (1973). *Organic Chemistry*, 3rd ed. New York: Allyn and Bacon, Inc.
16. SENZEL, A.J. (ed.). (1977). Analysis of thiglycolate hair straightener creams. Newburger's Man. Cosmet. Anal., 2nd ed., p. 85.
17. YANISHLIEVA, N. and POPOV, A. (1971). Effect of hydroxy compounds on the autoxidation of unsaturated fatty acid methyl esters in the initial stage of the process. *Izv. Otd. Khim. Nauki, Bulg. Akad. Nauk.* **4**(3), 389-400.
18. ARMSTRONG, N.A. (1968). The hydrolysis of monostearin in an acidic medium. *J. Soc. Cosmet. Chem.* **19**(11), 707-11.
19. NOVITSKAYA, G.V. and VERESHCHAGIN, A.G. (1969). Chromatographic separation of higher fatty acid monoglycerides to chain and unsaturation. *J. Chromatogr.* **40**(3-4), 422-30.
20. SAHASRABUDHE, M.R. (1967). Chromatographic analysis of polyglycerols and their fatty acid esters. *J. Am. Oil Chem. Soc.* **44**(7), 376-8.
21. BINDLER, F., LAUGEL, P., and HASSELMANN, M. (1979). Thin-layer chromatography with a flame ionization detector. Possibilities and limits of use of the method in food chemistry. *Dtsch. Lebensm.-Rundsch.* **75**(4), 111-8.
22. NEISSNER, R. (1978). Preparation, analysis and TLC separation of partial esters of fatty acids with polyvalent alcohols. *Fette, Seifen, Anstrichm.* **80**(8), 303-11.
23. SINSEL, J.A., LARUE, B.M., and MCGRAW, L.D. (1975). High-pressure liquid chromatographic analysis of glyceride-base lubricants. *Anal. Chem.* **47**(12), 1987-93.
24. SUCKER, H. (1964). Qualitative analysis of salves. IX. Adsorption chromatographic separation of emulsifiers. *Arch. Pharm.* **297**(9), 543-6.
25. WEKELL, J.C., HOULE, C.R., and MALINS, D.C. (1964). A method for the isolation of mono- and dihydric alcohols from complex mixtures. *J. Chromatog.* **14**(3), 529-31.
26. GOLUB, A.I. and PETROVA, L.M. (1972). Gas-chromatographic determination of stearin in phenol-formaldehyde resins. *Khim. Prom.* **48**(6), 470-1.
27. SUFFIS, R., SULLIVAN, T.J., and HENDERSON, W.S. (1965). Identification of surface active agents as trimethylsilyl ether derivatives by gas chromatography. *J. Soc. Cosmet. Chem.* **16**(13), 783-94.
28. WEAST, R.D. (ed.). (1978). *CRC Handbook of Chemistry and Physics*, 59th ed. West Palm Beach, Florida: CRC Press.
29. SCHWARTZBERG, S. (1961). Allergic eczematous contact dermatitis caused by sensitization to glyceryl monostearate. *Ann. Allergy* **19**(4), 402-3.
30. GOLDSMITH, H.A. (1943). Nonionic surface-active agents display unique characteristics. *Chem. Ind.* **52**, 326-8.
31. BALSAM, M.S. (ed.). (1972). *Cosmetics: Science and Technology*, 2nd ed. New York: Interscience Publishers.
32. NEWBURGER, S.H. (1947). Analysis of a sunburn-preventive cream. *J. Assoc. Offic. Agr. Chem.* **30**, 683-90.
33. GUERNET, M., ESPINASSOU, E., and HAMON, M. (1973). Periodimetric assay in nonaqueous medium. *Ann. Pharm. Fr.* **31**, 343-8.
34. VAN GORKOM, M., VAN DER MOLEN, M.H., and KORVER, O. (1975). ESR study of aqueous dispersions of beta-lactoglobulin and spin-labelled glyceryl monostearate. *Biochim. Biophys. Acta* **392**(1), 141-7.
35. NOLL, H. and JACKIM, E. (1958). The chemistry of the native constituents of the acetone-soluble fat of *Mycobacterium tuberculosis* (Brevannes). I. Glycerides and phosphoglycolipides. *J. Biol. Chem.* **232**(2), 903-17.
36. CHESHKO, F.F. and SHVAIKA, T.N. (1971). Synthesis and identification of some mono- and dicarboxylic acid esters. *Zh. Prikl. Khim.* **44**(5), 1107-16.
37. FORMAN, B.J. and GRADY, L.T. (1969). Inclusion compounds in pharmaceutical analysis. I. Determination of dieneol in dieneol cream. *J. Pharm. Sci.* **58**, 1262-5.
38. BEHR, M. and KASSEBAUM, H. (1977). Studies on the release rate of salicylic acid from ointment layers. 1. Hydrocarbon mixtures. *Fette Seifen Anstrichm.* **79**(11), 460-4.
39. CODE OF FEDERAL REGULATIONS (CFR). (1979). 21 CFR 121.101.
40. ATHERTON, J.G. and MAXCY, W.J. (1967). Effect of composition variations of glycerol esters on the physical properties of cosmetic emulsions. *Proc. Sci. Sect. Toilet. Goods Assoc.* **46**, 39-43.
41. ATHERTON, J.G. and MAXCY, W.J. (1967). Glycerol esters in cosmetic emulsions. *Drug Cosmet. Ind.* **100**(3), 50, 52, 54, 16206.

COSMETIC INGREDIENT REVIEW

42. IDSON, B. (1974). Nonionic skin lotions. *Cosmet. Perfum.* **89**, 59-61.
43. BOBBE, D., MATHIS, C., METZINGER, P., and GABLER, W. (1976). Oil suspensions for soft capsules. Rheological study of mixtures of fat excipients. *Labo-Pharma-Probl. Tech.* **24**(256), 651-61.
44. RUTKOWSKI, A. and ELSNER, Z. (1973). Rheological properties of lipophilic bases applied to cosmetics. *Cosmet. Perfum.* **88**, 23-6.
45. EROS, I. and UGRI-HUNYADVARI, E. (1977). Theoretical and practical questions of the structure-rheological research of ointments. Part 2. Effect of surface active components on the rheological properties. *Pharmazie* **32**(11), 731-6.
46. STEJSKAL, J. and UYHNANEK, K. (1957). The effect of the composition of wool-fat alcohols upon the stability of the emulsion forms in wool-fat alcohol ointments. *Parfum. Kosmet.* **38**, 566-67.
47. GOLUCKI, Z. (1966). α -Tocopherol acetate as stabilizer for ointment bases. *Farm. Pol.* **22**(5), 333-7.
48. FIERO, G.W. and DUTCHER, M.W. (1945). Glycol esters in ointment bases. *J. Am. Pharm. Assoc.* **34**, 56-9.
49. CATLAINE, E.L. (1945). Washable ointment bases. *Bull. Am. Soc. Hosp. Pharmacists* **2**, 32-3, 58.
50. MILJEVIC, D. and DANILOVIC, M. (1977). Possibility of using glycerin monostearate for hydrophylic ointments. *Arch. Farm.* (2792), 95-8.
51. FOOD and DRUG ADMINISTRATION (FDA). (Aug. 31, 1976). Product Formulation Data. Computer Printout. Washington, DC.
52. LANG, M., FORMENT, R., and DUNKLEY, W.L. (1976). Influence of composition and processing on sensory properties of nonfat milk. *J. Dairy Sci.* **59**(9), 1560-7.
53. BARRETT, F.F. (1970). New developments in multifunctional dough conditioners. *Baker's Dig.* **44**(1), 66-8.
54. BRADLEY, W.B., GASE, W.T., and LUCKA, L.O. (1948). Bread softeners. Open forum. *Proc. Am. Soc. Bakery Eng.* **24**, 53-63.
55. COPPOCK, J.B.M. (1950). Some remarks on the American baking industry. *Food* **19**(220), 14.
56. COPPOCK, J.B.M. (1954). Science and baker. *Chem. Ind.* **1954**(43), 1306-11.
57. EDELMANN, E.C., CATHCART, W.H., and BERQUIST, C.B. (1950). The effect of various ingredients on the rate of firming of bread crumb in the presence of polyoxyethylene (mono) stearate and glyceryl monostearate. *Cereal Chem.* **27**(1), 1-14.
58. HART, M.R., GRAHAM, R.P., GEE, M., and MORGAN, JR., A.I. (1970). Bread from sorghum and barley flours. *J. Food Sci.* **35**(5), 661-5.
59. HUSSAIN, M. and SATTI, M-U-H. (1970). Development of long-life roti bread. *Pakistan J. Sci. Ind. Res.* (1294), 408-10.
60. JAIN, S. and SHERMAN, P. (1976). The influence on bread texture of partially replacing wheat with potato products. *J. Texture Stud.* **7**(3), 297-311.
61. JONGH, G. (1961). The formation of dough and bread structures. I. The ability of starch to form structures, and the improving effect of glyceryl monostearate. *Cereal Chem.* (3892), 140-52.
62. JONGH, G., SLIM, T., and GREVE, H. (1968). Bread without gluten starch dough glyceryl monostearate. *Baker's Dig.* **42**(3), 24-9.
63. KIM, H.-S. and LEE, H.-J. (1977). Development of composite flours and their products utilizing domestic raw materials. Part IV. Effect of additives on the bread-making quality with composite flours. *Hanguk Sikpum Kwahakhoe Chi* **9**(2), 106-15.
64. FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY (FASEB). (1976). Evaluation of the Health Aspects of Glyceryl Stearate.
65. RUBBO, S.D. and DAVEY, M.E. (1945). Some laboratory findings pertaining to the clinical use of penicillin. *Med. J. Australia* **32**(25), 449-53.
66. MEZEY, G. (1971). Effect of lipophilic emulsifiers on drug release from suppositories made with cocoa butter. *Pharmazie* **26**(3), 166-9.
67. KEDVESSY, G. and REGDON, G. (1962). Viscosity of suppository masses. *Pharm. Zentralhalle* **101**, 389-98.
68. REGDON, G. and KEDVESSY, G. (1962). Effect of viscosity of the rat material on the homogeneity of suppositories prepared by a casting method. *Gyogyszereszet* **6**, 452-8.
69. TORRADO-VALEIRAS, J.J. (1969). Stability of suppositories. *Anales Real Acad. Farm.* **35**(3), 375-92.
70. LICHNEROVA, I. and CHALABALA, M. (1968). Glycerin esters of some higher fatty acids as pharmaceutical auxiliary substances. III. Melting and solidification of binary and ternary systems. *Cesk. Farm.* **17**(6), 279-81.

ASSESSMENT: GLYCERYL STEARATE AND GLYCERYL STEARATE/SE

71. LICHNEROVA, I. and CHALABALA, M. (1969). Glycerin esters of some higher fatty acids as pharmaceutical auxiliaries. IV. Rheological properties. *Cesk. Farm.* **18**(8), 369-72.
72. TOROSIAN, G. and LEMBERGER, A.P. (1968). Surface films of soybean lecithin. II. Interactions between lecithin and lipid substances in mixed monomolecular films. *J. Pharm. Sci.* **57**(1), 17-22.
73. TRIVEDI, B.M. and PATEL, R.K. (1970). Stability studies on dermostatin in selected ointment bases. *Hindustan Antibiot. Bull.* **12**(4), 131-7.
74. CONLEY, A.J. and KABARA, J.J. (1973). Antimicrobial action of esters of polyhydric alcohols. *Antimicrob. Agents Chemother.* **4**(5), 501-6.
75. WEDDEBURN, D.L. (1958). Preservation of toilet preparations containing nonionics. *J. Soc. Cosmet. Chem.* **9**, 210-28.
76. PINTER, K.G. and KARLE, I.P. (1966). Effect of ingestion of various mono- and triglycerides on serum triglyceride concentration. *Am. J. Clin. Nutr.* **18**(3), 165-8.
77. GALL, D. (1966). Adjuvant activity of aliphatic nitrogenous bases. *Immunology* **11**(4), 369-86.
78. BLONDER, E., KLIBANSKY, C., and DE VRIES, A. (1976). Effects of detergents and choline-containing phospholipids of human spleen glucocerebrosidase. *Biochim. Biophys. Acta.* **431**(1), 45-53.
79. BORNSCHEIN, M., VOIGHT, R., and PETRI, U. (1978). Effect of particle glycerides on the release of aminophenazone from suppositories. *Pharmazie* **33**(9), 591-3.
80. ELSNER, Z., KROWCZYNSKI, L., and LESZCZYNSKA-BAKAL, H. (1966). Effect of some viscosity-increasing substances on the suppository base Lasupol G. *Pharmazie* **21**(12), 761-5.
81. GYARMATI, L., RACZ, I., CSONTOS, A., and SATORY, E. (1972). Examination of Halidorfumarats release from suppositories. *Acta Pharm. Hung.* **42**(6), 278-85.
82. FUCHS, P., SCHOTKY, E., and SCHENCK, G. (1970). Effect of surface-active agents as lubricants for tablets on the release of active substance from compressed pharmaceutical products. *Pharm. Ind.* **32**(7), 581-3.
83. EROS, I., and HUNYADVARI, E. (1972). Effect of some water/oil emulsifiers on the structural rheological properties of salves. *Sci. Pharm.* **40**(1), 28-35.
84. SZEL, M. and REGDON, G. (1977). Biopharmaceutical investigation of suppositories containing phenazone. Part I. Description of the investigation methods and study of physical parameters of the suppositories. *Gyogyszereszet* **21**(10), 370-4.
85. SZEL, M. and REGDON, G. (1978). Biopharmaceutical investigation of suppositories containing phenazone. Part I. Description of the investigation methods and study of physical parameters of the suppositories. *Gyogyszereszet* **22**(2), 51-4.
86. GAIDENKO, M.V., NAZAROV, N.I., KALOSHINA, E.N., and TSVITSIVADZE, G.V. (1975). Effect of surfactants on the drying of macaroni. *Khlebopek. Konditer. Prom-st.* **6**, 29-31.
87. KALININA, M.A., FILINA, N.D., NAZAROV, N.I., GAIDENKO, M.V., LEKHTER, A.E., and MINAEVA, S.V. (1976). Effect of surfactants on macaroni extrusion. *Khlebopek. Konditer. Prom-st.* **7**, 33-4.
88. NAZAROV, N.I., EGOVA, N.I., and KONDRATENKO, S.S. (1972). Effect of surface-active agents on the amount of carotenoids in macaroni products. *Khlebopek. Konditer. Prom.* **2**, 20.
89. NAZAROV, N.I., GAIDENKO, M.V., LEKHTER, A.E., and OBYAKOVA, G.S. (1975). Surfactants to improve macaroni products. *Khlebopek. Konditer. Prom-st.* **4**, 27-8.
90. NAZAROV, N.I., GAIDENKO, M.V., KALININA, M.A., NECHAEV, A.P., BASKAEVA, A.E., and MALOFEEVA, L.S. (1973). Effect of surface-active substances on mechanical-structural characteristics of macaroni dough. *Khlebopek. Konditer. Prom.* **3**, 23-4.
91. GORRILL, A.D.L. and NICHOLSON, J.W.G. (1972). Use of the Willems polytron to homogenize fat and disperse insoluble ingredients in high fat liquid milk replacers. *Can. J. Anim. Sci.* **52**(3), 477-84.
92. MICKLE, J.B., SMITH, W., TIETZ, J.M., TITUS, T.C., and JOHNSTON, M. (1971). Influence of emulsifier type and solubility on the stability of milk fat-water emulsions. *J. Food Sci.* **(3693)**, 423-5.
93. KAPAS, M., REGDON, E., and REGDON, G. (1979). Effect of adjuvants on the physical properties and release from suppositories containing salicylic acid derivatives. Part 2. Measurement of in vitro drug release by membrane diffusion method. *Acta Pharm. Technol.* **25**(2), 109-18.
94. REGDON, E., KAPAS, M., and REGDON, G. (1979). Effect of adjuvants on the physical properties and release from suppositories containing salicylic acid derivatives. Part 1: Experimental methods and physical parameters of suppositories. *Acta Pharm. Technol.* **25**(2), 101-8.
95. PARROTT, E.L. (1971). Salicylate absorption from rectal suppositories. *J. Pharm. Sci.* **60**, 867-72.
96. REGDON, G., REGDON, E., and KAROLYI, I. (1976). Acetylsalicylic acid-containing suppositories.

COSMETIC INGREDIENT REVIEW

- The effect of viscosity-increasing additives on the physical and chemical stability. *Dtsch. Apoth.-Ztg.* **116**(35), 1280-2.
97. GORYACHEVA, A.F., SEMENOVA, V.A., SHKVARKINA, T.I., LEKHTER, A.E., CHERN-SHEVA, D.A., OBYAKOVA, G.S., and SHUKSHINA, T.F. (1973). Improving bread quality by use of surfactants. *Khlebopek. Konditer. Prom.* **5**, 9-11.
 98. EDELMANN, E.C. and CATHCART, W.H. (1949). Effect of surface-active agents on the softness and rate of staling of bread. *Cereal Chem.* **26**(4), 345-57.
 99. GOYAL, G.K. and SRINIVASAN, M.R. (1973). Quality of soft-serve ice cream as influenced by the levels of fat, emulsifier, sucrose substitutes and processing conditions. *J. Food Sci. Technol.* **10**(3), 122-4.
 100. NIELSEN, B.J. (1976). Function and evaluation of emulsifiers in ice cream and whippable emulsions. *Gordian* **76**(7-8), 220, 222-5.
 101. ZUBER, M., CHEMTOB, C., and CHAUMEIL, J.C. (1979). Availability from dermic forms. III. Comparative study of emulsified ointments (oil/water). Use of a cell with a cellulose acetate-based membrane. *Sci. Tech. Pharm.* **8**(1), 47-52.
 102. MIKHAILOV, V.S., DOROZHINA, T.P., and DZHAFAROVA, R.I. (1974). Effect of fats with various surfactants on cake quality. *Khlebopek. Konditer. Prom-st.* **8**, 22-4.
 103. GREEN, M. (1946). Some pharmaceutical necessities newly admitted to National Formulary. *J. Am. Pharm. Assoc. Prac. Pharm. Ed.* **7**(7), 297-303.
 104. SAVOSTIKOVA, N.F., LUKYANOV, A.B., BERKENGEM, B.M., and TATARNIKOVA, N.P. (1972). Starch treated with glycerol monostearate as an effective emulsifier for cosmetic creams. *Maslo-Zhir. Prom.* **38**(4), 21-2.
 105. ZAKRZEWSKI, Z. and PIETURA, A. (1976). Study of the effect of adjuvants on the release of oxytetracycline from ointments. *Farm Pol.* **32**(4), 287-91.
 106. OORAIKUL, B. and HADZIYEV, D. (1974). Effects of surfactants, freezing, and thawing on starch and pectic substances in the production of dehydrated mashed potatoes. *Can. Inst. Food Sci. Technol. J.* **7**(3), 213-9.
 107. CHRISTENSEN, E.V. (1960). An emulsified cream for dental use. *Arch. Pharm. Chem.* **67**, 185-7.
 108. ZAKRZEWSKI, Z. and PIASECKA, H. (1977). Effect of substrate, particle size, and drug concentration on drug release from ointments. *Farm Pol.* **33**(3), 137-43.
 109. NIJYA, I., KINOSHITA, Y., IMAMURA, M., OKADA, M., and MATSUMOTO, T. (1970). Deterioration of oils and fats of the hardened coconut oil series. 7. Deterioration prevention by the addition of surfactants. *Yakagaku* **19**(7), 473-81.
 110. HODGE, D.H. (1978). Monoglycerides in cake production. *Getrede, Mehl Brot* **32**(2), 39-43.
 111. KOZMINA, E.P., CHEKMAREVA, I.B., MIKHAILOV, V.S., and DOROZHINA, T.P. (1974). Effect of different fat compositions on the quality of plum-cake. *Izv. Ucheb. Zaved., Pisch. Tekhnol.* **3**, 149-50.
 112. STARHA, L. and CHALABALA, M. (1971). Peroral drugs with protracted action. V. Relation between the molding pressure and the release of drugs. *Cesk. Farm.* **20**(1), 23-5.
 113. MEISNER, D. (1969). Succinylated monoglyceride. *Baker's Dig.* **43**(3), 38-41.
 114. KOZMINA, N.P., PLAKHOV, V.I., and FOMENOK, S.K. (1973). Effect of emulsifiers on the properties on the gluten, dough, and quality of bread. *Khlebopek. Konditer. Prom.* **10**, 7-8.
 115. SHEKERDZHIISKI, R. and TRANDAFILOV, T. (1972). Effect of additives on the separation of a solid readily soluble drug from a hydrophobic tablet matrix. *Farmatsiya* **22**(3), 39-46.
 116. SHEKERDZHIISKI, R., TRANDAFILOV, A., and TRABDAFUKIV, T. (1972). Effect of adjuvants on the escape of slightly soluble drugs from hydrophobic tablet matrix. *Pharmazie* **27**(3), 167-8.
 117. GOLUCKI, Z. (1967). Influence of surface-active substances on the absorption of water by white petrolatum. *Diss. Pharm. Pharmacol.* **19**(4), 413-6.
 118. THOREN, I. (1972). Possibilities for emulsifiers in alimentary paste preparation. *Ber. Durum-Teigwaren-Tag.* 79-87.
 119. MAGGIO, B., and LUCY, J.A. (1976). Polar-group behavior in mixed monolayers of phospholipids and fusogenic lipids. *Biochem. J.* **155**(2), 353-64.
 120. GROVES, M.J. and GALINDEZ, F.E. (1976). The effect of environmental conditions on the release of brompheniramine from protein/wax matrix tablets. *Acta Pharm. Suec.* **(1394)**, 373-84.
 121. ABDEL-RAHMAN, A.-H.Y. (1975). Production of margarine oil from cottonseed oil and corn oil. *J. Oil Technol. Assoc. India* **7**(4), 99-100.
 122. ALLEN, B.F., and LEVINE, P.J. (1958). Dental lotion. *J. Am. Pharm. Assoc., Pract. Pharm. Ed.* **19**, 154-5.

ASSESSMENT: GLYCERYL STEARATE AND GLYCERYL STEARATE/SE

123. ORTHOEFER, F.T. (1976). Effect of type of fat on starch pastes containing glycerol monostearate. *Cereal Chem.* **53**(4), 561-5.
124. KASSEM, M.A., SALAMA, H.A., AMMAR, H.O., and EL-RIDY, M.S. (1977). On the dissolution and bioavailability of phenindion. III. Dissolution and bioavailability of phenindione capsules. *Pharm. Ind.* **39**(4), 396-9.
125. NEELAKANTAN, S. and MANIMEGALAI, G. (1978). Studies on peanut butter—a feasibility report and varietal trails. *Fats Oil Relat. Food Prod., Their Prep., Symp.* 33-7.
126. KASSEM, A.A., EL-GENDY, A.R., and RIFAAT, N.E. (1970). Release of isoprenaline sulfate from certain sublingual tablet bases. *Bull. Fac. Pharm., Cairo Univ.* **8**(1), 161-7.
127. ARMENGOL, J., GASULL, E., and MARQUES, J. (1974). Contents of mono-, di-, and triglycerides in food emulsions. *An. Bromatol.* **26**(4), 357-89.
128. TENNEY, R.J., and SKILLICORN, A.T. (1972). Comparative effects of sodium stearyl-2-lactylate and various emulsifiers in simple oil-water emulsions and food systems. *Food Prod. Develop.* **6**(5), 80-2, 84.
129. MISRA, A.L. and PONTANI, R.B. (1978). An improved long-acting delivery system for narcotic antagonists. *J. Pharm. Pharmacol.* **30**(5), 325-6.
130. BUENSOD, M. and FAVARGER, P. (1956). Digestibility of palmitic and stearic acids and their glycerol esters in the rat. *Helv. Physiol. Pharmacol. Acta.* **14**, 299-303.
131. JAMINET, F. and LOUIS, G. (1968). Effect of some lubricants on the stability of aspirin in compressed tablets. *Pharm. Acta Helv.* **43**(3), 153-7.
132. INOLEX LABS. (1975). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 1D.*
133. INOLEX LABS. (1975). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 1E.*
134. INOLEX LABS. (1975). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 1F.*
135. BIO-TOXICOLOGY LABS (BTL). (1975). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 2B.*
136. LEBERCO LABS. (1978). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 6.*
137. AVON PRODUCTS. (1976). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 3.*
138. HILL TOP RESEARCH. (1968). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 2C.*
139. INOLEX LABS. (1975). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 1C.*
140. INOLEX LABS. (1975). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 1B.*
141. INOLEX LABS. (1976). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 1A.*
142. HAZELTON LABS AMERICA. (1977). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 7.*
143. INTERNATIONAL RESEARCH and DEVELOPMENT. (1977). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 7.*
144. BTL. (1975). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 2D.*
145. AVON PRODUCTS. (1980). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 3.*
146. LEBERCO LABS. (1976). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 4.*
147. CTFA. (Nov. 4, 1980). Submission of data. Supplementary Information. Memorandum.*
148. AVON PRODUCTS. (1973). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 3.*
149. CTFA. (1978). Submission of data. Unpublished safety data on Glyceryl Stearates, Sec. 6.*
150. CTFA. (1979). Submission of data. Summary of unpublished data on Glyceryl Stearates, Sec. 6.*
151. AVON PRODUCTS. (1977). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 3.*
152. SZEPSENWOL, J. (1969). Brain nerve cell tumors in mice on diets supplemented with various lipids. *Pathol. Microbiol.* **34**(1), 1-9.

COSMETIC INGREDIENT REVIEW

153. SZEPESENWOL, J. (1978). Gastro-intestinal tumors in mice of three strains maintained on fat-enriched diets. *Oncology* **35**(4), 143-52.
154. SAFFIOTTI, U. and SHUBIK, P. (1963). Studies on promoting action in skin carcinogenesis. *Natl. Cancer Inst. Monogr.* **10**, 489-507.
155. KATO, A., ANDO, K., SUZUKI, S., TAMURA, G., and ARIMA, K. (1969). Anti-tumor activity of monoglycerides and other esters of fatty acids. *J. Antibiot.* **22**(2), 83-4.
156. LEBERCO LABS. (1976). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 2C.*
157. LEBERCO LABS. (1977). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 4.*
158. HILL TOP RESEARCH. (1968). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 2B.*
159. CTFA. (1979). Submission of data. Summary of unpublished data on Glyceryl Stearates.*
160. CTFA. (1978). Submission of data. Unpublished safety data on Glyceryl Stearates, Supplement.*
161. HANNUKSELA, M., KOUSA, M., and PRIILA, V. (1976). Contact sensitivity to emulsifiers. *Contact Dermatitis* **2**(4), 201-4.
162. FOOD and DRUG RESEARCH LABS (FDRL). (1978). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 6.*
163. RUDZKI, E., ZAKRZEWSKI, Z., PROKOPCZYK, G., and KOZLOWSKA, A. (1976). Application of emulsifiers for the patch test. I. Patch test with potassium dichromate. *Dermatologica* **153**(6), 333-8.
164. EMERY INDUSTRIES. (1979). Submission of data by CTFA. Unpublished safety data on Glyceryl Stearates, Sec. 2A.*

6

Final Report on the Safety Assessment of Glyceryl Oleate

Glyceryl Oleate, the glyceryl 1-monoester of oleic acid, is used in cosmetic products as an emulsifier at concentrations up to 5%.

Oral administration of a single 13 ml/kg dose of a sunscreen formulation containing 5% Glyceryl Oleate to rats produced no signs of toxicity and no lethality.

A single exposure of undiluted Glyceryl Oleate in animal dermal irritation studies produced only minimal irritation. Daily applications of 25.0% corn oil solution of a formulation containing Glyceryl Oleate for 20 days produced severe dermal irritation in rabbits. In a 4-week dermal toxicity/phototoxicity study, product formulations containing up to 5% Glyceryl Oleate produced slight reversible dermal irritation. Subchronic and chronic toxicity data from studies with animals and humans that were used in the safety assessment of glycerides, glycerol, oleic acid, and sodium oleate are presented.

Minimal to moderate eye irritation was produced by undiluted Glyceryl Oleate in rabbits.

Glyceryl Oleate administration was associated with development of a small number of brain tumors in a two-generation study in mice. Digestive tract tumors were found in mice fed 200 mg/mouse per day Glyceryl Oleate for four-seven generations. The results of these studies were considered equivocal. Doses of 1.5 and 6.0 mg/mouse per day of Glyceryl Oleate in saline increased the survival period of mice with implanted Ehrlich ascites tumors; the higher dose inhibited tumor growth.

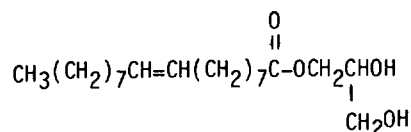
Formulations containing 5% Glyceryl Oleate were nonirritating in a human cumulative occlusive patch test and in repeat insult patch testing at 15%. Glyceryl Oleate in formulations is not phototoxic.

It is concluded that Glyceryl Oleate is safe as a cosmetic ingredient in the present practices of use and concentration.

CHEMISTRY

Chemical and Physical Properties

Glyceryl Oleate (CAS 111-03-5; 25496-72-4) is the glyceryl 1-monoester of oleic acid (*cis*-9-octadecenoic acid). The structural formula of Glyceryl Oleate is as follows⁽¹⁾:



Glyceryl Oleate occurs as off-white to yellow flakes or as a soft semisolid. It is dispersible in water and soluble in acetone, methanol, ethanol, cottonseed oil, and mineral oil.⁽²⁾ Glyceryl Oleate is also known as Monoolein, Glyceryl Monooleate, and Glycerol Monooleate.

A summary of the properties of Glyceryl Oleate appears in Table 1. In addition, the emulsifying and physicochemical properties of several monoglycerides have been measured in a Russian study.⁽³⁾

TABLE 1. Chemical and Physical Properties^(2,9,10)

<i>Glyceryl Oleate</i>	
Molecular weight	365.55
Melting point (°C)	35
Boiling point (°C)	238–240
Density	0.9420
Acid value	5 max
Saponification value	155–170
Iodine value	48–80

Analytical Methods

Gas chromatography has been used to isolate and identify monoglycerides (via comparison with standard retention values).⁽⁴⁾ Several other procedures have been coupled with gas chromatography for the determination of the separated monoglycerides or their hydrolysis products (hydrolysis products of Glyceryl Oleate are glycerol and oleic acids). These methods are nuclear magnetic resonance spectrometry⁽⁵⁾ and a battery of spectrophotometric analyses. The most widely used chemical assay for the quantitation of glycerol or its 1-monoglycerides involves periodate or lead tetraacetate oxidation of these compounds' primary alcohol groups.^(6,7) Qualitative chemical tests to assay for the presence of glycerol involve formation of colored derivatives.^(4,6) Infrared spectrometry may also be used for functional group identification or for fingerprinting upon comparison with stock standards.⁽⁴⁾

Method of Manufacture

"Monoglycerides do not occur naturally in appreciable quantities, except in fats and oils that have undergone partial hydrolysis."⁽⁷⁾ The most important method of monoglyceride preparation is the glycerolysis of fats and oils. Depending on the molar ratios of the reactants, this transesterification reaction can yield product mixtures containing varying quantities of monoglycerides, commercially noted as "40 percent monos" and "60 percent monos."⁽⁷⁾

Separation of the monoglycerides from di- and triglycerides is usually achieved by molecular distillation of the glycerolysis product mixture, resulting in the "90 percent mono" mixture used by the cosmetic industry. These commercial 90% monoglyceride mixtures predominantly consist of α -monoglycerides; β -monoglycerides are present in smaller quantities. Isomerization of β -monoglycerides to the more stable α -isomers occurs readily.⁽⁷⁾

The Glyceryl Oleate used by the cosmetic industry may be manufactured by the glycerolysis (glycerol is normally obtained from the triglycerides of oil and fats)⁽⁸⁾ of oils containing high concentrations of oleic acid: olive oil (80% oleic acid), peanut oil (60% oleic acid), teaseed oil (85% oleic acid), or pecan oil (85% oleic acid). The Glyceryl Oleate could then be distilled from the resulting product mixture (vapor pressure of Glyceryl Oleate at 186°C is 0.2 mm).⁽⁷⁾

Impurities

Glyceryl Oleate used by the cosmetic industry is a mixture of monoglycerides consisting mainly of the compound, glyceryl α -monooleate.⁽²⁾ The stated 90% minimum monoester content as written includes both α - and β -monoglycerides of oleic acid and glycerol and may also include glycerol monoesters containing other fatty acids depending on the method of manufacture (e.g., sources of reactants).

Constituents, such as free fatty acids and glycerol, may also exist in the Glyceryl Oleate preparation at maximal concentrations of 2.5% and 1.0%, respectively.⁽²⁾

USE

Purpose, Scope, and Extent of Use in Cosmetics

Glyceryl Oleate is used primarily as an emulsifier in cosmetic products. It has been reported to the Food and Drug Administration (FDA) that Glyceryl Oleate is an ingredient in 716 cosmetic formulations. Reported concentrations ranged from $\leq 0.1\%$ to 5%. The concentrations of Glyceryl Oleate in 455 of the 716 cosmetic formulations were not reported to FDA. Cosmetic formulations containing Glyceryl Oleate are predominantly lipsticks, eye shadows, makeup bases, and skin care preparations.⁽¹¹⁾

The cosmetic product formulation listing that is made available by FDA is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.⁽¹²⁾ Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic

ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. See Table 2 for a list of cosmetic products containing Glyceryl Oleate.

Surfaces, Frequency, and Duration of Contact

Cosmetics containing these ingredients are applied to all areas of the skin and mucous membranes. These cosmetics are frequently applied to the face and have the potential for contacting the eye or being ingested from the lips. Products containing these ingredients are applied up to several times a day and can remain in contact with the skin for long periods of time.

Noncosmetic Use

Monoglycerides consisting of a mixture of glyceryl mono- and diesters, and minor amounts of triesters, that are prepared from fats or oils or fat-forming acids derived from edible sources⁽¹³⁾ are affirmed as generally recognized as safe (GRAS) substances (21 CFR 182.4505, 182.90)⁽¹²⁾ and indirect food additives (21 CFR 175.105, 176.210)⁽¹²⁾ for human consumption without restriction on their concentration (at concentrations not to exceed good manufacturing practice, GMP). Federal regulations allow the use of Glyceryl Oleate as a prior-sanctioned food ingredient (21 CFR 181.27)⁽¹²⁾ and as both an indirect (21 CFR 175.300, 175.320)⁽¹²⁾ and direct (21 CFR 172.515)⁽¹²⁾ food additive. These regulatory decisions were based on a review of data in the following areas: subchronic⁽¹⁴⁻¹⁶⁾ and chronic (multigeneration reproduction)⁽¹⁷⁾ feeding studies using Glyceryl Oleate or monoglyceride mixtures derived from oils; subchronic^(18,19) and chronic⁽²⁰⁾ feeding studies of similar glycerides; studies on the absorption and storage of Glyceryl Oleate and other monoglycerides^(17,18,21); and the well-documented metabolic fate of glycerides in the human body. Studies on the metabolites of Glyceryl Oleate, glycerol, and oleic acid as they appear in reviews used by the FDA in the regulation of glycerol, glycerides, and oleic acid are summarized in this report.

The FDA proposed affirmation of GRAS status of Glyceryl Oleate (Proposed issuance of 21 CFR 184.1323) and monoglycerides (proposed issuance of 21 CFR 184.1505) for several additional purposes in human food and concurrent deletion of its listing as a direct food additive (amendment of 21 CFR 172.515).⁽²²⁾ The listing of the most prevalent fatty acids occurring in monoglycerides in Section 184.1505 included oleic acid.⁽¹³⁾

Glyceryl Oleate is used by the pharmaceutical industry as a carrier compound,⁽²³⁾ in mixed micellar form with bile salts for the enhancement of intestinal drug absorption,⁽²⁴⁾ and for the encapsulation and/or solubilization of partic-

TABLE 2. Product Formulation Data⁽¹¹⁾

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)						
			Unreported concentration	>25-50	>10-25	>5-10	>1-5	>0.1-1	≤0.1
Glyceryl Oleate									
Baby lotions, oils, powders, and creams	56	3	3	—	—	—	—	—	—
Other bath preparations	132	1	1	—	—	—	—	—	—
Eye shadow	2582	26	15	—	—	—	10	1	—
Mascara	397	3	—	—	—	—	—	3	—
Other eye makeup preparations	230	2	1	—	—	—	—	—	1
Hair conditioners	478	5	3	—	—	—	—	—	2
Hair shampoos (noncoloring)	909	2	1	—	—	—	—	—	1
Tonics, dressings, and other hair grooming aids	290	1	—	—	—	—	—	—	1
Blushers (all types)	819	9	8	—	—	—	1	—	—
Makeup foundations	740	8	8	—	—	—	—	—	—
Lipstick	3319	570	355	—	—	—	—	—	215
Makeup bases	831	25	24	—	—	—	—	—	1
Rouges	211	2	2	—	—	—	—	—	—
Other makeup preparations (not eye)	530	7	—	—	—	—	—	—	7
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	8	5	—	—	—	1	1	1
Face, body, and hand skin care prepa- rations (excluding shaving prepa- rations)	832	12	9	—	—	—	2	—	1
Hormone skin care preparations	10	1	—	—	—	—	—	—	1
Moisturizing skin care preparations	747	14	7	—	—	—	3	3	1
Night skin care preparations	219	5	2	—	—	—	1	2	—
Paste masks (mud packs)	171	1	—	—	—	—	—	—	1
Wrinkle smoothers (removers)	38	1	1	—	—	—	—	—	—
Suntan gels, creams, and liquids	164	7	7	—	—	—	—	—	—
Other suntan preparations	28	3	3	—	—	—	—	—	—
1981 TOTALS		716	455	0	0	0	18	10	233

ular drugs.⁽²⁵⁻²⁷⁾ Glyceryl Oleate is often used in controlled studies on the physiology and biophysics of laboratory-constructed lipid membranes.⁽²⁸⁾ The use of Glyceryl Oleate as a fusogen in heterokaryon formation is reported for the study of cell differentiation and genetics.⁽²⁹⁾

BIOLOGY

Absorption, Distribution, and Metabolism

Monoglycerides are metabolized by the same mechanisms as are the triglycerides of the diet.⁽³⁰⁾ Their digestion, intestinal absorption, and transport have been reviewed.⁽³¹⁻³⁷⁾

The catabolic fate of the glycerol and fatty acid components of glycerides is well documented.^(35,37-39) Glycerol, phosphorylated and oxidized, enters the glycolytic pathway as dihydroxyacetone phosphate, and fatty acids primarily undergo β -oxidative degradation to form acetyl-CoA.

Oleic acid, a monoenoic acid, requires an isomerase after partial cleavage to catalyze the isomerization and shifting of the *cis* double bond before β -oxidation continues. Oleic Acid is currently being reviewed by Cosmetic Ingredient Review.⁽⁴⁰⁾

The monoglyceride, Glyceryl Oleate, as well as its components, glycerol and oleic acid, are common intermediates in both lipid oxidation and synthesis.

General Effects

Addition of 1 mM Glyceryl Oleate plus 3 mM oleic acid to an incubation of the conjugated bile salt, sodium taurodeoxycholate, with segments of everted jejunal intestine from Sprague-Dawley rats diminished the tissue's permeability observed with the bile salt alone.⁽⁴¹⁾ The mixture also prevented changes in the gross appearance of the intestinal mucosa that were found with the bile salt alone.

Weanling rats were fed a diet of 25% tristearin supplemented with 5% Glyceryl Oleate or with 2.5% Glyceryl Oleate plus 2.5% oleic acid. The absorption of tristearin, calcium, magnesium, and phosphorus was not altered.⁽⁴²⁾

The presence of Glyceryl Oleate within the intestinal lumen enhanced the intestinal absorption of macromolecules. Glyceryl Oleate-bile salt mixed micellar solutions were necessary adjuvants to potentiate heparin absorption.⁽⁴³⁻⁴⁴⁾

The use of Glyceryl Oleate as a micelle promoter in chickens alleviated the toxic effects of T-2 toxin, a secondary metabolite of several species of the genus *Fusarium*.⁽⁴⁵⁾ Mixed micellar solutions containing taurocholate and Glyceryl Oleate prevented deoxycholate-induced malabsorption in the rat jejunum.⁽⁴⁶⁾

Micellar fat containing Glyceryl Oleate decreased the contractility of canine gastric muscles after stimulation with acetylcholine or 5-hydroxytryptophan.⁽⁴⁷⁾ A volume of 10 ml of micellar fat consisting of 0.25 mM Glyceryl Oleate, 0.5 mM oleic acid, and dog bile diluted by a salt solution was instilled into the duodena of dogs following intravenous injections of the following gastric stimuli: food, acetylcholine, or 5-hydroxytryptophan. Bile alone and saline did not produce these responses.

Glyceryl Oleate was a minor component (1.3%–6.7%) in Freund water-in-oil adjuvant mixtures that were used to sensitize mice to a protein antigen. Although the protein in emulsions containing Glyceryl Oleate succeeded in producing Arthus reactions and delayed hypersensitivities, no conclusion could be reached on the potential adjuvant properties of Glyceryl Oleate as an individual ingredient.⁽⁴⁸⁾

Inhibition of cow's milk lipoprotein lipase by a human plasma apolipoprotein was reversed by the addition of Glyceryl Oleate to the reaction mixture.⁽⁴⁹⁾

The addition of Glyceryl Oleate (1 w/v %) to a culture of the fungus, *Candida paraliopolytica*, increased the lipase activity.⁽⁵⁰⁾ The free fatty acids tested did not significantly increase lipase activity over controls.

Glyceryl Oleate prevented the fusion of chicken myoblasts in vitro at concentrations ranging from 40 to 70 $\mu\text{g/ml}$ under conditions that have been reported for erythrocytic fusion.⁽⁵¹⁾ Concentrations above 80 $\mu\text{g/ml}$ were toxic to the myoblastic cultures.

The interaction of fusogenic lipids, such as Glyceryl Oleate, with erythrocyte ghosts was studied using fluorescence probes.⁽⁵²⁾ Changes in the quantum yield, fluorescence intensity, and emission wavelength of the probe in the presence of Glyceryl Oleate were due to the production of a less ordered, functionally fluid membrane structure. The chemically related nonfusogenic lipid, glyceryl monostearate, had no effect on the observed fluorescence parameters.

The ability of Glyceryl Oleate to inhibit the antimicrobial activity of two imidazole antimycotic drugs against *Candida* was evaluated using an agar diffusion procedure.⁽⁵³⁾ Glyceryl Oleate decreased the diameter of the inhibition zone at a concentration of 0.25 mM. No decrease was observed at the lower concentrations of 0.13 mM and 0.06 mM.

The antimicrobial activity of Glyceryl Oleate and other polyhydric alcohols was assessed.⁽⁵⁴⁾ Glyceryl Oleate had slight activity, causing inhibition of growth of *Corynebacterium* sp. at concentrations above 1.40 $\mu\text{mol/ml}$. Other microorganisms, such as *Streptococcus pyogenes*, *Nocardia asteroides*, and *Staphylococcus aureus*, were not inhibited up to the highest concentration tested, 2.81 $\mu\text{mol/ml}$.

Glyceryl Oleate induced aggregation of nematodes (*Bursaphelenchus lignicolus*) as compared with untreated controls.⁽⁵⁵⁾

ANIMAL TOXICOLOGY

Acute Oral Toxicity

A sunscreen formulation containing Glyceryl Oleate (at 5%) was evaluated for acute toxicity upon oral administration to 10 Fischer rats.⁽⁵⁶⁾ After a 14-day observation period for signs of toxicity, the study directors concluded that the single 13 ml/kg dose was not lethal in rats.

Skin Irritation

Five studies using the single insult occlusive patch test were performed to evaluate the primary dermal irritation potential of Glyceryl Oleate at two concentrations.^(57–61) A volume of 0.5 ml was placed on the clipped dorsal skin of

nine rabbits. Sites were graded for erythema and edema 2 and 24 h after exposure (maximum score for either erythema or edema = 4). In the three studies with undiluted Glyceryl Oleate, it was concluded that it had minimal skin irritation potential; erythema scores ranged from 0.5 to 1.⁽⁵⁷⁻⁵⁹⁾ Similar results and conclusions were reported in the two studies using 50% Glyceryl Oleate in corn oil⁽⁶⁰⁻⁶¹⁾ (Table 3).

The dermal toxicity of a sunscreen formulation containing 5% Glyceryl Oleate was evaluated using three New Zealand White (NZW) rabbits.⁽⁵⁶⁾ Volumes of 0.5 ml were applied to the animals' clipped dorsal skin once daily for 4 days. After a 7-day assessment period for dermal irritation, which was characterized by well-defined to moderate erythema, slight edema, and subsequent slight desquamation, the resultant irritation index was 3.0 (max = 8.0) (Table 3).

Ocular Irritation

Glyceryl Oleate was evaluated for ocular irritation in six rabbits using the Draize Eye Test. Undiluted and 50.0% in corn oil preparations were administered at a volume of 0.1 ml. The Draize system,⁽⁶²⁾ which has a calculated maxi-

TABLE 3. Primary Skin Irritation and Dermal Toxicity of Glyceryl Oleate

<i>Material tested</i>	<i>No. of rabbits</i>	<i>Method</i>	<i>Conclusion</i>	<i>Reference</i>
Glyceryl Oleate undiluted	9	SIPT ^a —occlusive	Minimal skin irritation PII ^b = 0.72	57
Glyceryl Oleate undiluted	9	SIPT—occlusive	Minimal skin irritation PII = 0.67	58
Glyceryl Oleate undiluted	9	SIPT—occlusive	Minimal skin irritation PII = 0.67	59
Glyceryl Oleate 50% in corn oil	9	SIPT—occlusive	Minimal skin irritation PII = 1.00	60
Glyceryl Oleate 50% in corn oil	9	SIPT—occlusive	Practically nonexistent skin irritation PII = 0.33	61
Glyceryl Oleate 5% in sunscreen formulation	3	Dermal toxicity of 0.5 ml applied to clipped dorsal skin once daily for 4 days	Mild dermal irritation PII = 3.0	56
Glyceryl Oleate at unspecified concentration in cosmetic formulation	10	Subchronic dermal toxicity (28 days). 25.0% w/v formulation in corn oil applied to shaved abraded and intact skin 5 days per week for 4 weeks	Severe irritation at application site of treated rabbits; gross and microscopic alterations noted	66

^aSIPT, single insult patch test.

^bPII, primary irritation index. Maximum possible score = 8.00.

imum irritation score of 110, was used to score the extent of irritation. In the two studies using undiluted Glyceryl Oleate, results were similar after 2 days of observation; mean scores were 0 and 1 in 110. Glyceryl Oleate produced minimal eye irritation.^(63,64) The 50.0% Glyceryl Oleate preparation was also minimally irritating, and the mean scores were 1 and 2 for Days 1 and 2, respectively⁽⁶⁵⁾ (Table 4).

A fragrance preparation containing Glyceryl Oleate at 19.0% concentration was tested in rabbits with the standard Draize Test. The total mean score of 12 on Day 1 decreased to 8 on Day 2, 6 on Day 4, and 2 on Day 7. Individual mean scores for two of the six rabbits tested were in the 25 to 35 range on the first day, decreasing to approximately 18 by Day 4 and to 7 by Day 7. All other rabbits had negative to transient minimal responses. The formulation produced moderate eye irritation⁽⁶⁷⁾ (Table 4).

A 0.1 ml volume of a sunscreen formulation containing 5% Glyceryl Oleate was evaluated for eye irritation in six NZW rabbits.⁽⁵⁶⁾ Scoring was performed 1 h after treatment and on Days 1, 2, 3, and 7. Slight conjunctivitis was observed after 1 h, clearing within 24 h, and no signs of irritation to other tissues were noted (Table 4).

Subchronic Dermal Toxicity and Phototoxicity

A 28-day subchronic dermal toxicity study assessed the safety of a cosmetic formulation containing Glyceryl Oleate (at an unspecified concentration) in 10 albino rabbits.⁽⁶⁶⁾ A 25.0% (w/v) solution of the formulation in corn oil was applied to shaved skin that had been either abraded or left intact. The 2.0 ml/kg

TABLE 4. Ocular Irritation of Glyceryl Oleate

<i>Material tested</i>	<i>No. of rabbits</i>	<i>Results</i>	<i>Reference^a</i>
Glyceryl Oleate undiluted	6	Minimal eye irritation; mean score = 1 (max score = 110) on Day 1 following treatment	63
Glyceryl Oleate undiluted	6	Minimal eye irritation; mean score = 1 on Day 1	64
Glyceryl Oleate 50% in corn oil	6	Minimal eye irritation; mean score = 1 on Day 1	65
Glyceryl Oleate 19.0% in fragrance preparation	6	Moderate eye irritation; mean score = 12 on Day 1, 8 on Days 2 and 3, 6 on Day 4, 2 on Day 7	67
Glyceryl Oleate 5% in sunscreen formulation	6	Slight conjunctivitis 1 h after treatment; cleared within 24 h	56

^aAll studies followed methods of Draize.⁽⁶²⁾

dose was left in contact with the skin for an indefinite period of time. The rabbits were treated 5 days per week for a period of 4 weeks. The major response to repeated administration of this formulation was "severe irritation" of the skin at the site of application. Alterations included erythema, severe edema, and desquamation, fissures, hemorrhages, and pustules. Microscopic changes included acanthosis, hyperkeratosis, focal epidermal ulceration, focal dermal inflammation, abscess formation, and/or focal escharosis at some of the treated sites. No skin reactions were noted in controls. Other results (e.g., mortality, gross behavior/appearance, and results of hematological, clinical chemistry, and urine analyses) were negative or not treatment-related (Table 3).

Three formulations containing two sunscreen ingredients (maximum concentrations 2.0% and 4.0%) were evaluated in a 28-day subchronic dermal toxicity/phototoxicity study in NZW rabbits.⁽⁶⁸⁾ The sunscreens contained Glyceryl Oleate at a 5% concentration. Topical applications of 6 mg cream per cm² to clipped dorsal intact and abraded skin sites of the animals (four animals per group) were followed by a 4-minute exposure (at one-half the minimum erythema dose) to UV radiation (Westinghouse FS-20 sunlamp) and a 6-h occlusion of the test sites. This treatment was repeated 5 days each week followed by 2 nontreatment days for 4 weeks. Animals were then observed for 2 weeks before necropsy. The four deaths (one control, three treated) were reportedly due to naturally occurring chronic enteritis. Body weights, mean group feed consumption, and hematological and urinalysis data from treated animals reflected normal variability. The organ:body weight disparity of some treated animals with controls was not considered toxicologically significant. All three formulations caused slight dermal irritation during the first week of treatment that was similar to that observed in several control animals exposed to UV light alone. Maximal irritation during the second week, which was sustained through the remainder of the treatment period, was characterized by slight to moderate erythema, slight edema, and scaly desquamation. The severity of dermal irritation was equivalent at both abraded and intact sites. Normal healing occurred during the 2-week observation period following treatment.

Subchronic and Chronic Toxicity of Glycerol and Oleic Acid

Toxicological data on glycerol and oleic acid, metabolic products of Glyceryl Oleate, were obtained from subchronic and chronic ingestion studies used to regulate these GRAS substances.^(30,69-73)

Subchronic Oral Toxicity of Glycerol

Rats fed glycerol at concentrations up to 20% in their diets or by stomach tube for periods of 4-11 weeks had no adverse effects that could be attributed to glycerol consumption.⁽⁷⁴⁻⁷⁹⁾ Criteria, such as body weight gain, food and water intake, resistance to cold, mortality, behavior, blood chemistry, hematology, and gross and microscopic features of major internal organs and tissues, were observed.

Oral doses of up to 3 g of undiluted glycerol given three times per day for a total of eight doses resulted in hyperemia, petechial hemorrhages, and erosion of the gastrointestinal mucosa of rats and dogs.⁽⁸⁰⁾

Volumes greater than 5 ml of a 50% aqueous saline solution of glycerol administered to guinea pigs by stomach tube or from a drinking cup daily for a period of 30–40 days produced signs of acute toxicity and death.⁽⁸¹⁾ Doses of 10 ml of the 50% solution for 30–40 days were well tolerated by rabbits.⁽⁸¹⁾ The red blood cell count of the treated guinea pigs had decreased. No gross pathological changes and no glycerol-related changes in plasma or erythrocytic cholesterol concentrations were found in either species.

Three-month administration of up to 20% solutions of glycerol to rats as drinking water resulted in the death of 2/12 rats receiving the highest concentration and temporary impairment in the development of the remaining rats.⁽⁷⁷⁾ Growth of rats was normal at concentrations of glycerol of less than or equal to 10%. Temporary growth impairment was observed in rats administered 20% glycerol solutions for 3 months.⁽⁸²⁾

After the oral administration of 2.0 ml/kg doses of glycerol to two dogs twice weekly for 4 months, growth was normal and no abnormalities were found in urine and the internal organs.⁽⁸³⁾

The feeding of glycerol to rats at concentrations up to 41% (as a dietary supplement) for 21–25 weeks did not produce changes in growth or in the liver, kidneys, or intestines of these animals.⁽⁷⁴⁾ In another study, subnormal growth was found in rats fed diets containing greater than 30% glycerol for 20 weeks.⁽⁸⁴⁾ Pathological changes were observed in rats fed diets containing glycerol at concentrations greater than 10%. The most marked changes were hydropic and fatty changes of hepatocytes.

Subchronic Dermal Toxicity of Glycerol

Doses of 0.5–4.0 ml (0.6–5 g) per kg natural or synthetic glycerol were applied to the shaved dorsal skin of 24 albino rabbits for an 8-h exposure, 5 days per week, for 18 weeks.⁽⁸⁵⁾ No evidence of skin irritation was observed; no abnormalities were found in urine or blood or after gross and microscopic examinations of internal organs.

Chronic Oral Toxicity of Glycerol

The only untoward effect in a 6-month study of rats given 5% solutions of either synthetic or natural glycerol as drinking water was calcified masses in the renal tubules of 6/10 rats.⁽⁸⁶⁾ Administration of 1.0 ml/kg of a 50% aqueous glycerol solution to 60 rats for 6 months had no adverse effects on development, survival, internal organs, skeletal system, or hepatic glycogen.⁽⁷⁷⁾

Three dogs fed glycerol at a concentration of 35% (as a dietary supplement) for 31 weeks had normal growth.⁽⁷⁴⁾ In the 14-week period following a reduction in feed consumption, treated dogs lost an average of 16% of their previously attained weight; control dogs maintained their weight. Diuresis was observed in treated dogs, but no hemoglobinuria, albuminuria, liver degeneration, or gross or microscopic abnormalities of internal organs were found.

Growth impairment, reduced activity, and dull coats were observed in rats fed 61% glycerol substituted for starch for 40 weeks. These changes were considered due to a lack of starch rather than to glycerol toxicity. Rats fed 20% and 40% glycerol diets for 40 weeks had normal growth.⁽⁷⁴⁾

In 2-year toxicity studies using rats and dogs fed 0, 5, 10, and 20% glycerol, no treatment-related adverse effects were found.^(85,87) Although Hine et al.⁽⁸⁵⁾ observed high incidences of albuminuria and glycosuria in treated rats and high liver:body weight ratios in females fed diets with 20% glycerol, they concluded that glycerol at concentrations below 20% would not cause untoward effects in rats.

Subchronic Oral Toxicity of Oleic Acid

A volume of 10 ml of oleic acid (approximate dose 2 g/kg) administered to four albino rabbits by stomach tube every other day for 4 days resulted in the death of one of the four rabbits.⁽⁸⁸⁾ Other signs included hair loss and seborrheic lesions on the rabbits' ears. No adverse effects were observed after administration of a volume of 2.5 ml (approximate dose 0.6 g/kg).

Feeding of a 5% oleic acid diet (approximate dose 6 g/kg daily) to chicks for 4 weeks had no adverse effect.⁽⁸⁹⁾

Chronic Toxicity of Oleic Acid

The growth rates of albino mice receiving weekly subcutaneous injections of 0.25 ml and 0.5 ml of a 5% oleic acid emulsion (approximate dose 12–15 g/kg) for 15 months were normal.⁽⁹⁰⁾

Rats fed a 15% Oleic Acid diet for 5 months had normal development and good general health.⁽⁹¹⁾ A progressive reduction in spermatogenesis and prolonged estrus cycles (although most females bore living young) were noted; these signs were considered typical of animals fed diets deficient in essential fatty acids.

Carcinogenicity

Several egg lipids were examined for their potential to produce brain tumors in mice of the T.M. strain.⁽⁹²⁾ Purina mice chow, which was fed to controls ad libitum, corn oil, cholesterol, Glyceryl Oleate, corn oil plus cholesterol, or Glyceryl Oleate plus cholesterol were mixed with sugar and presented to mice once a day. Doses of these supplements were 50–100 mg/mouse per day Glyceryl Oleate, 4–5 mg/mouse per day cholesterol, and 100–150 mg/mouse per day corn oil; the purity of these supplements was not stated. Four-week-old mice were fed these diets and then bred within the same group. Their offspring were maintained on the same diets as their parents from birth "until they died or became moribund and were killed." Survival rates for the individual groups were not provided. The incidence of brain tumors in treated mice is shown in Table 5. The report contained general histopathological descriptions of the tumors; however, no specific tumor type induced by Glyceryl Oleate was described. The diets supplemented with lecithin, cholesterol, and cholesterol, in combination with any other lipid, induced brain tumors in the largest number of mice.

In a similar experiment, the carcinogenicity of Glyceryl Oleate was evaluated in T.M. strain mice that were fed Purina Chow supplemented with refined corn oil (Group 2), crude corn oil (Group 3), refined corn oil plus up to 1.5% free fatty acids, oleic and linoleic acids (Group 4), and Glyceryl Oleate (Group 5) at concentrations of 200 mg/mouse per day.⁽⁹³⁾ Controls (Group 1) were fed

TABLE 5. Incidence of Brain Tumors in Mice Fed Various Egg Lipids⁽⁹²⁾

<i>Diet supplement</i>	<i>Total no. of mice treated</i>	<i>No. of mice examined^a</i>	<i>No. of mice with brain tumors</i>
Control, no supplement	360	188	0
Corn oil	159	11	1
Cholesterol	212	80	20
Glyceryl Oleate	144	63	3
Corn oil and cholesterol	106	22	7
Glyceryl Oleate and cholesterol	158	64	7

^aIt was not stated whether or not the mice that were not examined within each group died, and, if they died, whether or not their deaths were associated with their respective dietary supplements.

Purina Chow alone. Offspring of the intragroup bred mice were maintained on the same diets for a total of four–seven generations of mice. Mice were killed when they were observed to lose weight rapidly. Three of the 195 control mice in Group 1 developed gastric papillomas and squamous cell carcinomas, and none developed pyloric or intestinal tumors. Gastric papillomas were also found in 6/209 mice of Group 2, 49/196 mice of Group 3, 87/328 mice of Group 4, and 31/166 mice of Group 5 (Glyceryl Oleate-supplemented diet). Fewer squamous cell carcinomas were observed in all treatment groups: Group 2, 1/209; Group 3, 6/196; Group 4, 10/328; Group 5, 6/166. Pyloric tumors were also recorded for all treatment groups at the following frequencies: Group 2, 2/209; Group 3, 9/196; Group 4, 41/328; Group 5, 31/166. Free fatty acids in the preparations fed to the mice that developed gastric tumors were considered the cause of the tumors; however, the relative purity of the Glyceryl Oleate was not detailed. Detailed gross and microscopic descriptions of the tumors were recorded.

Antitumorogenicity

The *in vivo* antitumor activity of Glyceryl Oleate was studied using implanted Ehrlich ascites tumors in mice.⁽⁹⁴⁾ Saline solutions at two doses (6.0 and 1.5 mg/mouse per day) of Glyceryl Oleate were administered once daily for 5 successive days to two mice per dose. Tumor growth and body weight gain after 7 days and life spans were recorded. Whereas control mice died within 17 days, both doses of Glyceryl Oleate prolonged the survival period of the mice (>30 days at 6.0 mg and an average of 24 days at 1.5 mg). Although both doses resulted in an increase in body weight over 7 days, inhibition of tumor growth was observed in mice only at the higher dose. Moderate tumor growth occurred at the lower dose.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

Glyceryl Oleate, used in hand cream at 1.5%, was evaluated for primary dermal irritation in 15 and 30% aqueous preparations.⁽⁹⁵⁾ Twenty subjects participated in the single insult occlusive patch test using the Draize-Shelanski tech-

nique. The 15% concentration yielded 18 negative responses; the remaining 2 subjects had scores of 0.5 and 1 (max = 3). Seventeen individuals had negative responses, and 3 had scores of 1 after treatment with the 30% solution (Table 6).

A single insult occlusive patch test was performed using 20 panelists by applying a fragrance preparation that contained 19.0% Glyceryl Oleate.⁽⁹⁶⁾ Negative results were found in 17 of 20 subjects (doubtful reactions were observed in 3 of 20 subjects), and the formulation's skin irritation potential was "practically nonexistent" (Table 6).

Cumulative Dermal Irritation

The Lanman-Maibach test^(97,98) was used to assess the cumulative irritation potential of two sunscreen formulations containing 5% Glyceryl Oleate.⁽⁹⁹⁾ A dose of 50 $\mu\text{L}/\text{cm}^2$ was administered to the backs of 10 subjects under 23-h closed patches for a total of 21 consecutive applications. Sites were cleaned before scoring and at reapplication at the 24th hour. The total converted numerical scores for all applications and subjects of the two formulations were 23 and 38 (maximum score = 630), ranking them as mild materials causing no experimental irritation. Positive responses to both formulations were not observed until at least the 12th application in most subjects. Most of the points for the cumulative total scores were contributed by 1 subject alone (22/23 points, 26/38 points), whereas the remaining 9 subjects had individual scores of 0–3 (Table 6).

Sensitization

A repeated insult patch test (RIPT) using 200 people was used to evaluate a 15% aqueous solution of Glyceryl Oleate as a primary irritant, fatiguing agent, and/or sensitizer.⁽¹⁰⁰⁾ Sixteen 24-h occlusive patches were applied to the upper arm on Mondays, Wednesdays, and Fridays. Nontreatment periods were stated to be the days between alternate day applications and on weekends. No signs of skin irritation were observed after exposure to Glyceryl Oleate in any of the applications (Table 6).

An RIPT with a sunscreen formulation containing 5% Glyceryl Oleate was conducted using an occlusive patch technique.⁽¹⁰¹⁾ Ten 24-h induction patches on Tuesdays, Thursdays, and Saturdays (sites were evaluated after removal of each patch) were followed by a 12–16-day nontreatment period and a 24-h challenge patch at an adjacent site. These challenge sites were then evaluated immediately after patch removal and 24 h later. None of the 15 subjects participating in this study alone had positive reactions during the induction phase or when challenged. Of the 37 others who were being tested simultaneously for photoallergic and phototoxic responses to treatment, 2 subjects had transient reactions of slight erythema (scores of 1 on scale of 0–4) to induction patches, and all subjects had no reaction to the challenge patch (Table 6).

Photoallergy and Phototoxicity

The potential of a sunscreen formulation containing 5% Glyceryl Oleate for inducing photoallergy and phototoxicity in humans was evaluated by modifications of an RIPT.⁽¹⁰¹⁾ Approximately 200 mg of the formulation was applied under an occlusive patch to the inner forearms of 29 subjects for the photoal-

lergy test and of 10 subjects for the phototoxicity test. After a 24-h exposure period, the contact sites were evaluated after patch removal and irradiated with UVA light (15 minutes at 4400 $\mu\text{W}/\text{cm}^2$). The sites of subjects in the phototoxicity test were then evaluated immediately following irradiation and 24 h and 48 h later. The 24-h patch application and irradiation were repeated 10 times for subjects in the photoallergy test on Mondays, Wednesdays, and Thursdays. After a 12–16 day nontreatment period, 24-h challenge patches were applied to adjacent sites. Photoallergy test sites were evaluated before and after irradiation upon patch removal in both induction and challenge phases. Scoring was performed at 48 and 72 h after application of challenge patches. No skin reactions were observed in the 10 subjects participating in the phototoxicity test, and only 1 photoallergy test subject ($n = 29$) had a grade 1 reaction (scale 0–4) to the sixth induction patch at the nonirradiated control site. No positive reactions to induction or challenge patches were observed at any irradiated site (Table 6).

Oral Exposure to Glycerol

Data from subchronic human studies on the oral administration of glycerol, a metabolic product of Glyceryl Oleate, were used in the safety assessment process of glycerol for the federal regulation of GRAS substances.^(30,69)

SUMMARY

Glyceryl Oleate, the glyceryl 1-monoester of oleic acid, is dispersible in water and soluble in acetone, simple alcohols, and cottonseed oil. Glyceryl Oleate is manufactured by the partial hydrolysis of corresponding tri- and diglycerides, by esterification of glycerol with oleic acid, or by glycerolysis of common fats and oils.

Glyceryl Oleate is used primarily in cosmetic products as an emulsifier and was listed as an ingredient in 716 of the cosmetic formulations reported to the FDA in 1981. The FDA table had Glyceryl Oleate concentrations ranging from ≤ 0.1 to 5% in formulations that were predominantly lipsticks, eye shadows, makeup bases, and skin care preparations.

Monoglycerides of edible fats or oils are considered GRAS and indirect food additives for human consumption by the FDA. Glyceryl Oleate can be used as a prior-sanctioned food ingredient and as a direct and indirect food additive. The pharmaceutical industry uses Glyceryl Oleate as an inert carrier compound and to enhance intestinal drug absorption.

Oral administration of a single 13 ml/kg dose of a sunscreen formulation containing 5% Glyceryl Oleate to rats produced no signs of toxicity and no lethality.

Undiluted and 50% in corn oil concentrations of Glyceryl Oleate used in dermal irritation studies with rabbits were found to be minimally irritating. A volume of 0.5 ml of a sunscreen formulation containing 5% Glyceryl Oleate produced erythema and slight edema in rabbits.

Minimal to moderate eye irritation was produced by undiluted Glyceryl Oleate, 50% Glyceryl Oleate in corn oil, and a fragrance preparation containing

TABLE 6. Clinical Assessment of Safety of Glyceryl Oleate

<i>Material tested</i>	<i>Glyceryl Oleate concentration</i>	<i>Type of test</i>	<i>No. of humans</i>	<i>Results/Comments</i>	<i>Reference</i>
Glyceryl Oleate	15% aqueous	Test for skin irritation by Draize-Shelanski SIOPT ^a	20	18/20 had score of 0 1/20 had score of 1/2 1/20 had score of 1 (max = 3)	95
Glyceryl Oleate	30% aqueous	Test for skin irritation by Draize-Shelanski SIOPT	20	17/20 had score of 0 3/20 had score of 1 (max = 3)	95
Glyceryl Oleate	15% aqueous	RIPT ^b (16 patches, Mon., Wed., Fri.)	200	No signs of skin irritation observed during induction or challenge (week- ends considered nontreatment period)	100
Fragrance preparation	19.0%	Test for skin irritation by SIOPT	20	17/20 had score of 0 3/20 had score of $\pm$ (max = 4)	96
Sunscreen formulation	5%	21-day Cumulative Irritancy Test	10	Total converted numerical score of 23 (max = 630); mild material causing no irritation	99

Sunscreen formulation	5%	21-day Cumulative Irritancy Test	10	Total converted numerical score of 38 (max = 630); mild material causing no irritation	99
Sunscreen formulation	5%	RIPT	52	15/52 were involved in RIPT alone; none of the 15 had positive reactions; 37/52 were involved in simultaneous photoallergy and phototoxicity testing; 2/37 had transient, slight erythema to induction patches; no reactions to challenge patches observed	101
Sunscreen formulation	5%	Photoallergy test by RIPT + UVA irradiation	29	One subject had a score of 1 to the sixth induction patch at a nonirradiated control site (max = 4); no positive reactions to induction or challenge patches at any irradiated site	101
Sunscreen formulation	5%	Phototoxicity test single patch test + UVA irradiation	10	No skin reactions observed	101

^aSIOPT, single insult occlusive patch test.

^bRIPT, repeated insult patch test.

19.0% Glyceryl Oleate when administered to rabbits. A formulation containing 5% Glyceryl Oleate administered at a 0.1 ml dose to rabbit eyes induced slight conjunctivitis.

Daily applications of 2.0 ml/kg of a 25.0% corn oil solution of a formulation containing Glyceryl Oleate for 20 days produced severe dermal irritation in rabbits. In another 4-week dermal toxicity/phototoxicity study, product formulations containing varying concentrations of two sunscreen ingredients produced slight, reversible dermal irritation. Each sunscreen ingredient contained 5% Glyceryl Oleate.

Glyceryl Oleate administration was associated with development of a few brain tumors (3 tumors in 63 mice) in a two-generation study in mice of the T.M. strain whose feed was supplemented with 50–100 mg/mouse per day Glyceryl Oleate. Digestive tract tumors were found in T.M. strain mice fed 200 mg/mouse per day Glyceryl Oleate (feed supplement) for four–seven generations and were considered due to free fatty acid impurities. The Expert Panel found the results of these studies equivocal.

Doses of 1.5 and 6.0 mg/mouse per day of Glyceryl Oleate in saline increased the survival period of mice with implanted Ehrlich ascites tumors; the higher dose inhibited tumor growth.

Two aqueous Glyceryl Oleate preparations (15% and 30% concentrations) and a fragrance preparation containing 19.0% Glyceryl Oleate were negative for cutaneous irritation when tested on human skin using single insult occlusive patch tests.

Two sunscreen formulations containing 5% Glyceryl Oleate were considered mild compounds and caused no irritation in a cumulative occlusive patch test using human subjects.

No signs of irritation or sensitization were observed in humans after repeated insult patch testing of a 15% aqueous Glyceryl Oleate preparation and a sunscreen formulation containing 5% Glyceryl Oleate. A few subjects involved in simultaneous photoallergy and phototoxicity tests had slight, transient erythematous responses. No positive reactions were observed at any irradiated site during induction and challenge phases of the photoallergy test.

The metabolic products of Glyceryl Oleate are glycerol and oleic acid. The use of these compounds in and for foods is regulated by the FDA. Subchronic and chronic toxicity data from studies with animals and humans that were used in the safety assessment of glycerides, glycerol, oleic acid and sodium oleate are presented in this report.

CONCLUSION

Based on the data from animal and human studies included in this report, the CIR Expert Panel concludes that Glyceryl Oleate is safe as a cosmetic ingredient in the present practices of use and concentration.

ACKNOWLEDGMENT

Mauri Y. Okamoto, Scientific Analyst and writer, prepared the technical analysis used by the Expert Panel in developing this report. Word processing for this report was performed by Karen Swanson.

REFERENCES

1. ESTRIN, N.F., CROSLY, P.A., and HAYNES, C.R. (eds.). (1982). *Cosmetic, Toiletry and Fragrance Association (CTFA) Cosmetic Ingredient Dictionary*, 3rd ed. Washington, D.C.: Cosmetic, Toiletry and Fragrance Association.
2. ESTRIN, N.F., HAYNES, C.R., and WHELAN, J.M. (eds.). (1982). *CTFA Compendium of Cosmetic Ingredient Compositions. Cosmetic Ingredient Descriptions*. Washington, D.C.: Cosmetic, Toiletry and Fragrance Association.
3. MALOVA, I.D., GRETSKII, V.M., BALANDINA, E.A., KABACHNYI, G.I., and LEKHTER, A.E. (1980). Study of the emulsifying properties of esters of glycerin and higher fatty acids. *Farmatsiya (Moscow)* **29**(4), 19-22.
4. SENZEL, A.J. (ed.). (1977). *Newburger's Manual of Cosmetic Analysis*, 2nd ed. Washington, D.C.: AOAC.
5. KRESZE, G., BEDERKE, K., and SCHAEVFFELHUT, F. (1965). Analysis of mixtures of mono- and diglycerides by gas chromatography and nuclear magnetic resonance. *Z. Anal. Chem.* **209**(2), 329-337.
6. HORWITZ, W. (ed.). (1980). *Official Methods of Analysis of the Association of Official Analytical Chemists (AOAC)*, 13th ed. Washington, D.C.: AOAC.
7. SWERN, D. (ed.). (1979). *Bailey's Industrial Oil and Fat Products*, 4th ed. New York: John Wiley and Sons, Vol. 1.
8. WINDLHOLZ, M., BUDAVARI, S., BLUMETTI, R.F., and OTTERBEIN, E.S. (eds.). (1983). *The Merck Index*, 10th ed. Rahway, N.J.: Merck and Co., Inc.
9. GREENBERG, L.A., and LESTER, D. (1954). *Handbook of Cosmetic Materials*. New York: Interscience Publishers.
10. WEAST, R.C. (ed.). (1982). *Handbook of Chemistry and Physics*, 63rd ed. Boca Raton, FL.: CRC Press.
11. FOOD AND DRUG ADMINISTRATION (FDA). (1981). Computer printout of voluntary submission of cosmetic ingredient data.
12. CODE OF FEDERAL REGULATIONS (CFR). (1984). Title 21, Food and Drugs, Sections 172.515, 175.105, 175.300, 175.320, 176.210, 181.27, 182.90, 182.4505. Washington, D.C.: U.S. Government Printing Office.
13. FOOD CHEMICAL NEWS (FCN). (February 14, 1983). FDA Proposes GRAS affirmations for glycerides. **24**(49), 40.
14. PROCTER AND GAMBLE CO. (September 8, 1950). Submission of unpublished data to FDA. The comparative nutritive value of certain mono-, di-, and tri-glycerides. FAP 9A0018 Vol. 1, pp. 2-108.
15. HARRIS, R.S., and SHERMAN, H. (1954). Comparison of the nutritive values of mono-, di- and triglycerides by a modified pair-feeding technique. *Food Res.* **19**(2), 257-262.
16. MATTSO, F.H., ALEXANDER, J.C., BAUR, F.J., and RELLER, H.H. (1956). Short-term feeding studies on acetin fats. *J. Nutr.* **59**, 277-285.
17. AMES, R., O'GRADY, M.P., EMBREE, N.D., and HARRIS, P.L. (1951). Molecularly distilled monoglycerides. III. Nutritional studies on monoglycerides derived from cottonseed oil. *J. Am. Oil Chem. Soc.* **28**, 31-33.
18. BRAUN, W.Q., and SHREWSBURY, C.L. (1941). The nutritive properties of monoglycerides. *Oil and soap.* **18**(12), 249-250.
19. ROSNER-HIXSON LABORATORIES. (June 29, 1959). Submission of unpublished data to FDA. Digestibility of monoglyceride citrate by in vitro and in vivo methods. GRM 23 vol. 5, pp. 1081-1085.
20. ORTEN, J.M., and DAJANI, R.N. (1957). A study of the effects of certain food emulsifiers in hamsters. *Food Res.* **22**, 529-541.
21. TIDWELL, H.C. (1957). Absorption of monoglycerides. *Am. J. Physiol.* **189**(3), 537-540.
22. FCN. (January 28, 1985). FDA GRAS affirmation proposals pending on December 31, 1984. **26**(47), 11-12.

23. THOMPSON, E.D., CARTER, S.B., and MANRING, G.L. (1978). Antimicrobial agent for topical use. Ger. Offen. Patent No. 2748399.
24. MURANUSHI, N., NAKAJIMA, Y., KINUGAWA, M., MURANISHI, S., and SEZAKI, H. (1980). Mechanism for the inducement of the intestinal absorption of poorly absorbed drugs by mixed micelles. II. Effect of the incorporation of various lipids on the permeability of liposomal membranes. *Int. J. Pharm.* **4**(4), 281-290.
25. ASHER, W.J., BOVEE, K.C., VOGLER, T.C., HAMILTON, R.W., and HOLTZAPPLE, P.G. (1980). Secretion moderated release of urease from liquid membrane capsules. *Trans. Am. Soc. Artif. Intern. Organs* **26**, 120-3.
26. ECKERT, T., and KEMPER, F.H. (1980). Enterally highly absorbable pharmaceutical preparations. Austrian Patent No. 360161.
27. GRAHAM, N.B., RASHID, A., and RAO, K.P. (1983). Unsaturated monomer reaction products with glycerin or monoglycerides for encapsulation of active materials. *Eur. Pat. Appl. Patent No.* 76158.
28. LAPRADE, R., GRENIER, F., LAPOINTE, J.Y., and ASSELIN, S. (1982). Effects of variation of ion and methylation of carrier on the rate constants of macrotetralide-mediated ion transport in lipid bilayers. *J. Membr. Biol.* **68**(3), 191-206.
29. CRAMP, F.C., and LUCY, J.A. (1974). Glyceryl monooleate as a fusogen for the formation of heterokaryons and interspecific hybrid cells. *Exp. Cell Res.* **87**, 107-110.
30. FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY (FASEB), Life Sciences Research Office. (1975). Evaluation of the health aspects of glycerin and glycerides as food ingredients. U.S. Department of Commerce. NTIS PB-254536.
31. TWU, J-S, GARFINKEL, A.S., and SCHOTZ, M.C. (March 7, 1984). Hepatic lipase. Purification and characterization. *Biochim. Biophys. Acta* **792**(3), 330-337.
32. BICKERSTAFFE, R., and ANNISON, E.F. (1969). Triglyceride synthesis by the small intestinal epithelium of the pig, sheep, and chicken. *Biochem. J.* **111**(4), 419-429.
33. BORGSTROM, B. (1974). Fat digestion and absorption. *Biomembranes* **4B**(0), 555-620.
34. BRINDLEY, D.N. (1974). The intracellular phase of fat absorption. *Biomembranes* **4B**(0), 621-671.
35. FLORKIN, M., and STOTZ, E.H. (eds.). (1971). *Lipid Metabolism. Comprehensive Biochemistry*. New York: Elsevier Publ. Co., Vol. 18.
36. SMITH, L.C., and SCOW, R.O. (1979). Chylomicrons. Mechanism of transfer of lipolytic products to cells. *Prog. Biochem. Pharmacol.* **15**, 109-138.
37. ELDER, R.L. (ed.). (1982). Final report on the safety assessment of decyl and isodecyl oleates. *J. Am. Coll. Toxicol.* **1**(2), 85-95.
38. STUMPF, P.K. (1969). Metabolism of fatty acids. *Ann. Rev. Biochem.* **38**, 159-212.
39. FULCO, A.J. (1974). Metabolic alterations of fatty acids. *Ann. Rev. Biochem.* **43**, 215-241.
40. COSMETIC INGREDIENT REVIEW (CIR). (1985). Scientific literature review of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid and Stearic Acid.
41. FELDMAN, S., and GIBALDI, M. (1969). Physiologic surface-active agents and drug absorption. VI. Bile salt-induced permeability changes in the isolated rat intestine. *Proc. Soc. Exp. Biol. Med.* **132**(3), 1031-1033.
42. TADAYYON, B., and LUTWAK, L. (1969). Interrelation of triglycerides with calcium, magnesium, and phosphorus in the rat. *J. Nutr.* **97**(2), 246-254.
43. TOKUNAGA, Y., MURANISHI, S., and SEZAKI, H. (1978). Enhanced intestinal permeability to macromolecules. I. Effect of monoolein-bile salts mixed micelles on the small intestinal absorption of heparin. *J. Pharmacobio-Dyn.* **1**(1), 28-38.
44. TANIGUCHI, K., MURANISHI, S., and SEZAKI, H. (1980). Enhanced intestinal permeability to macromolecules. Part 2. Improvement of the large intestinal absorption of heparin by lipid surfactant mixed micelles in rat. *Int. J. Pharm.* **4**, 219-228.
45. COFFIN, J.L., and COMBS, G.F. (1981). Impaired vitamin E status of chicks fed T-2 toxin. *Poult. Sci.* **60**(2), 385-392.
46. LAMBADUSURIYA, S.P., GUIRALDES, E., and HARRIES, J.T. (1975). Influence of mixtures of taurocholate, fatty acids, and monoolein on the toxic effects of deoxycholate in rat jejunum in vivo. *Gastroenterology* **69**(2), 463-469.
47. ANDERSON, J.J., BOLT, R.J., ULLMAN, B.M., and BASS, P. (1968). Effect of bile and fat on gastric motility under the influence of various stimulants. *Am. J. Dig. Dis.* **13**(2), 157-167.
48. CROWLE, A.J., and HU, C.C. (1966). A comparison of n-hexadecane and mineral oil emulsions in induction of hypersensitivity in mice. *Proc. Soc. Exp. Biol. Med.* **123**(1), 94-97.

49. BAGINSKY, M.L., and BROWN, W.V. (1976). Effects of monoolein on hydrolysis of triglyceride by lipoprotein lipase in the presence of an inhibitory apolipoprotein. *Physiol. Chem. Phys.* **8**(3), 197-206.
50. OTA, Y., SUZUKI, M., and YAMADA, K. (1968). Lipids and related substances inducing the lipase production by *Candida parapolytica*. *Agr. Biol. Chem.* **32**(3), 390-391.
51. NAKORNCHAI, S., FALCONER, A.R., FISHER, D., GOODALL, A.H., HALLINAN, T., and LUCY, J.A. (1981). Effects of retinol, fatty acids and glycerin monooleate on the fusion of chick embryo myoblasts in vitro. *Biochim. Biophys. Acta* **643**, 152-160.
52. KENNEDY, A., and RICE-EVANS, C. (1976). A spectrofluorimetric study of the interaction of glycerol monooleate with human erythrocyte ghosts. *FEBS Lett.* **69**(1), 45-50.
53. YAMAGUCHI, H. (1977). Antagonistic action of lipid components of membranes from *Candida albicans* and various other lipids on two imidazole antimycotics, clotrimazole and miconazole. *Antimicrob. Agents Chemother.* **12**(1), 16-25.
54. CONLEY, A.J., and KABARA, J.J. (1973). Antimicrobial action of esters of polyhydric alcohols. *Antimicrob. Agents Chemother.* **4**(5), 501-506.
55. TOMINAGA, Y., NAGASE, A., KUWAHARA, Y., and SUGAWARA, R. (1982). Aggregation of *Bursaphelenchus lignicolus* (Nematoda: Aphelenchoididae) to several compounds containing oleyl group. *Appl. Entomol. Zool.* **17**(1), 46-51.
56. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION (CTFA). (July 20, 1981). Submission of unpublished data by CTFA. Rat oral toxicity, rabbit dermal irritation and rabbit ocular irritation studies on a sunscreen formulation containing 5 percent Glyceryl Oleate. (2-47-6).*
57. CTFA. (February 27, 1978). Submission of unpublished data by CTFA. Rabbit primary dermal irritation study on undiluted Glyceryl Oleate. (2-47-9).*
58. CTFA. (August 28, 1978). Submission of unpublished data by CTFA. Rabbit primary dermal irritation study on undiluted Glyceryl Oleate. (2-47-10).*
59. CTFA. (May 7, 1979). Submission of unpublished data by CTFA. Rabbit primary dermal irritation study on undiluted Glyceryl Oleate. (2-47-11).*
60. CTFA. (November 15, 1976). Submission of unpublished data by CTFA. Rabbit primary dermal irritation study on 50.0 percent Glyceryl Oleate in corn oil. (2-47-7).*
61. CTFA. (April 25, 1977). Submission of unpublished data by CTFA. Rabbit primary dermal irritation study on 50.0 percent Glyceryl Oleate in corn oil. (2-47-8).*
62. DRAIZE, J.H. (1959). In: *Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics*. Austin, Texas: The Association of Food and Drug Officials of the United States.
63. CTFA. (April 25, 1977). Submission of unpublished data by CTFA. Rabbit ocular irritation study on undiluted Glyceryl Oleate. (2-47-4).*
64. CTFA. (August 28, 1978). Submission of unpublished data by CTFA. Rabbit ocular irritation study on undiluted Glyceryl Oleate. (2-47-5).*
65. CTFA. (November 2, 1976). Submission of unpublished data by CTFA. Rabbit ocular irritation study on 50.0 percent Glyceryl Oleate in corn oil. (2-47-3).*
66. INDUSTRIAL BIO-TEST LABORATORIES. (August 30, 1973). Submission of unpublished data by CTFA. Subchronic dermal toxicity study in rabbits on a product containing Glyceryl Oleate at unspecified concentration. (2-47-15).*
67. CTFA. (April 8, 1984). Submission of unpublished data by CTFA. Rabbit ocular irritation study on a fragrance preparation containing 19.0 percent Glyceryl Oleate. (2-47-1).*
68. CTFA. (October, 1977). Submission of unpublished data by CTFA. Subchronic dermal toxicity and phototoxicity study in rabbits on products containing sunscreen ingredients with 5 percent Glyceryl Oleate. (2-47-14).*
69. INFORMATICS. (1973). Monograph on glycerin and glycerides. DHEW Contract No. FDA 72-104. NTIS PB-221 227/2.
70. INFORMATICS. (1973). Monograph on vegetable oils, oleic acid, and linoleic acid. Vol. 1. DHEW Contract No. FDA 72-104. NTIS PB-228 546/8.
71. TRACOR Jitco. (1974). Monograph on sodium salts of fatty acids. DHEW Contract No. FDA 72-100. NTIS PB-241 968/7.

*Available upon request: Director, Cosmetic Ingredient Review, 1110 Vermont Ave., NW, Washington, DC 20005.

72. FASEB. (1977). Evaluation of the health aspects of coconut oil, peanut oil, and oleic acid as they may migrate to food from packaging materials, and linoleic acid as a food ingredient. DHEW Contract No. FDA 223-75-2004. Report No. SCOGS-65.
73. FASEB. (1977). Evaluation of the health aspects of sodium oleate and sodium palmitate as substances migrating to food from paper and paperboard used in food packaging. DHEW Contract No. FDA 223-75-2004. Report No. SCOGS-86. NTIS PB-276 414.
74. JOHNSON, V., CARLSON, A.J., and JOHNSON, A. (1933). Studies on the physiological action of glycerin on the animal organism. *Am. J. Physiol.* **103**(3), 517-534. *In: Informatics, Ref. 69.*
75. HOLCK, H.G.O. (1937). Glycerin, ethylene glycol, propylene glycol and diethylene glycol. Report on feeding experiments with rats. *JAMA* **109**, 1517-1520. *In: Informatics, Ref. 69.*
76. FISCHER, L., KOPF, R., LOESER, A., and MEYER, G. (1949). Chemical structure and pharmacological effects of glycols, particularly 1,3-butylene glycol. *Z. Ges. Exp. Med.* **115**, 22-39. *In: Informatics, Ref. 69.*
77. LOESER, A., BORNMANN, G., GROSSKINSKY, L., HESS, G., KOPF, R., RITTER, K., SCHMITZ, A., STUERMER, E., and WEGENER, H. (1954). Diethylene glycol. Pharmacology and toxicology of polyglycols. *Naunyn-Schmiedeberg's Arch. Expt. Pathol. Pharmacol.* **221**, 14-33. *In: Informatics, Ref. 69.*
78. STOEWSAND, G.S., DYMSZA, H.A., SWIFT, S.M., MEHLMAN, M.A., and THERRIAULT, D.G. (1966). Effect of feeding polynaryic alcohols on tissue lipids and the resistance of rats to extreme cold. *J. Nutr.* **89**(4), 414-418. *In: Informatics, Ref. 69.*
79. STOEWSAND, G.S., and DYMSZA, H.A. (1967). Synthetic sources of calories in the diets of rats and dogs. *Proc. 7th Int. Congr. Nutr.*, 1966, **4**, 1082-1087. *In: Informatics, Ref. 69.*
80. STAPLES, R., MISHNER, A., and WARDELL, J. Jr. (1967). Gastrointestinal irritant effect of glycerin as compared with sorbitol and propylene glycol in rats and dogs. *J. Pharm. Sci.* **56**, 398-400. *In: FASEB, Ref. 30.*
81. OSTWALD, R. (1962). Glycerol intake, blood cholesterol level, and anemia in the guinea pig and rabbit. *Proc. Soc. Exp. Biol. Med.* **111**, 632-634. *In: Informatics, Ref. 69.*
82. BORNMANN, G. (1955). Physiological properties of glycols and their toxicity. *Arzneimittel-Forsch.* **4**, 613-616. *In: Informatics, Ref. 69.*
83. KOPF, R., LOESER, A., and MEYER, G. (1951). Biologic actions of 1,2,4-buta-netriol and 1,2,3,-propane-netriol (glycerin). *Arch. Exp. Pathol. Pharmacol.* **212**, 405-415. *In: Informatics, Ref. 69.*
84. GUERRANT, N.B., SHITLOCK, G.P., WOLFF, M.L., and DUTCHER, R.A. (1947). Response of rats to diets containing varying amounts of glycerin and propylene glycol. *Bull. Natl. Formulary Comm.* **15**, 205-229. *In: Informatics, Ref. 69.*
85. HINE, C.H., ANDERSON, H.H., MOON, H.D., DUNLAMP, M.K., and MORSE, M.S. (1953). Comparative toxicity of synthetic and natural glycerin. *Arch. Indust. Hyg. Occup. Med.* **7**(4), 282-291. *In: Informatics, Ref. 69.*
86. ANDERSON, R.C., HARRIS, P.N., and CHEN, K.K. (1950). Toxicologic studies on synthetic glycerin. *J. Am. Pharm. A. (Scient. Ed.)* **39**, 583-585. *In: Informatics, Ref. 69.*
87. ATLAS CHEMICAL INDUSTRIES. (1969). Glycerin: A two-year feeding study in rats. Report No. 11392. FDA Food Additive Petition No. 925. *In: Informatics, Ref. 69; FASEB, Ref. 30.*
88. FLESCH, P. (1953). Studies on the mode of action of vitamin A. *J. Invest. Dermatol.* **21**, 421-434. *In: FASEB, Ref. 73.*
89. SUNDE, M.L. (1956). The effect of fats and fatty acids in chick rations. *Poultry Sci.* **35**, 362-368. *In: FASEB, Ref. 73.*
90. ROBERTSON, T.B., DAWBARN, M.C., THOMAS, R.G., WALTERS, J.W., and WILSON, J.D.O. (1933). Experiments on the growth and longevity of the white mouse. I. The influence of injections of thorium oleate in oleic acid, and of oleic acid alone, on growth and longevity. *Aust. J. Exp. Biol. Med. Sci.* **11**, 99-108.
91. CARROLL, K.K., and NOBLE, R.L. (1957). Influence of a dietary supplement of erucic acid and other fatty acids on fertility in the rat: Sterility caused by erucic acid. *Can. J. Biochem. Physiol.* **35**, 1093-1105. *In: FASEB, Ref. 73.*
92. SZEPSENWOL, J. (1969). Brain nerve cell tumors in mice on diets supplemented with various lipids. *Pathol. Microbiol.* **34**, 1-9.
93. SZEPSENWOL, J. (1978). Gastrointestinal tumors in mice of three strains maintained on fat-enriched diets. *Oncology* **35**(4), 143-152.
94. KATO, A., ANDO, K., SUZUKI, S., TAMURA, G., and ARIMA, K. (1969). Antitumor activity of monoglycerides and other esters of fatty acids. *J. Antibiot. (Tokyo).* **22**(2), 83-84.
95. CTFA. (January 10, 1977). Submission of unpublished data by CTFA. Human dermal irritation study on 15 percent and 30 percent aqueous solutions of Glyceryl Oleate using a single insult occlusive patch test. (2-47-16).*

96. CTFA. (August 11, 1983). Submission of unpublished data by CTFA. Human dermal irritation study on a fragrance preparation containing 19.0 percent Glyceryl Oleate. (2-47-2).*
97. LANMAN, B.M. (April 21-23, 1968). Joint Conference of Cosmetic Sciences. Washington, D.C.
98. PHILLIPS, L., STEINBERG, M., MAIBACH, H., and AKERS, W. (1972). *Toxicol. Appl. Pharmacol.* **21**, 369-382.
99. HILL TOP RESEARCH. (November 16, 1981). Submission of unpublished data by CTFA. Human cumulative dermal irritation study on a sunscreen formulation containing 5 percent Glyceryl Oleate. (2-47-13).*
100. FOOD AND DRUG RESEARCH LABORATORIES (FDRL). (April 12, 1973). Submission of unpublished data by CTFA. Repeated insult patch test on a 15 percent aqueous solution of Glyceryl Oleate. (2-47-17).*
101. FDRL. (1981). Submission of unpublished data by CTFA. Human photoallergy, phototoxicity and primary irritation/sensitization study on a sunscreen formulation containing 5 percent Glyceryl Oleate. (2-47-12).*

Final Report of the Amended Safety Assessment of Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate¹

The safety of 43 glyceryl monoesters listed as cosmetic ingredients was reviewed in a safety assessment completed in 2000. Additional safety test data pertaining to Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate were received and served as the basis for this amended report. Glyceryl monoesters are used mostly as skin-conditioning agents—emollients and/or surfactant—emulsifying

agents in cosmetics. The following 20 glyceryl monoesters are currently reported to be used in cosmetics: Glyceryl Laurate, Glyceryl Alginate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Cocoate, Glyceryl Erucate, Glyceryl Hydroxystearate, Glyceryl Isostearate, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Myristate, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Stearate/Acetate, and Glyceryl Undecylenate. Concentration of use data received from the cosmetics industry in 1999 indicate that Glyceryl Monoesters are used at concentrations up to 12% in cosmetic products. Glyceryl Monoesters are not pure monoesters, but are mostly mixtures with mono-, di-, and tri-esters. The purity of commercial and conventional Monoglyceride (Glyceryl Monoester) is a minimum of 90%. Glyceryl Monoesters (monoglycerides) are metabolized to

Received 12 February 2004; accepted 4 June 2004.

¹Reviewed by the Cosmetic Ingredient Review Expert Panel. This report was prepared by Wilbur Johnson, Jr., Senior Scientific Analyst and Writer. Address correspondence to Wilbur Johnson, Jr., 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

free fatty acids and glycerol, both of which are available for the resynthesis of triglycerides. Glyceryl Laurate enhanced the penetration of drugs through cadaverous skin and hairless rat skin in vitro and has been described as having a wide spectrum of antimicrobial activity. A low-grade irritant response was observed following inhalation of an aerosol containing 10% Glyceryl Laurate by test animals. Glyceryl monoesters have little acute or short-term toxicity in animals, and no toxicity was noted following chronic administration of a mixture consisting mostly of glyceryl di- and mono- esters. Glyceryl Laurate did have strong hemolytic activity in an in vitro assay using sheep erythrocytes. Glyceryl Laurate, Glyceryl Isostearate, or Glyceryl Citrate/Lactate/Linoleate/Oleate were not classified as ocular irritants in rabbits. Undiluted glyceryl monoesters may produce minor skin irritation, especially in abraded skin, but in general these ingredients are not irritating at concentrations used in cosmetics. Glyceryl monoesters are not sensitizers, except that Glyceryl Rosinate and Hydrogenated Glyceryl Rosinate may contain residual rosin, which can cause allergic reactions. These ingredients are not photosensitizers. Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic in the Ames test system. Glyceryl Laurate exhibited antitumor activity and Glyceryl Stearate was negative in a tumor promotion assay. At concentrations higher than used in cosmetics, Glyceryl Laurate did cause moderate erythema in human repeat-insult patch test (RIPT) studies, but the other glyceryl monoesters tested failed to produce any significant positive reactions. Glyceryl Rosinate was irritating to animal skin at 50%, but did not produce sensitization in clinical tests at concentrations up to 10% and covered with semiocluded patches. There is reported use of Glyceryl Rosinate at 12% in mascara, which is somewhat higher than the concentration in the clinical testing. It was reasoned that the available data do support the safety of this use because there would be minimal contact with the skin and no occlusion. The safety of Arachidonic Acid was not documented and substantiated for cosmetic product use in an earlier safety assessment and those same safety questions apply to Glyceryl Arachidonate. Based on these data, the Cosmetic Ingredient Review (CIR) Expert Panel found that these glyceryl monoesters are safe as cosmetic ingredients in the present practices of use and concentration: except that the available data are insufficient to support the safety of Glyceryl Arachidonate. Additional data needed to support the safety of Glyceryl Arachidonate include (1) dermal absorption data; and, based on the results of the absorption studies, there may be a need for (2) immunomodulatory data; (3) carcinogenicity and photocarcinogenicity data; and (4) human irritation, sensitization, and photosensitization data.

INTRODUCTION

Glyceryl monoesters are a group of ingredients comprising esters of glycerin and assorted fatty acids or fatty acid derivatives. The 43 glyceryl monoesters listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Pepe et al. 2002), which have uses in a wide variety of cosmetic products, mostly as conditioning agents, are included in this safety assessment. A final safety assessment of glyceryl monoesters was updated with additional safety test data for Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate and an amended conclusion was reached.

Only 16 of the 43 ingredients were reported to the U.S. Food and Drug Administration (FDA) by industry as being used in cosmetics, but data received directly from industry indicate that

an additional 4 ingredients are being used in cosmetics. If ingredients that are currently not used were to be used in the future, the Cosmetic Ingredient Review (CIR) Expert Panel expects that the types of products and the concentrations used would be similar to those in current use.

Safety test data are available for only a limited number of ingredients. The CIR Expert Panel also considered safety assessments of related ingredients to be relevant. These include the earlier safety assessments of Glyceryl Stearate and Glyceryl Stearate SE (Elder 1982), Glyceryl Oleate (Elder 1986), and Arachidonic Acid (Andersen 1993).

CHEMISTRY

Chemical and Physical Properties

The glyceryl monoesters of fatty acids are primarily white to yellow oils or oily waxes with faint fatty odors. These substances are not pure monoesters, but are mixtures with mono-, di-, and tri-ester contents of approximately 4:4:2 (Unichema International 1997b). Danisco Ingredients (1999c, 1999d) guarantees that the purity of their commercial and conventional Monoglyceride is a minimum of 90%.

The octanol/water partition coefficient (K_{ow}) is normally a measured value defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. The partition coefficient is normally represented by its $\log_{10}$ value.

The octanol/water partition coefficient may be calculated. One method for calculating $\log(K_{ow})$ involves the use of fragment constants (Leo, Hansch, and Elkins 1971; Lyman, Reehl, and Rosenblatt 1982). The development of a method for calculation of $\log(K_{ow})$ for glycerol monoesters is based on the known values of glycerol monoacetate and glycerol monobutyrate. Knowing these values, the fragment-constant of the glycerol-ester part can be calculated. From this value, the $\log(K_{ow})$ of any glycerol monoester can be calculated using the chain-length and the number of double bonds (DB) of the acid part.

Physical properties of glyceryl monoesters are listed in Table 1.

These ingredients may be supplied as trade mixtures. The physical properties of one such trade mixture (50% Glyceryl Rosinate with 50% octyldecyl myristate) are shown in Table 2.

Further descriptions of the ingredients in this safety assessment follow.

Glyceryl Laurate (CAS nos. 142-18-7 and 27215-38-9) is the monoester of glycerin and lauric acid that conforms generally to the formula (Pepe, Wenninger, and McEwen 2002):

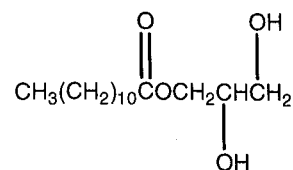


TABLE 1
Physical properties of Glyceryl Monoesters

Property	Description	Reference
<i>Glyceryl Laurate</i>		
Form	Cream-colored paste White crystalline White to cream-colored powder Off-white pellets	Lewis 1993 Hüls America, Inc., no date Henkel KgaA 1996 Danisco Ingredients 1996
Solubility	Dispersable in water; soluble in methanol, ethanol, toluene, naphtha, mineral oil, cottonseed oil, and ethyl acetate Practically insoluble in water; hardly soluble to readily soluble in acetone, diethyl ether, and heptane	Lewis 1993 Hüls America, Inc., no date
Odor	Faint Faint, fatty odor	Lewis 1993 Hüls America, Inc., no date
Molecular weight	274.4	Kabara 1984
Melting point	23–27°C 56–60°C	Scientific & Technical Information Network (STN) International 1997 Hüls America, Inc., no date Henkel KgaA 1996
Dropping point	56°C	Hüls America, Inc., no date Henkel KgaA 1996
Density	0.98	Lewis 1993
pH	8.0–8.6 (25°C for 5% aqueous dispersion) 4–5 (10% in methanol/water 1:1)	Lewis 1993 Hüls America, Inc., no date
Hydroxyl value	395	Danisco Ingredients 1996
Iodine value	5–8 2% max. (based on I ₂)	Lewis 1993 Hüls America, Inc., no date Henkel KgaA 1996
Iodine color	<1 3 mg/100 ml max. (based on I ₂)	Danisco Ingredients 1996 Hüls America, Inc., no date
Saponification value	200–206 195–205 mg KOH/g	STN International 1997 Hüls America, Inc., no date Henkel KgaA 1996
Acid value	205 3 mg KOH/g max. 3% max.	Danisco Ingredients 1996 Hüls America, Inc., no date Henkel KgaA 1996
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 295 nm	Danisco Ingredients 1999e
<i>Glyceryl Behenate</i>		
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 288 nm and 290 nm	Danisco Ingredients 1999e
<i>Glyceryl Caprate</i>		
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 287 nm and 291 nm	Danisco Ingredients 1999e
<i>Glyceryl Caprylate</i>		
Form	White crystalline	Hüls America, Inc., no date
Solubility	Practically insoluble in water; hardly soluble to readily soluble in various water/ethanol mixtures; readily soluble in acetone, diethyl ether, and heptane	Hüls America, Inc., no date
Iodine value	1 g/100 g max. (based on I ₂)	Hüls America, Inc., no date
Iodine color	3 mg/100 ml max. (based on I ₂)	Hüls America, Inc., no date
Saponification value	245–265 mg KOH/g	Hüls America, Inc., no date
Acid value	3 mg KOH/g max.	Hüls America, Inc., no date

(Continued on next page)

TABLE 1
Physical properties of Glyceryl Monoesters (*Continued*)

Property	Description	Reference
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 295 nm	Danisco Ingredients 1999e
<i>Glyceryl Caprylate/Caprate</i>		
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 295 nm	Danisco Ingredients 1999e
<i>Glyceryl Citrate/Lactate/Linoleate/Oleate</i>		
Form	Viscous, yellowish liquid	Hüls America, Inc., no date
Odor	Odor likened to soya bean oil; neutral taste	Hüls America, Inc., no date
pH	6–7 (10% in water)	Hüls America, Inc., no date
Saponification value	230–250 mg KOH/g	Hüls America, Inc., no date
Acid value	15 mg KOH/g max.	Hüls America, Inc., no date
<i>Glyceryl Cocoate</i>		
Form	White to slightly yellowish liquid	Hüls America, Inc., no date
Solubility	Practically insoluble in water; hardly soluble to soluble in various water/ethanol mixtures; readily soluble in acetone, soluble in diethyl ether, and hardly soluble in heptane	Hüls America, Inc., no date
Odor	Odor likened to coconut oil	Hüls America, Inc., no date
Melting point	31–37°C	Hüls America, Inc., no date
Iodine value	3 g/100 g max. (based on I ₂)	Hüls America, Inc., no date
Iodine color	5 mg/100 ml max. (based on I ₂)	Hüls America, Inc., no date
Saponification value	200–300 mg KOH/g	Hüls America, Inc., no date
Acid value	2 mg KOH/g max.	Hüls America, Inc., no date
<i>Glyceryl Collagenate</i>		
Appearance	Clear to hazy amber liquid	Brooks Industries 1998
Odor	Proteinaceous odor	Brooks Industries 1998
Solubility	At 5%, soluble in water, glycerine, 40% aqueous alcohol, sodium lauryl sulfate, and cocamidopropyl betaine	Brooks Industries 1998
Specific gravity at 20°C	1.2	Brooks Industries 1998
Boiling point	215°C	Brooks Industries 1998
% volatile by volume	80%	Brooks Industries 1998
<i>Glyceryl Erucate</i>		
Calculated Octanol/water partition coefficient (log(<i>K</i> _{ow}))	8.61	Danisco Ingredients 1999a
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 287 nm and 291 nm	Danisco Ingredients 1999e
<i>Glyceryl Isostearate</i>		
Form	Crystals; color <6 on Gardner scale	Gattefossé 1998
Odor	Faint	
Specific gravity at 20°C	0.930 to 0.970	Gattefossé 1998
Refractive index at 20°C	1.455 to 1.475	Gattefossé 1998
Viscosity at 20°C	0.7 to 1.2 Pa	Gattefossé 1998
Hydroxyl value	180–280 mg KOH/g	Gattefossé 1998
Iodine value	<15 g/100 g (based on I ₂)	Gattefossé 1998
Saponification value	150–170 mg	Gattefossé 1998
Acid value	<4 mg KOH/g	Gattefossé 1998
<i>Glyceryl Linoleate</i>		
Form	Crystals obtained from benzene as solvent	Lide and Frederikse 1993
	Soft plastic	Danisco Ingredients 1996
Solubility	Soluble in ether, benzene, and chloroform	Lide and Frederikse 1993

(Continued on next page)

TABLE 1
Physical properties of Glycerol Monoesters (*Continued*)

Property	Description	Reference
Refractive index	1.4758 at 20°C	Lide and Frederikse 1993
Molecular weight	354.53	Lide and Frederikse 1993
Melting point	14.5°C	Lide and Frederikse 1993
	45°C (completely melted)	Danisco Ingredients 1996
Hydroxyl value	310	Danisco Ingredients 1996
Iodine value	105	Danisco Ingredients 1996
Saponification value	160	Danisco Ingredients 1996
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 270 nm	Danisco Ingredients 1999e
	<i>Glycerol Myristate</i>	
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 293 nm	Danisco Ingredients 1999e
	<i>Glycerol Oleate/Elaidate</i>	
UV absorption	$\lambda_{\max}$ at 239 nm; $\lambda_{\min}$ at 270 nm	Danisco Ingredients 1999e
	<i>Glycerol Palmitate</i>	
Specific rotation	−4.37 (in pyrimidine)	Lide and Frederikse 1993
Calculated Octanol/water partition coefficient ($\log(K_{ow})$)	6.38	Danisco Ingredients 1999a
Molecular weight	330.51	Lide and Frederikse 1993
Melting point	71–72°C	Lide and Frederikse 1993
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 295 nm	Danisco Ingredients 1999e
	<i>Glycerol Palmitate/Lactate</i>	
Form	Off-white pellets	Danisco Ingredients 1996
Dropping point	50°C	Danisco Ingredients 1996
Hydroxyl value	160	Danisco Ingredients 1996
Iodine value	<2	Danisco Ingredients 1996
Saponification value	245–265	Danisco Ingredients 1996
Acid value	5 max.	Danisco Ingredients 1996
UV absorption	$\lambda_{\max}$ at 239 nm; $\lambda_{\min}$ at 287 nm	Danisco Ingredients 1999e
	<i>Glycerol Palmitate/Stearate</i>	
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 295 nm	Danisco Ingredients 1999e
	<i>Glycerol Palmitoleate</i>	
UV absorption	$\lambda_{\max}$ at 238 nm; $\lambda_{\min}$ at 270 nm and 280 nm	Danisco Ingredients 1999e
	<i>Glycerol Sesquioleate</i>	
UV absorption	$\lambda_{\max}$ at 239 nm	Danisco Ingredients 1999e
	<i>Glycerol Stearate/Citrate</i>	
Form	White ivory-colored powder	Hüls America, Inc., no date
Solubility	Well soluble in acetone; insoluble in alcohols and ethers; sparingly soluble in ethanol; and turbid soluble in medium shain triglycerides and fatty oils	Hüls America, Inc., no date
Odor	Neutral, fatty odor	Hüls America, Inc., no date
Melting point	59–63°C	Hüls America, Inc., no date
pH	10–30 (10% in water 1:1)	Hüls America, Inc., no date
Saponification value	230–260 mg KOH/g	Hüls America, Inc., no date
Acid value	15–25 mg KOH/g max.	Hüls America, Inc., no date

TABLE 2

Physical properties of Purified Ester Gum-2-OctylDodecyl Myristate (Purified Ester Gum/M.O.D.), a trade mixture containing 50% Glyceryl Rosinate and 50% Octyldecyl Myristate

Property	Description	Reference
Appearance	Viscous transparent light-brown liquid with almost no odor	Shin-Ei Chemical Company Ltd. 1998
Description	Viscous liquid made up of purified ester gum dissolved in 2-octyl dodecyl myristate in a 50:50 ratio. Ester gum is a rosin ester whose main component is ester of abietic acid and glycerol	Cosmo Trends, no date
Specific Gravity (d_{25}^{25})	0.9625 to 0.9725	U.S. Cosmetics Corporation 1998
Refractive Index (n_D^{20})	1.4930 to 1.4980	U.S. Cosmetics Corporation 1998
Solubility	Soluble in olive oil, castor oil, petrolatum, and liquid paraffin. Insoluble in glycerin, water, and propylene glycol	Shin-Ei Chemical Company Ltd. 1998
Melting point	No data available	Shin-Ei Chemical Company Ltd. 1998
Flash point	272°C	U.S. Cosmetics Corporation 1998
Acid value	<12	U.S. Cosmetics Corporation 1998
Heavy metals (ppm)	<20	U.S. Cosmetics Corporation 1998
Arsenic (ppm)	<2	U.S. Cosmetics Corporation 1998
Moisture (%)	<0.1 g	U.S. Cosmetics Corporation 1998
Solid content (%)	50 ± 2	U.S. Cosmetics Corporation 1998
Percent volatile	Almost none	Shin-Ei Chemical Company Ltd. 1998
Volatile organic compounds	None identified	Shin-Ei Chemical Company Ltd. 1998
Oxidation	Little tendency to oxidize	Shin-Ei Chemical Company Ltd. 1998
Stability	Stable with almost no reactivity	Shin-Ei Chemical Company Ltd. 1998
Hazardous decomposition products	Almost none	Shin-Ei Chemical Company Ltd. 1998

According to Danisco Ingredients (1999c), two isomeric forms (α and β) exist; the structure above is the α form. Glyceryl Laurate also has been described as a distilled monoglyceride that is made from edible vegetable fatty acids (mainly lauric acid) (Danisco Ingredients 1999c) as well as a molecular distilled lauric acid monoglyceride (Henkel KgaA 1994). Other names for this chemical include Dodecanoic Acid, 2,3-Dihydroxypropyl Ester; Dodecanoic Acid, Monoester with 1,2,3-Propanetriol; Glyceryl Monolaurate; and Lauricidin (Pepe, Wenninger, and McEwen 2002); Laurin, 1-Mono; alpha-Monolaurin; 1-Glyceryl Laurate; 1-Monododecanoylglycerol; 1-Monolaurin; Dodecanoic Acid alpha-Monoglyceride; Glycerin 1-Monolaurate; Glycerol alpha-Monolaurate; Glycerol 1-Laurate; Glycerol 1-Monolaurate; Glyceryl Monododecanoate; Glyceryl Monolaurate; Lauric Acid alpha-Monoglyceride; and Lauric Acid 1-Monoglyceride (Scientific & Technical Information Network [STN] International 1997).

Commercial Glyceryl Laurate consists of 90% monoester, free glycerol (maximum 4%), and free fatty acid (maximum 1%). Its fatty acid profile is as follows: C_{10} (maximum 10%), C_{12} (maximum 90%), and C_{14} (maximum 8%) (Kabara 1984).

Henkel KgaA (1996) confirmed the 90% monoester content of Glyceryl Laurate and indicated that free glycerin is present at concentrations up to 2%.

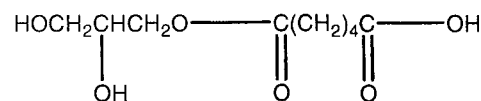
Hüls America, Inc. (no date) states that Glyceryl Laurate contains free glycerol (1%), monoglycerides (95%), diglycerides (2%), and water (maximum 1%).

Danisco Ingredients (1996) states that the composition of Glyceryl Laurate is as follows: monoester content (minimum 90%), free glycerol (maximum 1%), and free fatty acids (maximum 1.5%).

Glyceryl Laurate SE is a self-emulsifying grade of Glyceryl Laurate that contains some sodium and/or potassium laurate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Laurate/Oleate is the monoester of glycerin and a blend of lauric and oleic acids (Pepe, Wenninger, and McEwen 2002).

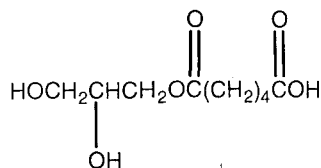
Glyceryl Adipate (CAS no. 26699-71-8) is the ester of glycerin and adipic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Hexanedioic Acid, Monoester with 1,2,3-Propanetriol is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

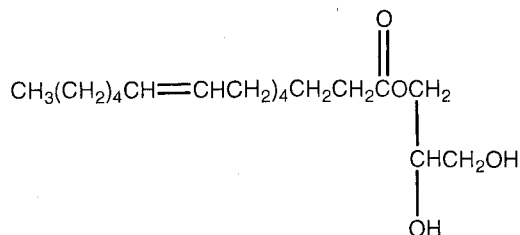
Glyceryl Alginate is the ester of glycerin and alginic acid. Alginic Acid, Glyceryl Ester is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

Glyceryl Arachidate (CAS nos. 30208-87-8 and 50906-68-8) is the ester of glycerin and arachidic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



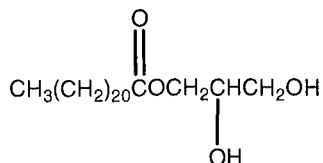
Other names for this chemical include 2,3-Dihydroxypropyl Eicosanoate; Eicosanoic Acid, 2,3-Dihydroxypropyl Ester; Eicosanoic Acid, Monoester with 1,2,3-Propanetriol; and Glyceryl Monoarachidate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Arachidonate (CAS no. 35474-99-8) is the monoester of glycerin and arachidonic acid that conforms to the following formula (Wenninger et al. 2000):



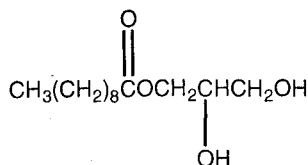
Other names for this chemical include: Arachidonic Acid, Monoester with 1,2,3-Propanetriol; 2,3-Dihydroxypropyl 5,8,11,14-Eicosatetraenoate; 5,8,11,14-Eicosatetraenoic Acid, 2,3-Dihydroxypropyl Ester; and Glyceryl Monoarachidonate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Behenate (CAS nos. 6916-74-1 and 30233-64-8) is the monoester of glycerin and behenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



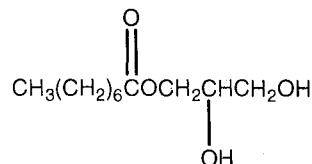
Other names for this chemical include 2,3-Dihydroxypropyl Docosanoate; Docosanoic Acid, 2,3-Dihydroxypropyl Ester; Docosanoic Acid, Monoester with 1,2,3-Propanetriol; and Glyceryl Monobehenate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Caprate (CAS no. 26402-22-2) is the monoester of glycerin and capric acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Decanoic Acid, Monoester with 1,2,3-Propanetriol and Glyceryl Monocaprate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Caprylate (CAS no. 26402-26-6) is the monoester of glycerin and caprylic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):

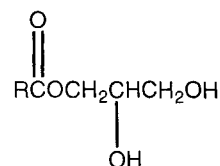


It has a molecular weight of 218.29 (Budavari 1989). Other names for this chemical include Glyceryl Monocaprylate and Octanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002), and Monooctanoic (Budavari, 1989). The typical composition of Glyceryl Caprylate is described as follows: free glycerol (1%), monoglycerides (90%), diglycerides (7%), triglycerides (1%), and water (maximum 1%) (Hüls America, Inc., no date).

Glyceryl Caprylate/Caprate is a mixture of monoglycerides of caprylic and capric acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Citrate/Lactate/Linoleate/Oleate is the ester of glycerin and a blend of citric, lactic, linoleic and oleic acids (Pepe, Wenninger, and McEwen 2002). More specifically, it is a partially neutralized ester of mono- and diglycerides of unsaturated edible fatty acids with citric acid and lactic acid (Hüls America, Inc., no date).

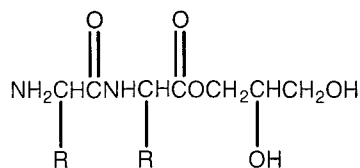
Glyceryl Cocoate (CAS no. 61789-05-7) is the monoester of glycerin and coconut fatty acids that conforms to the following formula, where R represents the fatty acids derived from coconut oil (Pepe, Wenninger, and McEwen 2002):



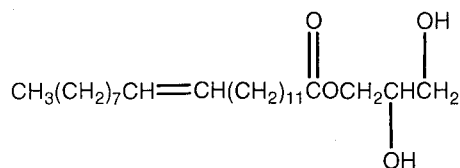
More specifically, it is composed of partial glycerides (mono/di/triglycerides) of the saturated fatty acids of coconut oil. The chain length is C₁₀ to C₁₈; the main component is C₁₂, as in coconut oil (Hüls America, Inc., no date). Other names for this chemical include: Glycerides, Coconut Oil Mono-; Glycerol Mono Coconut Oil; Glyceryl Coconate; and Glyceryl Monococoate (Pepe, Wenninger, and McEwen 2002). The typical composition of Glyceryl Cocoate is described as follows: free glycerol (1%), monoglycerides (45%), diglycerides (35%), triglycerides (15%), and water (maximum 1%) (Hüls America, Inc., no date).

Glyceryl Collagenate is the ester of glycerin and collagen (q.v.) (Pepe, Wenninger, and McEwen 2002). It consists

of ~25% solids and its chemical structure, where R is an amino group typical of collagen, is included below (Brooks Industries 1998):



Glyceryl Erucate (CAS no. 28063-42-5) is the monoester of glycerin and erucic acid that conforms generally to the following formula (Pepe, Wenninger, and McEwen 2002):

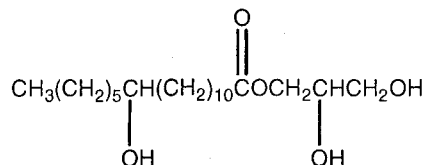


Other names for this chemical include Glyceryl Monoerucate and Erucic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Hydrogenated Rosinate is the monoester of glycerin and hydrogenated mixed long chain acids derived from rosin (Pepe, Wenninger, and McEwen 2002). It also exists as a mixture of 50% Glyceryl Hydrogenated Rosinate and 50% Octyldodecyl Myristate (McEwen 2000).

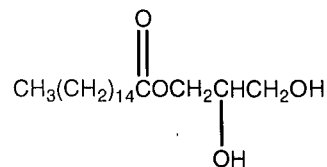
Glyceryl Hydrogenated Soyate is the monoester of glycerin (q.v.) and hydrogenated mixed long chain acids derived from soy (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), this ingredient is a distilled monoglyceride made from edible, fully hydrogenated vegetable oil.

Glyceryl Hydroxystearate (CAS no. 1323-42-8) is the monoester of glycerin and hydroxystearic acid (q.v.) that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



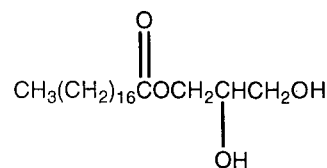
Other names for this chemical are as follows: Glyceryl Hydroxystearate (1); Glyceryl Hydroxystearate (2); Glyceryl Monohydroxystearate; Hydroxystearic Acid, Monoester with Glycerol; and Stearic Acid, Hydroxy-, Monoester with Glycerol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isopalmitate is the monoester of glycerin and a branched chain 16-carbon aliphatic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Isopalmitic Acid, 2,3-Dihydroxypropyl Ester and Isopalmitic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isostearate (CAS nos. 66085-00-5 and 61332-02-3) is the monoester of glycerin and isostearic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Glyceryl Isostearate (1), Glyceryl Monoisostearate, and Isooctadecanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Gattefossé s.a. (1998) described the composition of Glyceryl Isostearate as containing 1-monoglycerides (>30%), free glycerol (<7%), and water (<0.50%).

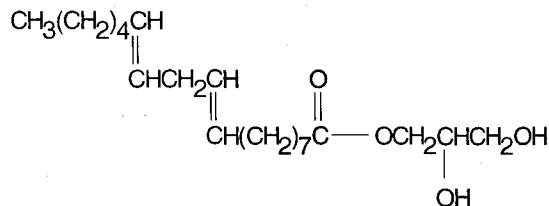
Glyceryl Isostearate/Myristate is the monoester of glycerin and a blend of isostearic and myristic acids. Glyceryl Monoisostearate Monomyristate is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isostearates is a mixture of the mono-, di-, and triesters of glycerin and isostearic acid. This chemical is also known as Glyceryl Isostearate (2) (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isotridecanote/Stearate/Adipate is the ester of glycerin (q.v.) and a blend of isotridecanoic acid, stearic acid, and adipic acid (Pepe, Wenninger, and McEwen 2002).

Glyceryl Lanolate is the monoester of glycerin and lanolin acid (q.v.). Other names for this chemical include Glyceryl Monolanolate and Lanolin Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Linoleate (CAS no. 2277-28-3) is the monoester of glycerin and linoleic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):

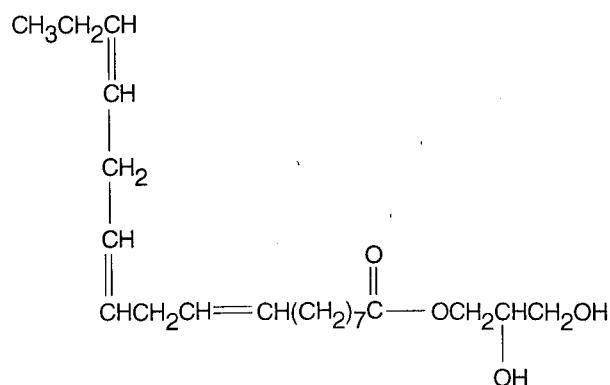


Other names for this chemical include 2,3-Dihydroxypropyl 9,12-Octadecadienoate; Glyceryl Monolinoleate; Linoleic Acid,

Monoester with 1,2,3-Propanetriol; Monolinolein; 9,12-Octadecadienoic Acid, 2,3-Dihydroxypropyl Ester; and 9,12-Octadecadienoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Danisco Ingredients (1996) stated that the composition of Glyceryl Linoleate is as follows: monoester content (minimum 90%); free glycerol (maximum 1%); free fatty acid (maximum 1.5%); butyl hydroxy anisole (BHA), as antioxidant (maximum 200 ppm); and citric acid, as antioxidant (maximum 200 ppm) (Note: Citric acid is dissolved in propylene glycol.)

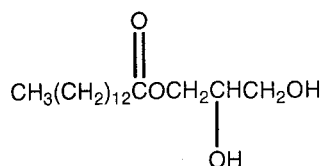
Glyceryl Linolenate (CAS no. 18465-99-1) is the monoester of glycerin and linolenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



According to Danisco Ingredients (1999c), Glyceryl Linolenate is a distilled monoglyceride that is made from edible, refined sunflower oil. Other names for Glyceryl Linolenate include 2,3-Dihydroxypropyl 9,12,15-Octadecatrienoate; Glyceryl monolinolenate; Linolenic Acid, Monoester with 1,2,3-Propanetriol; and 9,12,15-Octadecatrienoic Acid, 2,3-Dihydroxypropyl Ester (Pepe, Wenninger, and McEwen 2002).

Glyceryl Montanate (CAS no. 68476-38-0) is the monoester of glycerin and montan acid wax. Other names for this chemical include 2,3-Dihydroxypropyl Octacosanoic Acid; Glycerides, Montan-Wax; Montan-Wax Fatty Acids, Glyceryl Esters; and Octacosanoic Acid, 2,3-Dihydroxypropyl Ester (Pepe, Wenninger, and McEwen 2002).

Glyceryl Myristate (CAS nos. 589-68-4 and 27214-38-6) is the monoester of glycerin and myristic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):

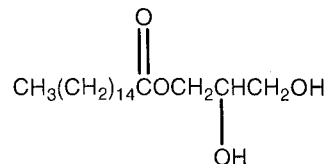


According to Danisco Ingredients (1999c), it is a distilled monoglyceride that is made from vegetable fatty acids (mainly myristic acid). Other names for this chemical include: Glyceryl Monomyristate; Monomyristin; and Tetradecanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Oleate SE is a self-emulsifying grade of Glyceryl Oleate (q.v.) that contains some sodium and/or potassium oleate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Oleate/Elaidate is a mixture of monoglycerides of oleic and elaidic acids (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), it is a distilled monoglyceride made from edible, partially hydrogenated soya bean oil.

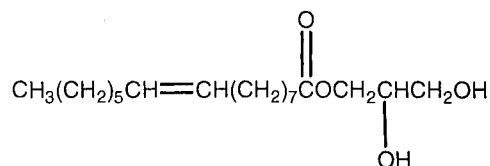
Glyceryl Palmitate (CAS no. 26657-96-5) is the monoester of glycerin and palmitic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include: Glyceryl Monopalmitate; Hexadecanoic Acid, 2,3-Dihydroxypropyl Ester; and Hexadecanoic Acid, Monoester with 1,2,3-Propanetriol; Hexadecanoic acid α -monoglyceride; Palmitic Acid Monoglyceride; Palmitin, mono-; and Palmitin, 1-mono- (Pepe, Wenninger, and McEwen 2002).

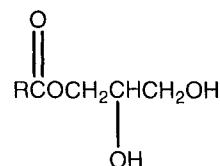
Glyceryl Palmitate/Stearate (CAS no. 68002-71-1) is the monoester of glycerin and a blend of palmitic and stearic acids (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), it is a distilled monoglyceride made from edible, fully hydrogenated lard or tallow.

Glyceryl Palmitoleate is the monoester of glycerin and palmitoleic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



According to Danisco Ingredients (1999c), it is a distilled monoglyceride that is made from edible, refined palm oil. Other names for this chemical include Glyceryl Monopalmitoleate; Palmitoleic Acid, 2,3-Dihydroxypropyl Ester; and Palmitoleic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Pentadecanoate is the monoester of glycerin and pentadecanoic acid that conforms to the following formula, where RCO- represents the pentadecanoyl radical (Pepe, Wenninger, and McEwen 2002):



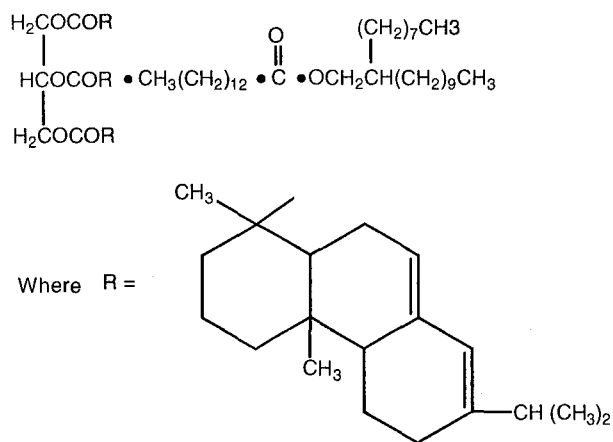
Another name for this chemical is 2,3-dihydroxypropane-pentadecanoate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Polyacrylate is the ester of glycerin (q.v.) and polyacrylic acid (q.v.) (Pepe, Wenninger, and McEwen 2002).

Glyceryl Rosinate (CAS no. 8050-31-5) is the monoester of glycerin and mixed long chain acids derived from rosin (q.v.). Glycerin monorosinate and resin acids and rosin acids, esters with glycerin are two other names for this chemical (Pepe, Wenninger, and McEwen 2002).

In an FDA review of safety (FDA 1988), rosin is the residue remaining when the volatile oil is distilled from turpentine or a product of the distillation, solvent extraction, or both, of the stumps or fallen trees of various species of *Pinus*. Abietic acid and dehydroabietic acid are the main components that have been identified. Rosin nomenclature is based on the source from which it is obtained. Thus, rosin obtained from officinal (gum) turpentine is known as gum rosin. Wood rosin is rosin distilled or extracted out of the wood of stumps of fallen trees. These rosins differ in color, % resene, and in the softening point.

Glyceryl Rosinate is supplied as a trade mixture that is known as Purified Ester Gum-2-Octyldodecyl Myristate (Purified Ester Gum/M.O.D.) (US Cosmetics Corporation, no date). Purified Ester Gum-2-Octyldodecyl Myristate consists of 50% Glyceryl Rosinate and 50% octyldodecyl myristate (Shin-Ei Chemical Company Ltd. 1998), and properties of this trade mixture are presented in Table 2. The structural formula for Purified Ester Gum-2-Octyldodecyl Myristate is indicated below (US Cosmetics Corporation, no date):



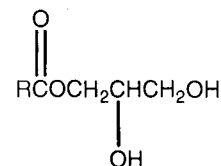
Glyceryl Sesquioleate is a mixture of mono- and di-esters of glycerin and oleic acid (Pepe, Wenninger, and McEwen 2002).

Glyceryl/Sorbitol Oleate/Hydroxystearate is the mixed esterification product of glycerin and sorbitol with hydroxystearic and oleic acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Stearate/Acetate is the monoester of glycerin and a blend of stearic and acetic acids. Glyceryl monostearate monoacetate is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

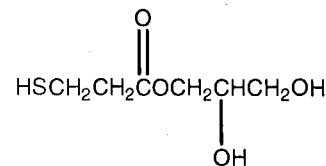
Glyceryl Stearate/Maleate is the monoester of glycerin and a blend of stearic and maleic acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Tallowate is the monoester of glycerin and tallow fatty acids that conforms to the following formula, where RCO- represents the fatty acids derived from tallow (Pepe, Wenninger, and McEwen 2002):

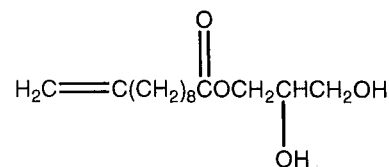


Another name for this chemical is glyceryl monotallowate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Thiopropionate is the organic compound that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Glyceryl Undecylenate is the ester of glycerin and undecylenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical are glyceryl monoundecylenate and undecylenic acid, monoester with 1,2,3-propanetriol (Pepe, Wenninger, and McEwen 2002).

Octanol/Water Partition Coefficients

Measured octanol/water partition coefficients were not available. Calculated values received from one supplier are given in Table 3.

Analytical Methods

Glyceryl Laurate has been analyzed by thin-layer chromatography, gas-liquid chromatography (Kabara 1984), reverse-phase high performance liquid chromatography (HPLC) (Maruyama and Yonese 1986; Takano and Kondoh 1987), capillary supercritical fluid chromatography (Giron, Link, and Bouissel 1992), and ultraviolet (UV) spectral analysis—results are summarized in Table 1 (Danisco Ingredients 1999e).

TABLE 3
Calculated octanol/water partition coefficients
of Glyceryl Monoesters (Danisco Ingredients 1999a)

Ingredient	log (Ko/w)
Glyceryl Laurate	4.22
Glyceryl Oleate	7.00
Glyceryl Behenate	9.62
Glyceryl Caprate	3.14
Glyceryl Caprylate	2.06
Glyceryl Erucate	8.61
Glyceryl Linoleate	5.44
Glyceryl Linolenate	4.60
Glyceryl Myristate	5.30
Glyceryl Elaidate	6.45
Glyceryl Palmitate	6.38
Glyceryl Stearate	7.69
Glyceryl Palmitoleate	5.37
Glyceryl Hydroxystearate	5.59

Methods of Production

According to Kabara (1984), industrial monoglycerides can be prepared by the direct esterification of glycerol with a fatty acid, yielding mixtures of mono-, di-, and tri- glycerides, depending on the molar ratio of the reactants. In the case of Glyceryl Laurate, the lauric acid that is used for esterification is generally derived from the oil of various species of palm, such as coconut and babassu. The glycerolysis of fats and oils, a transesterification reaction, is a common commercial method for the preparation of monoglycerides.

Glyceryl Collaginate is produced via the esterification of hydrolyzed collagen with United States Pharmacopeia (USP) glycerine 99% (Brooks Industries 1998).

Glyceryl Rosinate is contained in a trade mixture of purified ester gum-2-octyldodecyl myristate (containing 50% Glyceryl Rosinate and 50% octyldodecyl myristate), which is prepared by mixing (with heat) purified ester gum and 2-octyldodecyl myristate in a 1:1 ratio. The mixture is then subjected to purification processes such as decoloration, dehydration, deodorization and filtration (US Cosmetics Corporation, no date).

Composition/Impurities

Data on the chemical characterization of Glyceryl Monoesters are shown in Table 4.

Danisco Ingredients (1999d), indicated that a content of 3.5% to 4% total (mono)glycerol diester's are common in the manufacturing of distilled monoglyceride's. In the manufacturing of any less than 90% monoglyceride (commonly referred to as mono-diglycerides, albeit the INCI name does not differentiate), the content of (mono)glycerol diester's is higher. Because there is some diglycerol then there is also a "family" of diglycerol esters (mono- and di-esters). Consequently one can read from the tabulation of "impurities" for instance for a main product like DIMODAN PM [Glyceryl Palmitate/Stearate], that out of approximately 4% (mono)glycerol diester's, then approximately 29% of this is 1,2 (mono)glycerol diester. This would correspond to an approximate concentration of 1,2 (mono)glycerol diester of 1.2%.

Glyceryl Laurate contains ash (maximum 0.1%) (Hüls America, Inc., no date) and heavy metals, as Pb (<10 mg/kg) (Danisco Ingredients 1996).

TABLE 4
Impurities data on Glyceryl Monoesters (Danisco Ingredients 1999c, 1999d)

Ingredients	% glycerol	% diglycerol	% free fatty acid	% diglycerol monoester	Ratio of 1,2-(mono)glycerol diester to total (mono)glycerol diester
Glyceryl Laurate	0.07	0.24	0.16	—	24.8
Glyceryl Behenate	0.03	0.09	0.15	—	29.1
Glyceryl Caprate	1.03	0.43	0.06	—	21.0
Glyceryl Caprylate/Caprate	5.37	—	—	—	34.3
Glyceryl Linolenate	0.03	0.15	0.11	—	35.8
Glyceryl Myristate	0.30	0.57	0.14	—	27.8
Glyceryl Oleate/Elaidate	0.03	0.12	0.35	—	33.4
Glyceryl Palmitate	0.03	0.06	0.79	—	10.6
Glyceryl Palmitate/Lactate	0.04	—	0.82	—	30.6
Glyceryl Palmitate/Stearate	0.27	0.10	0.98	0.28	29.2
Glyceryl Palmitoleate	0.04	0.14	0.41	—	27.3
Glyceryl Sesquioleate	0.24	—	0.42	—	30.5
Glyceryl Hydrogenated Soyate	0.60	0.28	0.11	—	26.0

Glyceryl Caprylate and Glyceryl Cocoate contain ash at a maximum concentration of 0.1% (Hüls America, Inc., no date).

Glyceryl Collagenate contains a low level of sodium chloride, byproduct of the production process (Brooks Industries 1998). It also contains nonvolatile matter (25% to 31%) and moisture (67% to 73%).

Glyceryl Hydrogenated Soyate specifications, given by Danisco Ingredients (1999c), include: monoester content (minimum 90%), iodine value (maximum 2%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point ($\approx 72^{\circ}\text{C}$), and form (beads). Specifications for heavy metal impurities include: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), Cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg).

Glyceryl Isostearate impurities are as follows: alkaline impurities (< 80 ppm NaOH), sulfated ash content ($< 0.2\%$), and heavy metals (< 10 ppm Pb) (Gattefossé s.a. 1998).

Glyceryl Linoleate contains heavy metals (as Pb) at < 10 mg/kg (Danisco Ingredients 1996).

Glyceryl Linolenate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), iodine value (approximately 10%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), temperature at which completely melted ($\approx 45^{\circ}\text{C}$), and form (paste). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). Glyceryl Linolenate also contains the antioxidants, BHA (maximum 200 ppm) and citric acid dissolved in propylene glycol (maximum 200 ppm).

Glyceryl Myristate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), free glycerol (maximum 1%), and free fatty acids (maximum 1.5%). The typical value for heavy metals (as Pb) in Glyceryl Myristate is < 10 mg/kg.

Glyceryl Oleate/Elaidate specifications, given by Danisco Ingredients (1999c), include arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). It also contains the antioxidants, citric acid ester (maximum 300 ppm), α -tocopherol (maximum 200 ppm), and ascorbyl palmitate (maximum 200 ppm).

Glyceryl Palmitate/Stearate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), iodine value (maximum 2%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point ($\approx 70^{\circ}\text{C}$), and form (beads). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg).

Glyceryl Palmitoleate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%),

iodine value (≈ 40), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point ($\approx 60^{\circ}\text{C}$), and form (plastic). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). Glyceryl Palmitoleate also contains the antioxidants, BHA (maximum 200 ppm) and citric acid dissolved in propylene glycol (maximum 200 ppm).

Stability/Reactivity

Glyceryl Laurate is classified as a combustible material (Lewis 1993). It is compatible with most emulsifiers, but is inactivated in the presence of sodium lauryl sarcosine and ethoxylated and propoxylated nonionics (e.g., Tween 80, a.k.a. Polysorbate 80) (Kabara 1984).

Glyceryl Cocoate is stable against oxidation and forms an emulsion with water when heated (Hüls America, Inc., no date).

Glyceryl Isostearate reacts with strong acids and oxidizing agents. Additionally, incomplete combustion of Glyceryl Isostearate leads to the release of monoxycarbon and dioxycarbon (Gattefossé s.a. 1999).

USE

Cosmetic Use

Glyceryl Monoesters are used mostly as skin conditioning agents—emollients and/or surfactant-emulsifying agents, but several other uses are reported (Pepe, Wenninger, and McEwen 2002). The current function in cosmetics for each ingredient in this safety assessment is summarized in Table 5.

Table 6 presents information on the types of products in which these ingredients are used (FDA 1998; CTFA 1999), the frequency with which they are used as reported by industry to FDA (FDA 1998), and the current concentration at which the ingredients are used as reported by industry (CTFA 1999). Although only 16 of the 43 ingredients in this safety assessment were reported to FDA as being used in cosmetics, the current concentration of use data received from the cosmetics industry indicates that four additional glyceryl monoesters are in use. Also, concentrations of use are reported in product groups for which no uses were reported in 1998.

Cosmetic products containing glyceryl monoesters are applied to most areas of the body, and could come in contact with the ocular and nasal mucosae. These products could be used on a daily basis, and could be applied frequently over a period of several years.

None of the 43 ingredients reviewed in this safety assessment is included among the substances listed as prohibited from use in cosmetic products marketed in the European Union (European Economic Community 2001).

Japan describes the following 11 categories of cosmetic preparations: 1. skin cleansing; 2. hair care; 3. treatment;

TABLE 5
Functions of Glyceryl Monoesters in Cosmetics (Pepe, Wenninger, and McEwen 2002)

Ingredients	Functions
Glyceryl Laurate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Laurate SE	As above
Glyceryl Laurate/Oleate	As above
Glyceryl Adipate	As above
Glyceryl Alginate	Skin-conditioning agent—emollient; viscosity-increasing agent—aqueous
Glyceryl Arachidate	Skin-conditioning agent—emollient; surfactant-emulsifying agent; viscosity-increasing agent—nonaqueous
Glyceryl Arachidonate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Behenate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Caprate	As above
Glyceryl Caprylate	As above
Glyceryl Caprylate/Caprate	As above
Glyceryl Citrate/Lactate/Linoleate/Oleate	As above
Glyceryl Cocoate	As above
Glyceryl Collagenate	Hair-conditioning agent; skin-conditioning agent—emollient; skin-conditioning agent—miscellaneous
Glyceryl Erucate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Hydrogenated Rosinate	As above
Glyceryl Hydrogenated Soyate	As above
Glyceryl Hydroxystearate	As above
Glyceryl Isopalmitate	As above
Glyceryl Isostearate	As above
Glyceryl Isostearate/Myristate	As above
Glyceryl Isostearates	As above
Glyceryl Isotridecanoate/Stearate/Adipate	As above
Glyceryl Lanolate	Hair-conditioning agent; Skin-conditioning agent—emollient; surfactant—emulsifying agent
Glyceryl Linoleate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Linolenate	As above
Glyceryl Montanate	As above
Glyceryl Myristate	As above
Glyceryl Oleate SE	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Oleate/Elaidate	As above
Glyceryl Palmitate	As above
Glyceryl Palmitate/Stearate	As above
Glyceryl Palmitoleate	As above
Glyceryl Pentadecanoate	As above
Glyceryl Polyacrylate	Film former
Glyceryl Rosinate	As above
Glyceryl Sesquileate	As above
Glyceryl/Sorbitol Oleate/Hydroxystearate	As above
Glyceryl Stearate/Acetate	As above
Glyceryl Stearate/Maleate	As above
Glyceryl Thiopropionate	Hair-waving/straightening agent; reducing agent
Glyceryl Undecylenate	Skin-conditioning agent—emollient; surfactant—emulsifying agent

4. makeup; 5. fragrance; 6. suntan/ sunscreen; 7. nail makeup; 8. eyeliner; 9. lip product; 10. oral product; and 11. bath product. Table 7 lists the ingredients in this safety assessment according to the *International Cosmetic Ingredient*

Dictionary and Handbook name (INCI name), the categories for which there is precedent (or not) for use in Japan, and any limitations on use (Rempe and Santucci 1997).

TABLE 6
Product formulation data on Glyceryl Monoesters

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Glyceryl Laurate		
Eye shadow (551)	2	—
Eye makeup remover (99)	1	0.1
Other fragrance preparations (173)	1	—
Permanent waves (211)	9	—
Shampoos (noncoloring) (851)	—	0.3–2
Tonics, dressings, and other hair-grooming aids (577)	—	0.4
Wave sets (53)	—	0.4
Other hair preparations (noncoloring) (276)	—	0.4
Bath soaps and detergents (405)	4	—
Deodorants (underarm) (247)	4	—
Douches (5)	—	0.3
Other personal cleanliness products (307)	3	—
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	4
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	5	—
Other skin care preparations (715)	—	4
1998 total uses for Glyceryl Laurate	29	
Glyceryl Alginate		
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	1	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	0.5
1998 totals for Glyceryl Alginate	1	
Glyceryl Arachidonate		
Suntan gels, creams, and liquids (136)	2	—
1998 totals for Glyceryl Arachidonate	2	
Glyceryl Behenate		
Mascara (187)	—	2
Suntan gels, creams, and liquids (131)	—	5
1998 totals for Glyceryl Behenate	—	
Glyceryl Caprylate/Caprate		
Hair sprays (aerosol fixatives) (267)	1	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
1998 totals for Glyceryl Caprylate/Caprate	1	
Glyceryl Cocoate		
Bubble bath (209)	—	1
Lipstick (942)	—	0.3–2
Bath soaps and detergents (405)	—	4
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	1	1–5
1998 totals for Glyceryl Cocoate	1	
Glyceryl Erucate		
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	0.5
1998 totals for Glyceryl Erucate	—	

TABLE 6
Product formulation data on Glyceryl Monoesters (*Continued*)

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Glyceryl Hydroxystearate		
Other eye makeup preparations (151)	—	2
Lipstick (942)	1	—
Deodorants (247)	—	2
Other personal cleanliness products (307)	1	—
Shaving Cream (133)	1	—
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	4	—
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	5	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	2
Foot powders and sprays (35)	1	—
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	8	0.8
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	4	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	3	—
Suntan gels, creams, and liquids (131)	1	—
1998 totals for Glyceryl Hydroxystearate	32	
Glyceryl Isostearate		
Bath oils, tablets, and salts (140)	—	1
Eye shadow (551)	23	0.5–2
Eye lotion (23)	—	0.8
Face powders (301)	1	—
Foundations (319)	24	4–6
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	3
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	1	2
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	3
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	—	0.3
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Isostearate	32	
Glyceryl Lanolate		
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	—
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	1	—
1998 totals for Glyceryl Lanolate	3	
Glyceryl Linoleate		
Eye shadow (551)	1	—
Other fragrance preparations (173)	1	—
Face powders (301)	1	—

(Continued on next page)

TABLE 6
Product formulation data on Glyceryl Monoesters (*Continued*)

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Foundations (319)	2	0.7
Lipstick (942)	3	0.7
Other personal cleanliness products (307)	—	0.7
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	3	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	2	1
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	—
Paste masks (mud packs) (269)	1	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Linoleate	17	
Glyceryl Linolenate		
Eye shadow (551)	1	—
Foundations (319)	—	0.7
Lipstick (942)	3	0.7
Other personal cleanliness products (307)	—	0.7
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	1	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	2	1
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Linolenate	10	
Glyceryl Myristate		
Other fragrance preparations (173)	1	—
Makeup bases (136)	1	—
Deodorants (underarm) (247)	1	—
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	3	1-6
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	6
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	4	—
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	3	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	6
Suntan gels, creams, and liquids (131)	1	—
Other suntan preparations (37)	1	—
1998 totals for Glyceryl Myristate	19	
Glyceryl Oleate/Elaidate		
Foundations (319)	—	2
Makeup bases (136)	—	0.3

TABLE 6
Product formulation data on Glyceryl Monoesters (*Continued*)

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	2
Moisturizing creams, lotions, powders, and sprays (881)	—	2
1998 totals for Glyceryl Oleate/Elaidate	—	
Glyceryl Polyacrylate		
Hair conditioners (630)	—	0.4
Tonics, dressings, and other hair-grooming aids (577)	—	0.2
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	1	2
1998 totals for Glyceryl Polyacrylate	1	
Glyceryl Rosinate		
Eye brow pencil (99)	—	10
Eye shadow (551)	—	2
Mascara (187)	2	0.08–12
Other hair coloring preparations (59)	—	3
Blushers (all types) (243)	—	2
Foundations (319)	1	0.06–4
Lipstick (942)	—	0.4–6
Depilatories (28)	1	—
1998 totals for Glyceryl Rosinate	4	
Glyceryl Stearate/Acetate		
Tonics, dressings, and other hair-grooming aids (577)	—	7
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	2
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
Moisturizing creams, lotions, powders, and sprays (881)	—	3
Suntan gels, creams, and liquids (131)	—	3
Indoor tanning preparations (68)	—	2
1998 totals for Glyceryl Stearate/Acetate	—	
Glyceryl Undecylenate		
Moisturizing creams, lotions, powders, and sprays (881)	2	—
1998 totals for Glyceryl Undecylenate	2	

Noncosmetic Use

Glyceryl Laurate has noncosmetic uses as an emulsifying and dispersing agent for food products, oils, waxes, and solvents; an antifoaming agent; and a dry-cleaning soap base (Lewis 1993). It has also been detected in pharmaceutical excipients (Giron, Link, and Bouissel 1992).

Glyceryl Caprylate has been used to dissolve gallstones by direct biliary infusion (Budavari 1989).

Glyceryl Isostearate is used in textiles (Unichema International 1997b).

Glyceryl Behenate has been approved for use as a direct food additive (21 CFR 184.1328). Additionally, Glyceryl Mo-

noesters have been approved for use as components of adhesives, coatings, paper and paperboard, and other materials that come in contact with food (i.e., indirect food additive uses) (21 CFR 175.105; 175.300; 176.170; 176.180; 176.200; 176.210; 177.1210; 177.2800; 178.3120; 178.3800; and 178.3870).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate both contain rosin. Rosin is regulated for use as a diluent in color additive ink mixtures for marking gum, confectionery, fruits, vegetables, and tablet forms of food supplements. Rosin (as colophony, a.k.a. Portuguese gum rosin) is listed for use as a flavoring agent in alcoholic beverages. Derivatized and some of the modified rosins are regulated as softeners for chewing gum

TABLE 7
Glyceryl Monoesters used in Japan (Rempe and Santucci 1997)

INCI name	Japanese name	Category with precedent for use*	Category with no precedent for use*
Glyceryl Laurate	Glyceryl Monoaurate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Behenate	Glyceryl Behenate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Cocoate	Glyceryl Cocoate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Erucate	Glyceryl Monoerucate	All	—
Glyceryl Hydroxystearate	Glyceryl Hydroxystearate (1)	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
	Glyceryl Hydroxystearate (2)	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
	Glyceryl Monohydroxystearate	All	—
Glyceryl Isostearate	Glyceryl Isostearate (1)	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Isostearate/Myristate	Glyceryl Monoisostearate Monomyristate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Lanolate	Glyceryl Monolanolate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Linoleate	Glyceryl Linoleate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Myristate	Glyceryl Monomyristate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Sesquioleate	Glyceryl Sesquioleate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Stearate/Acetate	Glyceryl Monostearate Monoacetate	1, 2, 3, 4, 5, 6, 7, 11	8, 9, 10
Glyceryl Stearate/Maleate	Glyceryl Stearate Maleate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11

*See text for explanation of categories.

base. Wood rosin and certain derivatized modified forms of rosin are listed for use as coatings on fresh citrus fruits. Indirect uses of derivatized rosin as components of paper and paperboard in contact with dry food are permitted (FDA 1988).

BIOLOGICAL PROPERTIES

Absorption and Metabolism

The metabolic fate of monoglycerides (glyceryl monoesters) is summarized below. Because monoglycerides are products of triglyceride and diglyceride metabolism, these compounds are also mentioned.

Triglyceride digestion begins in the intestinal tract. Initially, the triglyceride is hydrolyzed to α,β -diglyceride, which is then hydrolyzed to β -monoglyceride. These hydrolytic reactions occur at an oil-water interface. Approximately 28% of the β -monoglyceride is isomerized to α -monoglyceride, and approximately 75% of the α -monoglyceride is further hydrolyzed to free glycerol. Free glycerol enters the intestinal wall independent of the lipids, and it has no further use in terms of lipid absorption. The free fatty acids and glycerol are available for the resynthesis of triglycerides. β -Monoglycerides are not hydrolyzed because of their transfer to a water-soluble phase and, also, because of enzyme specificity. However, they can be acylated directly to triglyceride (Mattson and Volpenhein 1964).

Skin Penetration Enhancement

Glyceryl Laurate

The effect of Glyceryl Laurate or Dilaurate on the penetration of naloxone-HCl across cadaver skin was evaluated using Franz diffusion cells. Naloxone is a potent opioid antagonist used for

the reversal of narcosis. Naloxone concentrations in the reservoir were determined by HPLC using UV detection. Glyceryl Laurate was evaluated at a concentration of 10% in propylene glycol. The average flux through human cadaver skin (10 experiments) for naloxone alone was $1.6 \pm 0.4 \mu\text{g}/\text{cm}^2\cdot\text{h}$. In the presence of Glyceryl Dilaurate (10% in propylene glycol), average Naloxone flux increased to $18.7 \pm 1.8 \mu\text{g}/\text{cm}^2\cdot\text{h}$ (3 experiments), and increased even greater in the presence of Glyceryl Laurate ($23.4 \pm 3.6 \mu\text{g}/\text{cm}^2\cdot\text{h}$; 3 experiments). In the presence of urea (10% in propylene glycol), the average Naloxone flux was $0.4 \pm 0.1 \mu\text{g}/\text{cm}^2\cdot\text{h}$ (3 experiments) (Aungst, Rogers, and Shefter 1986).

In another study, the effect of Glyceryl Laurate on penetration of the water-soluble drug, papaverine HCl through hairless rat skin (from abdominal area) was demonstrated using diffusion cells. The mean flux of papaverine HCl was $23.7 \pm 5.2 \mu\text{g}/\text{cm}^2/\text{h}$ (three to five experiments) in the presence of 10% Glyceryl Laurate. This value was compared with the mean value for papaverine HCl flux in the presence of the water control ($1.1 \pm 0.2 \mu\text{g}/\text{cm}^2/\text{h}$) (Okumura et al. 1990).

Platelet Aggregation

Glyceryl Arachidonate

Phosphatidylcholine liposomes containing 1-Arachidonyl-Monoglyceride caused aggregation of human platelets in vitro (Gerrard and Graff 1980).

Enzyme Activity

Glyceryl Laurate

The effect of Glyceryl Laurate and various fatty acids and derivatives on 5α -reductase activity in vitro was evaluated

because of the established link between cancer of the prostate gland and high dietary fat intake. Prostate gland tissue specimens (human) were used. 5α -Reductase catalyzes the reduction of testosterone to dihydrotestosterone, which controls cellular division in the prostate gland. It has been suggested that the modulation/inhibition of this enzyme could prevent carcinogenesis in the prostate gland. Results indicated that the inhibitory effect of lauric acid on 5α -reductase activity was decreased by esterification to Glyceryl Laurate and was totally lost by esterification to Glyceryl Dilaurate and Trilaurin (Niederpruem et al. 1995).

Signal Transduction

This section is included because glyceryl diesters may be present in glyceryl monoester ingredients. Although most glyceryl diesters that are found would be expected to be 1,3-glyceryl diesters, some may be 1,2-diester, which can have signal transduction effects.

Lee and Severson (1994), in a review signal transduction in smooth muscle, state that the generation of intracellular second messengers is a common mechanism of signal transduction for external stimuli such as hormones, neurotransmitters, growth factors, and drugs (agonists) that interact with plasma membrane receptors. They go on to say that the established role of phospholipid turnover in signal transduction mechanisms is based on the observations that agonist-induced hydrolysis of a minor phospholipid in the plasma membrane, phosphatidylinositol 4,5-bisphosphate (PIP_2), in a reaction catalyzed by a phosphoinositide-specific phospholipase C (PI-PLC) enzyme generated the following two intracellular second messengers: (1) inositol 1,4,5-triphosphate (IP_3), responsible for the mobilization of Ca^{2+} from intracellular stores, and (2) diacylglycerol, responsible for the activation of protein kinase C (PKC). Lévy et al. (1994) reported that PKC consists of a family of 10 isozymes that phosphorylate serine and threonine residues. Classical PKC isozymes (α , β_1 , β_{II} , γ) are dependent on Ca^{2+} and phospholipids and are activated by diacylglycerol. These isozymes transduce mitotic signals induced by growth factors.

Sánchez-Piñera et al. (1999) studied the lipid activation of PKC α by comparing the activation capacity of different 1,2-diacylglycerols and 1,3-diacylglycerols incorporated into mixed micelles or vesicles. PKC α , as well as other isoenzymes in this family, are activated by Ca^{2+} , phosphatidylserine, and diacylglycerols. Diacylglycerols are considered to be hydrophobic anchors that may recruit PKC to the membrane, leading to an increase in the enzyme's membrane affinity and to the activation of PKC.

Unsaturated 1,2-diacylglycerols were more potent activators of protein kinase C α than saturated 1,2-diacylglycerols when 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoserine (POPS)/Triton X-100 mixed micelles and pure POPS vesicles were used. These differences were not observed when 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)/POPS (4:1 molar ratio) vesicles were used. Additionally, 1,2-diacylglycerols had a consid-

erably greater activating capacity than 1,3-diacylglycerols in POPS Triton X-100 mixed micelles and in POPC/POPS vesicles. However, the difference between 1,2- and 1,3-diacylglycerols was smaller when pure POPS vesicles were used. That is, both were able to activate PKC α practically to the same extent. Nevertheless, saturated diacylglycerols induced significant activation of PKC α in Triton X-100 micelles and in pure POPS vesicles in this study (Sánchez-Piñera et al. 1999).

Unlike the preceding study, a very low capacity for 1,3-diacylglycerol-induced activation was demonstrated in an earlier study (Nomura et al. 1986). In the Nomura et al. (1986) study, however, sonicated phosphatidylserine vesicles were used, whereas unsonicated preparations of multilamellar vesicles were used in the Sánchez-Piñera et al. (1999) study.

Cell Growth and Proliferation

This section is included because glyceryl diesters may be present in glyceryl monoester ingredients. Although most glyceryl diesters that are found would be expected to be 1,3-glyceryl diesters, some may be 1,2-diester, which can have cell growth and proliferation effects.

Huckle and Earp (1994) report that activation of the type 1 angiotensin II receptor rapidly increases intracellular levels of inositol phosphates, notably inositol 1,4,5-triphosphate (IP_3), and 1,2-diacylglycerol (DAG) in adrenal cortical cells, hepatocytes, and vascular smooth muscle. The type 1 angiotensin II receptor is responsible for all known physiologic actions of angiotensin II. Angiotensin II, an octapeptide, is well known as an acute regulator of vasomotor tone and fluid homeostasis. It exhibits many characteristics of the 'classical' peptide growth factors such as epidermal growth factor/transforming growth factor alpha (EGF/TGF α), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF)-1. Characteristics of these growth factors include the regulation of growth in a self-contained autocrine/paracrine fashion, and the ability to stimulate tyrosine phosphorylation, to activate MAPKs (mitogen-activated protein kinases), and to increase expression of nuclear proto-oncogenes. Angiotensin II has trophic or mitogenic (increases rate of cell division) effects on a variety of target tissues, including adrenal cells and vascular smooth muscle cells.

In vascular smooth muscle, hydrolysis via the lipase pathway is the predominant metabolic fate of diacylglycerol. The activation of PKC in vascular smooth muscle modulates agonist-stimulated phospholipid turnover, produces an increase in contractile force, and regulates cell growth and proliferation (Lee and Severson 1994).

Blobe, Obeid, and Hannun (1994) reviewed various studies indicating that the sustained activation or inhibition of PKC (diacylglycerol-activated isoenzyme) activity in vivo may play a critical role in the regulation of long term cellular events such as proliferation, differentiation, and tumorigenesis. Many of the signals transduced by PKC are mitogenic signals that have been sent by growth factors (e.g., platelet-derived growth factor [PDGF] and epidermal growth factor [EGF]). For

example, PGDF binds to its high-affinity receptor (PDGFR) and activates this receptor's intrinsic tyrosine kinase activity to mediate the initiation of DNA synthesis and other cellular effects. It is important to note that PKC has been linked directly to the pathogenesis of human skin, colon, and breast cancers. In the epithelium, long-term changes in PKC activity, either through the action of phorbol esters or by specific changes in PKC isoenzyme levels, either leads to growth of melanocytes, the differentiation of keratinocytes, or to transformation. In colon cancer, PKC acts as a tumor suppressor. Thus, decreasing the levels of PKC activity can result in transformation. In breast cancer, an increase in PKC activity appears to correlate with enhanced oncogenicity.

Evidence of increased PKC activity in hyperplastic pituitary cells has also been reported. Furthermore, the increase in diacylglycerol content paralleled the increase in PKC activity (Lévy et al. 1994).

Antimicrobial Activity

Glyceryl Laurate

Lauricidin (registered trademark for Glyceryl Laurate) has been described as having a wide spectrum of antimicrobial activity against diverse microbial species (viruses, fungi, molds, yeasts, and bacteria included). However, it is generally inactive against gram-negative bacteria. When Lauricidin was tested in cell culture using 16 human RNA- and DNA-enveloped viruses, all viruses were reduced in infectivity by 99.9% at relatively low concentrations (1.0%) of Lauricidin. Antifungal activity (inhibition of mycelial growth) of Glyceryl Laurate has been demonstrated in 12 strains at a concentration of 0.5%, and in three additional strains at a concentration of 0.05% (Kabara 1984).

Glyceryl Laurate inhibited the production of staphylococcal toxic shock toxin-1, the toxin responsible for toxic shock syndrome, at assay concentrations of 20, 100, and 300 $\mu\text{g/ml}$ (Schlievert et al. 1992) and 17 mg/L (Holland, Taylor, and Farrell 1994). Projan et al. (1994) reported that Glyceryl Laurate inhibited the synthesis of most staphylococcal toxins at the level of transcription. It blocked the induction but not the constitutive synthesis of β -lactamase, suggesting that transmembrane signal transduction was the target of Glyceryl Laurate action.

Other studies on the bactericidal activity of Glyceryl Laurate include inhibition of bacterial spores and vegetative cells (Chaibi, Ababouch, and Busta 1996a, 1996b); inhibition of *Listeria monocytogenes* (Oh and Marshall 1996); and susceptibility of *Helicobacter pylori* (Petschow, Batema, and Ford 1996).

ANIMAL TOXICOLOGY

General

The safety of mono- and diglycerides in food has been reviewed by the Food Protection Committee of the National Academy of Sciences National Research Council Food and Nutrition Board (National Academy of Sciences 1960). The Food

Protection Committee concluded that there appears to be no reason to question the safety of mono-, di-, or triglycerides of lauric acid (i.e., Glyceryl Laurate, Glyceryl Dilaurylate, or Glyceryl Trilaurylate [Trilauryl]) as food additives. This conclusion was based on the following: (1) Lauric acid glycerides are used in important foods, such as human and cow's milk, at concentrations of 3% to 6% and large quantities are present in coconut oil. The use of these foods has not been accompanied by recognized toxic effects. (2) Lauric acid glycerides undergo the usual metabolic changes of the higher fatty acids. (3) When lauric acid glycerides are fed in diets containing a variety of glycerides, there is not evidence of a specific toxic or harmful effect.

Acute Inhalation Toxicity

Glyceryl Laurate

A low-grade irritant response was noted following inhalation of an aerosol containing 10% Glyceryl Laurate. The strain of animals tested and details concerning the test protocol and study results were not included (Unichema International 1997b).

Acute Oral Toxicity

Glyceryl Laurate

The acute oral toxicity of Glyceryl Laurate was evaluated using 31 male rats (strain not stated; weights = 150 to 220 g). The test substance was administered by stomach tube after 18 h of fasting. An LD_{50} of 53.4 ml/kg was reported (Eagle and Poling 1955).

Glyceryl Laurate (in olive oil) was administered orally to young Wistar rats (weights not stated). Doses of 10,000 and 20,000 mg/kg were administered to five male and five female rats, respectively. The LD_{50} was >20,000 mg/kg. (Henkel KgaA 1994).

Glyceryl Isostearate

A single oral dose (2 g/kg body weight) of Glyceryl Isostearate did not result in any harmful effects in rats. Details concerning the test protocol were not provided (Unichema International 1997a).

Glyceryl Rosinate

The acute oral toxicity of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using fasted Wistar albino rats (five males, five females; weight range 220 to 292 g). A single oral dose of the test substance (5 g/kg) was administered to each animal. Dosing was followed by a 14-day observation period, and gross necropsy (results not included) was performed on all animals. None of the animals died, and it was concluded that the test substance was not toxic (LD_{50} > 5 g/kg) (Consumer Product Testing Company 1990a).

Glyceryl Citrate/Lactate/Linoleate/Oleate

Hüls AG (1996a) provided unpublished data on the acute oral toxicity of Glyceryl Citrate/Lactate/Linoleate/Oleate using five male and five female Wistar rats. The undiluted test substance (highly viscous) was liquefied by heating in a water bath and then administered to each animal using a rigid gastric pharyngeal probe. Each rat received a single oral dose of 2000 mg/kg (dose volume = 2.004 ml/kg body weight). The animals were observed over a period of 14 days after dosing. None of the animals died. Body weight gain was described as normal, and no signs of toxicity were noted. Grossly detectable organ changes were not noted at necropsy. The LD₅₀ was >2000 mg/kg in male and female rats.

Acute Dermal Toxicity*Glyceryl Citrate/Lactate/Linoleate/Oleate*

The acute dermal toxicity of Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated using five male and five female Wistar rats. The undiluted test substance (highly viscous) was liquefied by heating in a water bath and then applied dermally (dose = 2000 mg/kg; dose volume = 2.004 ml/kg) to each animal using a gauze patch. Each patch was secured with a semiocclusive dressing for 24 h. None of the animals died, and gross lesions were not observed. Particularly, no gross changes were observed in the subcutaneous tissue in the area of application. The acute dermal LD₅₀ was >2000 mg/kg in male and female rats (Hüls AG 1996b).

Short-Term Inhalation Toxicity*Glyceryl Laurate*

The short-term inhalation toxicity of Glyceryl Laurate was evaluated using rats. The animals were given a total of 14 1-hour exposures during a 3-week period. Although details concerning the test protocol and study results were not included, a no-effect level of 280 mg/m³ was reported (Unichema International 1997b).

Short-Term Oral Toxicity*Glyceryl Laurate*

The short-term oral toxicity of Glyceryl Laurate was evaluated using 10 weanling rats. The test substance was administered orally at a concentration of 25% in the diet for a period of 10 weeks. No gross or microscopic lesions were found that were attributable to administration of the test diet (Procter & Gamble Company 1950).

Chronic Oral Toxicity*Glyceryl Laurate*

Fitzhugh, Schouboe, and Nelson (1960) fed two groups of 24 albino rats of the Osborne-Mendel strain a mixture consisting of Trilaurin (8%), Glyceryl Dilaurate (45%), and Glyceryl Laurate (40% to 45%) at a concentration of 25% in the diet for 2 years.

The individual glyceryl esters were fed at effective dietary concentrations of ~2% (Trilaurin), ~11% (Glyceryl Dilaurate), and ~10% to 11% (Glyceryl Laurate). Of the two control groups, one was fed 25% hydrogenated cottonseed oil in the diet (concurrent control), and, the other, basal diet only.

After 26 or 52 weeks of dosing, no significant differences in weight gain between the test and concurrent control groups were noted. No significant differences in the total number of deaths were noted when the test group was compared with both control groups. At necropsy, no gross lesions were observed in test animals. At microscopic examination, a slight increase in hepatic cell fatty change was observed in test animals, compared to the control group fed the basal diet. However, this finding in test animals was no greater than that observed in the control group fed hydrogenated cottonseed oil. The same difference occurred to a lesser and questionably significant degree when the incidence of intrahepatic bile duct proliferation in test animals was compared to that noted in controls (Fitzhugh, Schouboe, and Nelson 1960).

Ocular Irritation*Glyceryl Laurate*

The ocular irritation potential of undiluted Glyceryl Laurate was evaluated in the Draize test using three albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of one eye of each animal. Untreated eyes served as controls. Ocular reactions were scored every 24 h up to day 7 post instillation. Mean scores (average of 24-, 48-, and 72-h readings) for corneal reactions and erythema of the conjunctiva were 0.17 (maximum score, corneal lesions = 80) and 1.33 (maximum score, conjunctival lesions = 20), respectively. Reactions were not observed in the iris (Henkel KgaA 1994).

Kabara (1984) evaluated the ocular irritation potential of a 20% Glyceryl Laurate emulsion using six albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of the right eye of each animal. Untreated left eyes served as controls. Ocular reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale: 0 to 110.

According to the test protocol, reactions would be classified as positive if the test substance induced any of the following: ulceration of the cornea (other than a slight dulling of the normal luster), inflammation of the iris (other than a slight circumcorneal injection of the blood vessels), or if the substance produced in the conjunctivae an obvious swelling with partial eversion of the lids or a diffuse crimson-red with individual vessels not easily discernible. Study results were positive only if four or more animals had positive reactions.

An average irritation score (six animals) of 0 was reported for both corneal opacity and inflammation of the iris. The average irritation score for conjunctival irritation was 3.7. Because only one rabbit had a positive reaction, the 20% Glyceryl Laurate emulsion was classified as a "negative ocular irritant" (Kabara 1984).

Glyceryl Isostearate

Although details concerning the test protocol were not provided, Unichema International (1997a) concluded that Glyceryl Isostearate was not an ocular irritant in rabbits. Reactions classified as minor ocular irritation had cleared by 48 h post instillation, reactions were not observed in the cornea or iris.

In a study by the Institut Français de Recherches et Essais Biologiques (1977), the ocular irritation potential of Glyceryl Isostearate was evaluated using six male New Zealand white rabbits. The test substance (undiluted, 0.1 ml) was instilled into the left conjunctival sac of each animal. Untreated right eyes served as controls. After instillation, the eyelids were held together for several seconds to avoid loss of the test substance. The animals were restrained for a period of 18 h. Ocular reactions were scored at 1, 2, 3, 4, and 7 days post instillation (maximum score = 20). Glyceryl Isostearate was classified as a nonirritant.

The Centre de Recherche et d'Élevage des Oncins (1975) evaluated a mixture consisting of Glyceryl Isostearate in an ocular irritation test. Other components of the mixture included glyceryl stearate, propylene glycol isostearate, propylene glycol stearate, ceteth-25, and oleth-25, but the concentration of each component was not provided. The mixture, 20% in sterile water, was instilled (0.1 ml) into the conjunctival sac of the left eye of each of six New Zealand rabbits. Contralateral eyes served as controls. Reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale. Mean Draize ocular irritation scores were 3.0 (at 24 h), 2.67 (at 48 h), and 1.67 (at 72 h). Total Draize scores (Scale: 0 to 110) were 18, 16, and 10 at 24 h, 48 h, and 72 h, respectively. The mixture was classified as a nonirritant based on the mean ocular irritation scores that were recorded.

Glyceryl Rosinate

The ocular irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using six New Zealand white rabbits. The test substance was instilled (0.1 ml) into the conjunctival sac of one eye of each animal. Untreated eyes served as controls. Eyes were not rinsed for up to 24 h post instillation. Ocular reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale (maximum total score = 110). Reactions were also scored at days 4 and 7 if irritation reactions persisted. Average Draize scores of 1.3 and 0.3 were reported at 24 and 48 h post instillation, respectively. At 72 h, an average score of 0 was reported. The test substance was not an ocular irritant (Consumer Product Testing Company 1990b).

Glyceryl Citrate/Lactate/Linoleate/Oleate

The ocular irritation potential of Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated using three female rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of one eye of each animal. At 24 h post instillation, the eyes were flushed with warm physiological saline solution. The conjunctivae, iris, and cornea were examined for any signs of ocular

irritation at 24, 48, and 72 h post instillation. Ocular irritation was not observed in either of the three rabbits tested (Hüls AG 1996c).

Skin Irritation*Glyceryl Laurate*

Kabara (1984) evaluated the skin irritation potential of a 20% Glyceryl Laurate emulsion using six albino rabbits. The test substance, 0.5 ml, was applied to both an abraded and intact skin site (clipped free of hair) on each animal, and each site was then covered with an occlusive patch. Patches were secured with adhesive tape, and the entire trunk of each animal was wrapped with an impervious material. The animals were immobilized during the 24-h contact period.

At 24 h and 72 h after patch removal, reactions at abraded and intact sites were scored according to the following scales: 0 (no erythema) to 4 (severe erythema to slight eschar formations); and 0 (no edema) to 4 (severe edema).

The primary irritation score for the group of six rabbits was 3.9, classifying the Glyceryl Laurate emulsion as a moderate skin irritant (Kabara 1984).

Henkel KgaA (1994) reported the results of a study to evaluate the skin irritation potential of undiluted Glyceryl Laurate using six rabbits. The test substance was applied (0.5 g under an occlusive patch) to dorsal skin of each animal. The test sites of three rabbits were shaved and those of the remaining three were scarified. Reactions were scored after 24 h and 72 h. Glyceryl Laurate induced minor erythema (mean score = 0.8) and edema (mean score = 0.9) in animals with intact skin. The scores for the three rabbits with scarified skin were not included.

Although details concerning the test protocol and study results were not included Unichema International (1997b) reported that Glyceryl Laurate was less irritating to the skin of rabbits, on an active for active basis, than sodium lauryl sulfate (SLS). Solutions of Glyceryl Laurate were equivalent in irritancy to SLS concentrations of approximately one fifth the strength.

Glyceryl Isostearate

Biogir S.A. Conseil Recherche (1989) conducted a study in which the skin irritation potential of Glyceryl Isostearate was evaluated using three New Zealand albino rabbits. The test substance (0.5 ml on hydrophilic gauze) was applied to skin, clipped free of hair, on the right side of each animal. Patches were secured with hypoallergenic microporous adhesive tape and then covered with elastic material that surrounded the animal's torso. After 4 h of contact, all patches were removed. A gauze square moistened with 0.5 ml of distilled water was applied to a control site on the left side of each animal according to the same procedure.

At 1, 24, 48, and 72 h post removal of the semioclusive bandage, reactions were scored according to the following scales: 0 (no erythema) to 4 (severe erythema, with or without formation of scars and presence of a lesion representing a significant reaction such as a burn or necrosis); 0 (no edema) to 4 (severe

edema). Because slight irritation persisted beyond 72 h post removal, the animals were observed until all lesions had regressed completely.

Mild erythema was observed in two rabbits at 1, 24, and 48 h post removal. A more severe reaction (moderate irritation) was observed in the third rabbit; the reaction did not clear until day 5. Very mild edema was noted in two rabbits at 1 h post removal, and persisted to 48 h post removal in one rabbit. Slowly reversible, slight changes in the structure of the skin were also observed. It was concluded that Glyceryl Isostearate was not a skin irritant in albino rabbits (Biogir S.A. Conseil Recherche 1989).

The Institut Français de Recherches et Essais Biologiques (1977) evaluated the skin irritation potential of Glyceryl Isostearate using six male New Zealand albino white rabbits. A sterile absorbent gauze pad containing the test substance (0.5 ml) was applied to a scarified site on the right flank and an intact site on the left flank of each animal. Both sites had been clipped free of hair. Each gauze pad was secured with a non-allergenic, adhesive occlusive patch.

The patches remained in place for 23 h; reactions were scored at 24 and 72 h post application according to the following scales: 0 (no erythema) to 4 (severe erythema, crimson red, with slight eschar formation [injuries in depth]) and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond area of application). The primary irritation index (PII) was calculated after all scores had been recorded. Glyceryl Isostearate was classified as a nonirritant (PII = 0.21) (Institut Français de Recherches et Essais Biologiques [IFREB] 1977).

The Centre de Recherche et d'Élevage des Oncins (1975) evaluated a mixture consisting of Glyceryl Isostearate and glyceryl stearate, propylene glycol isostearate, propylene glycol stearate, ceteth-25, and oleth-25 in a skin irritation test using rabbits. The concentrations of each component were not stated. The mixture (0.5 ml, 20% in sterile water) was applied to an intact site and an abraded site (each 2 cm² and clipped free of hair) on each of six male New Zealand rabbits. A nonallergenic, adhesive patch was placed over each test site, and the trunk of each animal was wrapped with an adhesive plaster. Patches were removed at 24 h post application and reactions scored (at 24 h and 72 h) according to the scales indicated in the preceding paragraph. The mixture was classified as a slight irritant (PII = 0.92).

Glyceryl Rosinate

The skin irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using six New Zealand white rabbits. The test substance (0.5 ml) was applied to abraded and intact skin (two sites per animal), and sites were covered with occlusive patches for 24 h. The patches were secured with hypoallergenic cloth tape and the entire trunk of each animal was encased in an impermeable plastic, occlusive wrapping. Reactions were scored at 24 and 72 h post application according to the following scales: 0 (very slight erythema, barely

perceptible) to 4 (severe erythema [beet redness] to slight eschar formation [injuries in depth]) and 1 (very slight edema, barely perceptible) to 4 (severe edema, area raised approximately 1 mm and extending beyond area of exposure). The mean scores at 24 and 72 h were averaged and a PII calculated. A PII of 3.40 (potential for severe irritation—warning label may be considered) was reported (Consumer Product Testing Company 1990c).

Glyceryl Citrate/Lactate/Linoleate/Oleate

In an acute dermal toxicity study summarized earlier in the report text, undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate (heated) was applied to the skin of Wistar rats (five males, five females). The test substance (dose = 2000 mg/kg; dose volume = 2.004 ml/kg) was applied to each animal using a gauze patch, and each patch was secured with a semiocclusive dressing for 24 h. Neither erythema nor edema was observed in any of the animals tested (Hüls AG 1996b).

Hüls AG (1996d) reported another study of the skin irritation potential of undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate using three rabbits (strain not stated). The test substance was applied to shaved, intact skin for 4 h. At 24 h post application, clearly circumscribed erythema and very mild to clear edema were observed. Barely perceptible to clearly circumscribed erythema and very mild edema were observed at 48 and 72 h post application. After day 6 post application, erythema and swelling were barely detectable. In one animal, a brown stain was noted at the application site; the skin surface was described as dry and squamous. Very slight erythema, dryness, and scaling were noted in all animals on day 8. These reactions were accompanied by slight swelling in one of the three animals. All reactions classified as erythema or edema had cleared by day 10 post application. Scaling was observed in one animal (day 10), but had cleared by day 14. The average score for erythema and scabbing (24, 48, and 72 h readings included) was 1.67. The average score for edema formation (24-, 48-, and 72-h readings included) was 1.11.

Comedogenicity

The comedogenicity of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using three male New Zealand white rabbits (3 months old). The test substance (0.1 ml) was applied to the internal base of the right ear of each rabbit 5 days per week for 3 weeks (15 applications per rabbit). Untreated left ears (internal base) served as controls. Test sites were evaluated for comedone formation and enlarged pores daily. Terminal biopsies of treated and control ears were performed. All specimens were graded for the extent of acanthosis, keratosis, and keratin ("plugging") according to the following scale: 0 (no different from untreated/treated control) to 3 (approximately 75% greater than untreated/treated control). At gross examination, erythema at the application site was noted in all three rabbits. At microscopic examination, all tissues were within normal histological limits. Follicular hyperkeratosis

(comedone formation) was not observed (Consumer Product Testing Company 1990d).

Skin Sensitization

Glyceryl Laurate

The Cosmetic, Toiletry, and Fragrance Association (CTFA) provided the results of a 1975 study of the skin sensitization potential of Glyceryl Laurate in a maximization test using guinea pigs.

Prior to study initiation, a preliminary irritation test (intradermal injection and topical application procedures) was performed using two groups of four males, respectively. In the intradermal injection test, the four animals were injected intradermally with Glyceryl Laurate (0.05% to 1% in 6% absolute alcohol/saline). Reactions described as faint, pink erythema predominated. In the topical application test, the other four males were tested with concentrations ranging from 5% to 25% in absolute alcohol. Scaling was observed in one guinea pig tested with 25% Glyceryl Laurate.

Ten guinea pigs (six males, four females) were tested in the maximization test. The animals were subjected to four sensitizing injections of 2% Glyceryl Laurate and then challenged with intradermal injections of 0.8% Glyceryl Laurate and topical applications of 25% Glyceryl Laurate. Four male guinea pigs served as controls. The grading scale for intradermal challenge reactions ranged from faint, pink erythema to deep, pink erythema. Topical challenge reactions were scored according to the following scale: $\pm$ (barely perceptible erythema) to ++++ (erythema-breakdown of surface-necrosis). Positive reactions were not observed in either of the ten animals tested. Glyceryl Laurate was classified as a nonsensitizer (CTFA 1975).

Kabara (1984) studied the skin sensitization potential of a 20% Glyceryl Laurate emulsion in a guinea pig maximization test. To induce sensitization, 10 animals were treated by intradermal injection in the shoulder region. At 7 days post injection, sensitization was boosted by placement of an occlusive patch over the injection site; an occlusive challenge patch was applied to the flank at 14 days post injection. Four additional guinea pigs were treated in a manner similar to that of the test group, except that the test substance was applied only during the challenge phase. Positive challenge reactions were observed in two test animals challenged with a 10% dilution of the test substance. No visible reactions were present in control animals challenged with a 10% dilution of the test substance or either test or control animals challenged with a 5% dilution.

A second challenge was initiated 7 days after the first. Positive reactions were observed in five test animals and two control animals challenged with a 10% dilution of the test substance. Positive reactions were also observed in four test animals challenged with a 5% dilution of the test substance; no reactions were present in the control group. It was concluded that because positive reactions were observed in test and control groups (after first and second challenge), it is likely that irritation, and not

sensitization, was responsible for these observations (Kabara 1984).

Glyceryl Isostearate

CTFA reported the results of a 1985 study of the skin sensitization potential of Glyceryl Isostearate using a guinea pig maximization test procedure. Eighteen guinea pigs (10 test, 4 treated controls, and 4 untreated controls; strain not stated) were used. During induction, the animals were injected intradermally (0.1-ml injections) in the shoulder region with 2.5% Glyceryl Isostearate in a vehicle consisting of polyethylene glycol (PEG), microcrystalline cellulose (MCC), and Dobs/saline (dodecyl benzene sulfonate in physiological saline).

At 5 to 7 days after the last injection, an occlusive induction patch saturated with 100% Glyceryl Isostearate was maintained in contact with the injection site for 48 h. Intradermal injection reactions were scored according to the following scale: fp (faint pink erythema) to dp (deep pink erythema). The challenge phase was initiated 12 to 14 days after application of the induction patch. An occlusive challenge patch containing 50% Glyceryl Isostearate (in PEG and MCC) was applied to the skin for 24 h. Further challenges were made at weekly intervals, or longer, as required. Challenge reactions were scored according to the following scale at 24 and 48 h: 0 (no reaction) to 3 (marked erythema).

The four treated controls consisted of four guinea pigs that were tested according to the preceding study protocol, with the exception that Glyceryl Isostearate was omitted only from the intradermal and covered patch induction procedures. The untreated control group consisted of four previously untreated animals that were challenged with Glyceryl Isostearate according to the procedure described earlier.

The results of the first challenge yielded one positive reaction at 24 h and two positive reactions at 48 h. Following the second challenge, positive reactions were not noted at 24 or 48 h. The slight sensitization reactions noted following the first challenge were confirmed by results of the third challenge (CTFA 1985).

Glyceryl Citrate/Lactate/Linoleate/Oleate

Hüls AG (1996e) reported results of the skin sensitization potential of Glyceryl Citrate/Lactate/ Linoleate/Oleate using 20 guinea pigs. Ten guinea pigs served as controls. Any reactions, particularly those classified as erythema and edema, were assessed 30 and 54 h after the initiation of treatment. Undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate was tested during induction phases I, II, and III (dermal application) because the undiluted material did not induce skin irritation in a preliminary test.

During the fourth week of testing, a "trigger concentration" was determined for initiation treatment on three guinea pigs that were the same ages as those in the main test. The undiluted test substance was administered (dermal application) as the highest, nonirritating concentration.

Glyceryl Citrate/Lactate/Linoleate/Oleate did not induce systemic effects or any adverse effects on body weight gain. At 30 h post application in induction phases I, II, and III, skin irritation was not observed in the 20 test animals or 10 vehicle-control animals. "Trigger" treatment with the undiluted test substance did not induce erythema or edema of the right rear flank at 30 or 54 h post application in test or control animals. Also, in patch tests, the vehicle did not cause skin reactions in animals of the test or control group. It was concluded that Glyceryl Citrate/Lactate/Linoleate/Oleate did not induce sensitization in guinea pigs (Hüls AG 1996e).

Glyceryl Rosinate

Shao et al. (1993) conducted a study to investigate whether the esterification of rosin with glycerol or other polyalcohols would alter the allergenicity of rosin. The allergenicity of Glyceryl Rosinate was evaluated using three groups of 15 female Dunkin-Hartley guinea pigs.

During induction, the first group (group I) received four closed epidermal applications of 8.3% glyceryl triabietate (GTA) in petrolatum (abietic acid, esterified to yield this compound, is the main component of rosin) on days 0, 2, 7, and 9 and two injections of Freund's complete adjuvant (FCA) on day 7. In the second group (group II), the induction procedure (same protocol) consisted of four closed epidermal applications of 20% gum rosin and two injections of FCA. The control group was sham treated.

All three groups were challenged with the following: 0.93%, 2.8%, and 8.3% GTA; 10% glycerol esterified tall oil rosin (TORG), 20% gum rosin; and petrolatum vehicle control. Challenge patches (Finn chambers) were removed after 24 h, and reactions scored at 48 and 72 h post application. Study results (challenge phase, 72-h reading) are summarized below.

In group I, results indicated one positive reaction to 0.93% GTA; 2.8% GTA; 20% gum rosin; and petrolatum. The incidence of positive reactions in group II was as follows: 1 (8.3% GTA); 2 (10% TORG); 3 (0.93% and 2.8% GTA); and 9 (20% gum rosin). One positive reaction to 0.93% GTA and two positive reactions to 8.3% GTA were observed in the control group. Scores at 48 and 72 h were not significantly different from one another. It is important to note that in group II, the incidence of positive reactions to 10% TORG (two reactions) was less than that of 20% gum rosin (nine reactions). The esterification of rosin with glycerol, in effect, reduced the allergenicity of rosin. GTA was nonallergenic and did not cross-react with allergens in unmodified gum rosin (Shao et al. 1993).

This same laboratory evaluated the allergenicity of GTA and other esters of glycerol and abietic acid (Gäfvert et al. 1994). Products formed from the esterification of abietic acid (mentioned in the preceding study) with glycerol include: glyceryl triabietate (GTA); glyceryl 1,2-diabietate ($GDA_{1,2}$); glyceryl 1,3-diabietate ($GDA_{1,3}$); and glyceryl 1-monoabietate (GMA).

The allergenicity of these compounds was evaluated according to the procedure in the preceding study using female Dunkin-

Hartley guinea pigs. Group I (14 animals) and Group II (15 animals) animals were induced with 3.3% GMA in petrolatum and 20% gum rosin in petrolatum, respectively. Petrolatum was applied to animals of Group III (control). The animals were challenged with the following: GMA (0.37%, 1.1%, and 3.3%); 5.7% $GDA_{1,3}$; 5.7% $GDA_{1,2}$; 8.3% GTA, and 10% unmodified gum rosin. Challenge reactions at 72 h post application were reported. All statistically significant findings are accompanied by *p* values.

In group I, GMA induced sensitization at concentrations of 0.37% (1 of 14 animals), 1.1% (4 of 14, $p < .05$), and 3.3% (6 of 14, $p < .01$). The incidence of sensitization reactions to GMA in group II was as follows: 0.37% GMA (1 of 15 animals), 1.1% (3 of 15), and 3.3% (2 of 15). No significant responses were noted when $GDA_{1,3}$ and $GDA_{1,2}$ were tested on animals that were sensitive to GMA. Gum rosin induced sensitization in 8 of 15 animals ($p < .01$) in group II and in 1 of 14 animals in group I. No significant cross-reactivity with GMA was noted in animals that were sensitive to unmodified gum rosin. Neither GTA nor petrolatum induced sensitization in either of the three groups (Gäfvert et al. 1994).

Phototoxicity and Photoallergy

Glyceryl Isostearate

The phototoxicity and photoallergenicity potentials of Glyceryl Isostearate was evaluated using 20 albino guinea pigs. The back and sides of each animal were divided into the following six treatment areas: test material + UVA, test material + UVB, test material alone, positive control (8-methoxypsoralen) + UVA, UVB alone, and UVA alone. Doses of the test material and positive control (dose for each = 0.02 ml/cm²) were applied 30 min prior to irradiation. UV irradiations were performed using Philips tubes (TL 20W/09 for UVA and TL 20W/12 UV for UVB). Cutaneous reactions were evaluated at 24 h post treatment. Glyceryl Isostearate did not induce significant cutaneous reactions with or without UV irradiation. The positive control (8-methoxypsoralen) induced severe reactions (Unichema International 1997a).

Immunologic Activity

Glyceryl Laurate

The effect of Glyceryl Laurate on delayed-type hypersensitivity to sheep erythrocytes was evaluated using mice. The four groups (10 mice per group) of female ICR mice used in the study were designated as treated (T; two groups), control (C), and normal (N). The mice in groups T and C were injected subcutaneously (s.c.) with 0.05 ml/mouse of sheep red blood cells (SRBCs) (3×10^9 cells/ml). Injections were made into the right hind footpads. The mice in group T were then immediately injected intraperitoneally (i.p.) with a saline suspension of Glyceryl Laurate, and group C mice were injected with saline alone. On day 4, mice of groups T, C, and N were injected (s.c.) in the left hind footpads with SRBCs (0.05 ml/mouse). Left footpad

thickness was measured with a caliper 24 h later. The i.p. administration of Glyceryl Laurate did not cause significant enhancement of the immunological response. Mean footpad thickness was 4.20 ± 0.44 mm, compared to 4.23 ± 0.36 mm and 3.55 ± 0.23 mm for untreated mice and saline controls, respectively (Kabara et al. 1985).

The modulation of immune cell proliferation in vitro by Glyceryl Laurate was evaluated using lymphocytes obtained from murine spleens. Lymphocyte proliferation was stimulated at Glyceryl Laurate concentrations between 10^{-5} and $5 \mu\text{g/ml}$ per 5×10^5 lymphocytes. At concentrations greater than $5 \mu\text{g/ml}$, Glyceryl Laurate inhibited lymphocyte proliferation and blocked the proliferative effects of the lymphocyte mitogens, phorbol myristate acetate and concanavalin A, and the toxic shock syndrome toxin-1 (potent T-cell mitogen). Furthermore, the results of experiments using purified immune cell subsets indicated that Glyceryl Laurate ($0.1 \mu\text{g/ml}$) optimally induced T-cell proliferation, but did not affect B cells. Glyceryl Laurate-induced T-cell proliferation was blocked by cyclosporin A (immunosuppressive drug) at concentrations as low as 20 ng/ml , suggesting that Glyceryl Laurate could be exerting its effect along the calcium-dependent inositol phospholipid, signal transduction pathway (Witcher, Novick, and Schlievert 1996).

In Vitro Hemolytic Activity

Glyceryl Laurate

Kato et al. (1971) evaluated the hemolytic activity of Glyceryl Laurate using sheep erythrocytes. The erythrocytes were washed with 0.86% NaCl and suspended in NaCl solution. Glyceryl Laurate was dissolved or suspended in NaCl solution at several dilutions (starting with 1 mg/ml), and an equal volume of the red blood cell suspension in NaCl was added. Hemolytic activity, expressed by the highest dilution in which hemolysis was observed, was determined after incubation for 4 h at 37°C . The highest dilution in which hemolysis was observed was a seven-fold dilution of the starting concentration of Glyceryl Laurate. Glyceryl Laurate had strong hemolytic activity.

GENOTOXICITY

Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated for its potential to induce reverse mutations in the following *Salmonella typhimurium* strains: TA 98, TA 100, TA 1535, and TA 1537. The Ames test (plate incorporation and preincubation methods) was used in this evaluation. Five concentrations of Glyceryl Citrate/Lactate/Linoleate/Oleate (50 to $5000 \mu\text{g/plate}$) were tested in triplicate both with and without metabolic activation. Tetrahydrofuran served as the solvent control, and the three positive controls were as follows: 2-nitrofluorene, sodium azide, and 9-aminoacridine. Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic (all strains) in the plate incorporation test or the preincubation test either with or without metabolic activation (Hüls AG 1996f).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, which is composed of diterpene resin acids. In studies on the mutagenicity of resin acids, only neoabietic acid (component of rosin) was mutagenic in the Ames/*Salmonella* assay (FDA 1988).

CARCINOGENICITY

Glyceryl Stearate was tested for tumor promoting activity (Saffioti and Shubik 1963) on the clipped dorsal skin of 20 female Swiss mice. One week after a single application of 9,10-dimethylbenz(a)anthracene (DMBA) (1% to 1.5% in mineral oil), 5% Glyceryl Stearate (in acetone) was applied to skin twice weekly. No tumors developed; slight epidermal hyperplasia at the site of application was noted.

Tumor Inhibition

Glyceryl Laurate

Kabara et al. (1985) evaluated the in vitro antitumor activity of Glyceryl Laurate using two leukemia cell lines, L-5178Y and L-1210. Leukemia cells were cultured (1.0×10^5 cells/ml, 48 h at 37°C) with various concentrations of the test substance, suspended in physiological saline containing 5.0% DMSO. Untreated cultures served as controls. The growth inhibitory effect was determined as the ratio of cell numbers in treated and control cultures at the end of the incubation period. Based on this ratio, the IC_{50} was obtained by probit diagramming analysis. The IC_{50} values were 50 and 62 mg/ml in L-1210 and L-5178Y cell lines, respectively. Thus, marked antitumor activity was demonstrated against both cell lines.

On the basis of the above results, these authors evaluated Glyceryl Laurate in a survival test using 5-week-old, female BDF₁ mice implanted intraperitoneally with L-1210 leukemia cells (1.0×10^5 cells/mouse). A suspension of the test substance in saline was injected i.p. into each animal once daily for five consecutive days (first injection, 24 h after tumor transplantation). One group of mice received daily injections of 30 mg/kg, and the other, daily injections of 100 mg/kg. Control mice were injected with saline.

Study results indicated that Glyceryl Laurate was ineffective in prolonging the life span of tumor-bearing mice. Survival times for test mice were 9.83 days (30 mg/kg dose group) and 9.66 days (100 mg/kg dose group). The survival time for control mice was also 9.83 days. The investigators stated that the in vivo inactivity of Glyceryl Laurate could have been due to the inappropriateness of the experimental conditions adopted, and that further tests should be performed using different routes of administration, dosages, or vehicles (Kabara et al. 1985).

In two earlier studies (Kato et al. 1969, 1971), the in vivo antitumor activity of Glyceryl Laurate in 5-week-old ddY mice (weights = 18 to 22 g) was evaluated using Ehrlich ascites tumor cells. In one study, 2×10^6 tumor cells were implanted i.p. into each of eight mice. Glyceryl Laurate was then administered i.p. daily for 5 successive days at doses of 2.5 mg/mouse/day

(2 mice) and 10 mg/mouse/day (2 mice). The four control mice were injected with tumor cells only. After 7 days, tumor growth and body weight gain were noted. Tumor growth was not observed in mice given either of the two doses. Survival was 27 and 24 days for the two mice dosed with 2.5 mg/day and 28 and >30 days for the two mice dosed with 10 mg/day. Tumor growth in four control mice was marked and survival was 13 to 17 days. Glyceryl Laurate inhibited tumor growth completely and increased the survival time of mice injected with tumor cells (Kato et al. 1969).

In a study by Kato et al. (1971), approximately one million tumor cells were implanted i.p. into 12 test mice (two groups of six) and six controls, and a solution or suspension of Glyceryl Laurate in 0.86% NaCl solution was administered i.p. daily for 5 successive days. The two test groups received doses of 2.5 and 10 mg/mouse/day, respectively, and control mice were injected with 0.2 ml of NaCl solution. After 7 days, tumor growth and body weight gain were noted. Tumor growth was marked in control mice (survival time = 16 days). However, no tumor growth was observed in either group of test mice. Survival times for 2.5 mg/day and 10 mg/day test mice were 26 and >29 days, respectively.

In an additional experiment, these authors evaluated the in vitro action of Glyceryl Laurate on Ehrlich ascites tumor. The hypothesis was that Glyceryl Laurate might have a specific affinity for the tumor cells, and, if strong enough, attack the cells. In vitro attack of the cells was measured using the viability of treated tumor cells. In the assay for viability, the viability of treated tumor cells (mixture of Glyceryl Laurate in phosphate-buffered saline with the tumor cell suspension) was determined by staining the cells with safranin dye. Glyceryl Laurate was tested at concentrations of 5, 50, and 500 $\mu\text{g/ml}$. The percentage of dead cells in the mixture was determined by counting the number of cells microscopically. Cell death (100%) was noted at concentrations of 50 and 500 $\mu\text{g/ml}$ (Kato et al. 1971).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Studies on the reproductive and developmental toxicity of the Glyceryl Monoesters reviewed in this report were not found in the published literature. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are derived from rosin. As stated earlier, rosin is defined as the residue remaining when the volatile oil is distilled from turpentine or a product of the distillation, solvent extraction, or both, of the stumps or fallen trees of various species of *Pinus*. FDA (1988) reported that, following the administration of hexane extracts of *Pinus ponderosa* needles to mice by stomach tube, increased embryonic resorptions were observed. Recall that it is important to note that the following active components of the extracts tested, diterpene resin acids, were identified: pimaric acid, isopimaric acid, sandaracopimaric acid, palustic/levopimaric acid, abietic acid, dehydroabietic acid, and neoabietic acid. Abietic acid and dehydroabietic acid have been identified as main components of rosin.

CLINICAL ASSESSMENT OF SAFETY

Inhalation Toxicity

Glyceryl Caprylate/Caprate is used in hair sprays. Jensen and O'Brien (1993) reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition.

The determination of the health consequences of exposure to an aerosol requires an analysis of the inhalation and deposition of the aerosol within the human respiratory system. The toxic action of an aerosol may be related to the number of particles, their surface area, or the mass deposited. Many occupational diseases are associated with the deposition of particles within a certain region of the respiratory tract.

The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, d_a , defined as the diameter of a sphere of unit density possessing the same terminal settling velocity as the particle in question.

Many particles present in the air do not enter the respiratory tract because of the size-selective sampling of the nose and the mouth. Still others are removed in the upper respiratory tract. The concept of size-selective air sampling calls for measurement of particles in industrial aerosols of the size that are associated with a specific health effect. For chemical substances present in inhaled air as suspensions of solid particles or droplets, the potential hazard depends on the particle size as well as on mass concentration. The American Conference of Governmental Industrial Hygienists (ACGIH) has defined three particle-size-selective threshold limit values (PSS TLVs) (ACGIH 1991): inhalable particulate mass TLVs (IPM TLVs) for those materials that are hazardous when deposited anywhere in the respiratory tract; thoracic particulate mass TLVs (TPM TLVs) for those materials that are hazardous when deposited anywhere within the lung airways and the gas-exchange region; and respirable particulate mass TLVs (RPM TLVs) for those materials that are hazardous when deposited anywhere in the gas-exchange region (Jensen and O'Brien 1993).

The mean aerodynamic diameter of $4.25 \pm 1.5 \mu\text{m}$ of respirable particles above may be compared with diameters of anhydrous hair spray particles of 60 to 80 μm (typically, <1% are below 10 μm) and pump hair sprays with particle diameters of $\geq 80 \mu\text{m}$ (Bower 1999).

Skin Irritation

Glyceryl Rosinate

The skin irritation potential of a lipstick containing 1.0% Glyceryl Rosinate, as supplied, was evaluated using 12 volunteers (21 to 45 years old). All subjects were in good health and free of any visible skin disease or anomaly. The lipstick was crushed (to mix the inner and outer layers) and applied to an

occlusive patch. Patches (one per subject) covered with the lipstick were applied to the back and remained in place for 24 h. Reactions were scored 3 days later according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]). A new patch containing the test substance was reapplied to the same site on each subject and removed after 24 h. Reactions were scored after patch removal and 24 h later. The grading period was followed by a second new patch application (24 h), and reactions were scored at the same intervals. The lipstick containing 1.0% Glyceryl Rosinate did not elicit an irritation response (all scores = 0) in either of the 12 subjects tested (Biosearch, Inc. 1992a).

Skin Sensitization

General

Human studies have indicated that the incidence of contact sensitization is dose dependent and that the induction of skin sensitization is dependent on the dose of a chemical per unit area of skin (Kimber, Gerberick, and Basketter 1999).

Glyceryl Laurate and Glyceryl Linoleate

Danisco Ingredients (1996), reported a study in which the skin irritation and sensitization potential of Glyceryl Laurate and Glyceryl Linoleate was evaluated using 91 healthy volunteers (males and females, 18 to 65 years old) in a modified Draize repeat-insult patch test. The study was classified as single-blind. Patches consisted of a 5 cm wide strip of Scanpor tape to which 10 "Finn-chambers" were fixed in pairs. The three glyceryl monoesters were tested at a concentration of 50% w/v in liquid paraffin. Glyceryl Linoleate (0.02 ml) was dispensed directly into individual Finn chambers. Glyceryl Laurate was heated to 60°C and 0.02 g was placed directly into individual Finn chambers; 0.02 ml liquid paraffin was dispensed onto a filter disc in the chamber. Liquid paraffin served as the negative control.

The 91 volunteers were divided into two groups, group 1 (39 subjects) and group 2 (52 subjects), respectively. In group 1, the first set of induction patches was applied to the upper back for 23 h and subsequent patch applications were 47 h in duration. The patch test schedule for these subjects was as follows: days 1, 2, 4, 7, 9, 11, 14, 16 and 18. In group 2, 47-h induction patch applications were made according to the following schedule: days 1, 3, 5, 8, 10, 12, 15, 17, and 19. In both groups, induction patches were applied to the same site, unless a reaction stronger than mild erythema was observed. Reactions were scored after patch removal according to the following scale: 0 (no visible reaction) to 5 (bullous reaction).

During the challenge phase, initiated on day 35, patches were applied to new sites on the upper back for 47 h. Challenge reactions were scored at 1 and 49 h after patch removal. Classification of either test substance as irritating was based on 10% of the induction scores defined as > 1 (mild erythema). Sensitization was defined as a rapid response to challenge patch application, characterized by severe erythema and edema (usually with papules and/or vesicles).

Seventeen of the 91 subjects withdrew for reasons either unrelated to treatment (16 subjects) or because the patch was painful (1 subject). Seventy-four subjects (64 women, 10 men) completed the study. Glyceryl Linoleate did not induce skin irritation or sensitization. However, Glyceryl Laurate induced mild, erythematous reactions during induction in most of the subjects and questionable reactions during the challenge phase in seven subjects. During induction and challenge (1 and 49 h post removal) phases, reactions to Glyceryl Laurate ranged from 1 (mild erythema) to 2 (moderate erythema) (Danisco Ingredients 1996).

Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate

Danisco Ingredients (1999f) reported results of a study in which the skin irritation and sensitization potential of Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate was evaluated in a single-blind study using 93 healthy volunteers (ages between 18 and 65 years). Ten of the original 107 subjects withdrew for reasons unrelated to the conduct of the study. The repeat-insult patch test procedure (similar to procedure in preceding study) was a modification of the Draize test. Glyceryl Laurate was tested at a concentration of 25% in liquid paraffin oil, whereas Glyceryl Myristate and Glyceryl Oleate were each tested at a concentration of 50% in liquid paraffin oil. Liquid paraffin oil served as the control. Induction patches (Finn chambers on Scanpor tape) containing either of the three test substances or the control were applied to the upper back of each subject. The subjects were instructed to remove and discard the patches at the end of the 47-h contact period. This procedure was repeated (same sites) for a total of nine induction applications.

Test sites were evaluated prior to application of the next patch and 1 hour after patch removal on the last day of the induction phase according to the following scale: 0 (no visible reaction) to 5 (bullous reaction). Challenge patches were applied to the upper back (distant from induction site) of each subject on day 36. The patches were removed and discarded at the end of the 47-h contact period. Reactions were evaluated at 1 and 49 h after challenge patch removal.

Glyceryl Laurate (25% in liquid paraffin oil) induced moderate erythema (score = 2) in eight subjects during induction and in one subject during the challenge phase. Glyceryl Myristate and Glyceryl Oleate did not induce irritation or sensitization at a concentration of 50% in liquid paraffin oil. The investigators concluded that the three test substances did not induce sensitization during induction or challenge phases (Danisco Ingredients 1999f).

Glyceryl Caprate

The skin sensitization potential of 15% Glyceryl Caprate in paraffinum perl. DAB 10 (pharmaceutical grade) was evaluated in a modified Draize assay using 63 subjects, 58 of whom completed the study. During induction, the test substance was applied (0.025 ml, occlusive patches-Finn chamber) to the scapular region of the back three times per week (on Mondays, Wednesdays, and Fridays) for a total of 10 applications. At the end of each

48-h period (72 h on weekend), patches were removed and sites rinsed with distilled water. Reactions were scored according to the following scale: 0 (no reaction) to 4 (erythema, edema, and bullae). A 12-day nontreatment period was initiated after reactions to the 10th induction patch were scored. At the end of the 12-day period, occlusive challenge patches were applied to new sites on the scapular back for 48 h. Challenge reactions were scored at 48 and 72 h post application. The test substance did not induce irritation or sensitization reactions in any of the subjects tested (International Research Services, Inc. 1995).

Glyceryl Rosinate

Shao et al. (1993) patch tested eight dermatitis patients who had previously reacted to colophony (gum rosin) using Finn chambers with various rosins and rosin esters. Ten healthy subjects served as controls. Results indicated that the number of reactions to the rosin esters was lower, compared to the results for rosin. Five of eight patients had positive reactions to 10% tall oil rosin (in petrolatum), whereas four of eight patients had positive reactions to 20% glycerol-esterified tall oil rosin (in petrolatum). Also, seven of eight patients had positive reactions to 5% Portuguese gum rosin (in petrolatum) and three of eight patients had positive reactions to 20% glycerol-esterified gum rosin (in petrolatum). Additionally, neither of the eight subjects had positive reactions to glyceryl triabietate or petrolatum.

Positive reactions to each test substance ranged from + (erythema and infiltration) to +++ (erythema, infiltration, and vesicles). Because abietic acid is a main component of rosin and is easily oxidized to form contact allergens, the concentrations of this acid in the following rosin esters and rosins that were tested are indicated as follows: Portuguese gum rosin (42% abietic acid); tall oil rosin (55%); glycerol-esterified gum rosin (0.3%); and glycerol-esterified tall oil rosin (3.7%). It is important to note that the methylated oxidation product of abietic acid, 15-hydroperoxyabietic acid methyl ester (contact allergen) induced positive reactions in six of the eight patients tested and that this incidence was lower than that reported for Portuguese gum rosin (seven of eight patients). The results of this study indicated that esterification with glycerol reduced the allergenicity of rosin (Shao et al. 1993).

Gäfvert et al. (1994) evaluated the allergenicity of the following compounds (in petrolatum) in patients with contact allergy to gum rosin, 5% Portuguese gum rosin (GR), 10% tall oil rosin (TOR), 20% glycerol-esterified gum rosin (GGR), 20% glycerol-esterified tall oil rosin (TORG), 5.4% glyceryl-monoabietate (GMA), 9.5% glyceryl-1,2-diabietate ($GDA_{1,2}$), and 9.5% glyceryl-1,3-diabietate ($GDA_{1,3}$). $GDA_{1,2}$, $GDA_{1,3}$, and GMA are products that result from the esterification of abietic acid with glycerol (mentioned in preceding study). Except for patch tests with $GDA_{1,2}$ and $GDA_{1,3}$ (6 patients), 12 patients were used in the evaluation of each compound. Patch tests (Finn chambers) involved the application of each compound to the skin for 48 h. Reactions were scored at 72 h post application.

Ten control subjects were patch tested according to the same procedure.

Results for the rosins and rosin esters were similar to those in the preceding study. Over half of the patients had reactions (++ to +++) to these compounds. Five of the 12 patients had positive reactions to GMA (++ to +++), and neither of the 6 patients had positive reactions to $GDA_{1,2}$, or $GDA_{1,3}$. The patch testing of an additional patient with the latter two compounds also yielded negative results. No reactions were observed in the 10 healthy control subjects. This study confirmed the contact sensitization potential of rosin and rosin esters in patients with contact allergy to gum rosin and identified glyceryl-1-monoabietate as a contact allergen (Gäfvert et al. 1994).

The Consumer Product Testing Company (1997) patch tested 53 subjects (males and females, 18 to 69 years old) with a test material consisting of 20% Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. PEGMODWP-20). (Because Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Glyceryl Rosinate in the test material is 10%.) Forty-nine of the original 53 subjects completed the study; 4 withdrew for reasons that were unrelated to testing.

Approximately 0.2 ml of the test material (contains 10% Glyceryl Rosinate) was applied to the upper back, between the scapulae, of each subject on Mondays, Wednesdays, and Fridays for a total of 10 induction applications. Sites were covered with a semioclusive patch immediately after each application of the test material. Nontreatment periods of 24 h followed patch removals on Tuesdays and Thursdays. Saturday patch removals were followed by 48 h nontreatment periods. The induction phase was followed by a 2-week nontreatment period, after which a challenge patch was applied to the same site and a previously untreated site. Challenge reactions were scored at 24 and 48 h post application according to the following scale: 0 (no visible reaction) to 4+ (erythema and edema with vesiculation and ulceration). Induction reactions were also evaluated according to this grading scale.

One subject had a score of 2+ (well-defined erythema, possible presence of barely perceptible edema) during induction and at 24 and 48 h during the challenge phase (at new test site, but not at original site). At 72 h, the same subject also had a challenge reaction of 3+ (erythema and edema) at the new test site, but not at the original site. None of the remaining 48 subjects had induction or challenge reactions. It was concluded that the test material did not have the potential for inducing skin irritation and/or sensitization in this study (Consumer Product Testing Company 1997).

Ivy Laboratories (1996) evaluated the sensitization potential of a foundation containing 4% Glyceryl Rosinate using 28 healthy adult volunteers (13 males and 15 females; 18 to 46 years old). Twenty-five subjects completed the study; 3 subjects were removed for reasons that were unrelated to application of the test substance. Patches were applied to the upper outer arm,

volar forearm, or to the back of each subject. During induction, approximately 0.1 ml of 0.25% aqueous sodium lauryl sulfate (SLS) was applied under an occlusive patch (secured with occlusive tape) that was removed after 24 h. The foundation (0.1 ml on semiopen induction patch) was then applied to the test site for 48 h (or 72 h, i.e., over the weekend). If skin irritation was not observed at the time of patch removal, an occlusive patch containing 0.25% aqueous SLS was reapplied for 24 h. Patch removal was followed by reapplication of a fresh induction patch (semi-open) containing the foundation.

This sequence of SLS and test substance application was repeated for a total of five induction exposures. If irritation was observed at any time during induction, SLS pretreatment was discontinued and replaced with a 24 h nontreatment period between applications of the test substance. Following a 10-day nontreatment period, the challenge phase was initiated. Pretreatment with SLS was performed prior to challenge patch application. Approximately 0.1 ml of 5% aqueous SLS was applied, under an occlusive patch, to a fresh skin site for 1 h. After patch removal, a semiopen challenge patch containing 0.1 ml of the foundation was applied to the same site for 48 h. Challenge reactions were graded 1 h after patch removal and 24 h later according to the following scale: 0 (not sensitized) to 3 (strong sensitization, large vesiculobullous reaction).

Contact allergy was not observed in any of the subjects during either of the two grading periods (all scores = 0). It was concluded that the foundation containing 4% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1996).

The maximization assay described in the preceding study was also used to evaluate the sensitization potential of a blush containing 2% Glyceryl Rosinate. Twenty-seven healthy adult volunteers (11 males and 16 females; 18 to 56 years old) were tested. Contact allergy was not observed in any of the subjects during either of the two grading periods (all scores = 0). It was concluded that the blush containing 2% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1997).

The sensitization potential of a lip gloss containing 2.0% Glyceryl Rosinate was evaluated using 27 healthy adult volunteers (7 males, 20 females; 18 to 60 years old). Basically, the same maximization assay procedure (indicated above), was used with the following modifications: Patches were applied to the upper outer arm of each subject. During induction, the application of 0.1 ml of 1% aqueous SLS (occlusive patch) was followed by the application of 0.1 g of the test material (site covered with occlusive tape, referred to as induction patch). Prior to initiation of the challenge phase, the challenge site (new site on opposite arm) was pre-treated with 0.1 ml of 10% aqueous SLS (under occlusive patch). Pretreatment was followed by application of the test substance (same site) under an occlusive challenge patch secured with occlusive tape. Contact allergy was not observed

in any of the subjects during either of the two grading periods (all scores = 0), and there were no unusual or unexpected side effects. It was concluded that the lip gloss containing 2% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1990).

Biosearch, Inc. (1992b) evaluated the skin irritation and sensitization potential of a lipstick containing 1% Glyceryl Rosinate, as supplied, using 78 volunteers (16 to 55 years old). Eleven of the original 89 subjects withdrew from the study for personal reasons. All subjects selected for the study were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Approximately 0.15 g of the test substance was placed on an occlusive patch that was applied to the back of each subject for 24 h. Reactions were scored at 48 h post application according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]).

At the end of the grading period, a second patch was reapplied (same site) to each subject according to the same procedure. The test procedure was repeated on alternate days (Monday, Wednesday, and Friday) for a total of nine applications. Patches applied on Friday were removed on Saturday, and reactions were scored at 72 h post application. After a 2-week nontreatment period, a challenge patch containing the test substance was applied for 24 h to a new test site (adjacent to initial site) on each subject. Challenge reactions were scored at 48 and 72 h post application. Neither irritation nor sensitization reactions were observed in any of the subjects tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a sensitization response (Biosearch, Inc. 1992b).

Glyceryl Hydrogenated Rosinate

The Consumer Product Testing Company (2000) patch tested sixty subjects (males and females, 17 to 75 years old) with a test material consisting of 20% Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. Hydrogenated PEGMOD [20]). (Because Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Hydrogenated Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Hydrogenated Glyceryl Rosinate in the test material is 10%.) Fifty-one of the original 60 subjects completed the study, because 9 withdrew for reasons that were unrelated to testing.

A semioclusive patch containing approximately 0.2 ml of the test material (contains 10% Hydrogenated Glyceryl Rosinate) was applied to the upper back, between the scapulae, of each subject on Mondays, Wednesdays, and Fridays for a total of nine, 24-h induction applications. Nontreatment periods of 24 h followed patch removals on Tuesdays and Thursdays. Saturday patch removals were followed by 48 h nontreatment periods. The induction phase was followed by a 2-week nontreatment period, after which a challenge patch was applied to a new test site, but not to the original site. Challenge reactions were scored at

24 and 72 h post application according to the following scale: 0 (no visible skin reaction) to 4 (severe erythema, possible edema, vesiculation, bullae and/or ulceration). The same scale was also used to evaluate induction reactions.

Neither skin irritation nor sensitization was observed in any of the subjects tested. It was concluded that the test substance did not have the potential for inducing dermal irritation or allergic contact sensitization in this study (Consumer Product Testing Company 2000).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate

These are esters of glycerin and acids derived from rosin. In its reviews of rosin in color additive lakes, the FDA assessed the safety of various rosins (FDA 1988, 1994a, 1994b). The agency's findings are summarized below.

Although rosin has a history of use as a skin salve and as a soap, there were no toxicological data (e.g., from dermal irritation studies) that would support the safe use of rosin in contact with the skin or mucous membranes (e.g., in the lip area). Gum and wood rosins may be safely ingested; however, there are no data that support the safe use of rosin(s) as a substratum in color additive lakes intended for external uses (FDA 1988). In a more recent toxicology review, after considering that the "worst case" estimate for rosin content in lipsticks is 7.7% and that a more realistic estimate for lipstick rosin content is 0.6%, it was determined that, based on human patch test results, there appears to be little risk of irritant reactions due to rosin contained in lipsticks (FDA 1994a).

Furthermore, data submitted to FDA in 1994 indicated that lipsticks, blush, lipliner pencil, and nail polish containing rosinated lakes did not induce skin irritation in human subjects. Specifically, no skin irritation was observed when 197 subjects were patch tested (48-h single application) with blush products containing rosinated color additive lakes (9.3%) or when 10 subjects were tested with a lipstick product containing 1.07% rosinated color additive lakes in a phototoxicity test. Thus, FDA concluded that rosinated color additive lakes in cosmetic products at concentrations up to 9.3% do not present a health hazard due to irritation (FDA 1994b).

Skin irritation reactions to rosin/colophony have been reported; however, the intensity of these reactions is dependent upon the test concentration as well as the particular rosin that is being tested. In a human study on 60% colophony (Portuguese gum rosin), patch test results indicated that skin irritation could have been observed. However, in other studies, no evidence of skin irritation was found in more than 2300 subjects tested with 60% rosin or in 1132 patients patch tested with 20% rosin. Additionally, a number of commercially available, structurally modified rosin acids have been reported to induce dermal irritation. Most have an irritation threshold at concentrations greater than 10% (FDA 1994a).

FDA concluded that rosin/colophony can be classified as a moderate sensitizer. Sensitization to gum rosin exhibits a dose-response relationship (0.001% to 20%), indicating that sensi-

tization can be minimized by reducing the concentration (details from the original study referenced in FDA's review of rosin are included in the next paragraph). It is important to note that positive allergic responses to rosin have been confirmed in both animal and human studies. Because of the allergenicity of rosin in human subjects, this compound is included in the standard 23-compound allergic contact dermatitis screen that is used by dermatologists (FDA 1994a).

FDA also considered results of a study by Karlberg (1988) using the method of Fregert (1981) in which patients with suspected rosin-allergy were patch tested with serial dilutions of Portuguese gum rosin in petrolatum according to the internationally accepted method for diagnosis of contact allergy by Fregert (1981). Finn chambers and Scanpor surgical tape were used. Patches were removed after 48 h of contact and reactions were scored at 72 h post application.

Twelve patients were tested with Portuguese gum rosin at concentrations ranging from 0.001% to 20%. Another group of 12 patients who had +++ reactions to 20% gum rosin in an earlier study was retested with two different preparations of Portuguese gum rosin (one in petrolatum) at concentrations ranging from 0.001% to 10%.

A clear dose-response relationship (with a maximum response at doses of 10% to 20%) was observed in the serial dilution test with 0.001% to 20% gum rosin (*w/w*) in petrolatum. The author stated that these results imply that a concentration of 10% gum rosin is worth considering for routine testing. The incidence of positive reactions to two different preparations of gum rosin in the second group of 12 patients is summarized as follows: 0.001% gum rosin (0 to 1 patient), 0.01% gum rosin (2 to 3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients), and 10% gum rosin (10 to 12 patients). In the results for 10% gum rosin, all but 2 patients were tested with both preparations of gum rosin (Karlberg 1988).

Overall, FDA concluded that there is little or no potential for dermal irritation reactions due to rosin at the concentrations used in lipsticks containing rosin lakes. Therefore rosin, at the concentrations that can be present in lipstick containing color additive rosin lakes, does not present a health hazard due to irritation. OCAC reports that unmodified rosin is a moderate sensitizer and can induce allergic reactions in sensitized individuals. At the concentration of rosin that can be present as a component of color additive lakes (up to 7%), rosin can cause sensitization in unsensitized individuals. It is possible that rosin is bound during the color laking process and is not available to induce sensitization. However, no information was available regarding the skin absorption and subsequent skin sensitization potential of rosin contained in color additive lakes. FDA recommended further studies be undertaken to address this issue (FDA 1994a).

FDA amended its conclusion after human skin sensitization data on various cosmetic products containing rosinated lakes of D&C Red No. 6, D&C Red No. 7, and D&C Red No. 34 at several different concentrations were received. FDA concluded that

the use of rosin as a substratum in color additive lakes is safe, up to rosinated color additive concentrations of 9.0% in cosmetics products. This conclusion was based on the observation that no skin sensitization or photoallergic reactions to cosmetic formulations containing rosinated color additives at concentrations up to 9.0% were noted in human subjects. The human data included a photoallergy test using 312 subjects and a composite of repeat insult patch tests on a total of 2,381 subjects (FDA 1994b).

FDA also included in its consideration the components of rosin. Abietic acid and dehydroabietic acid, resin acids, are the main component of rosin. Abietic acid was not considered a contact allergen and the risk of resin acids inducing contact sensitivity in workers exposed to tall oil-containing products was considered minimal (FDA 1988).

The later review noted that oxidation products of abietic and dehydroabietic acid (which can be formed during storage) have been found to be allergenic. Hydrogenation of rosin acid reduced the allergenic potency of these oxidized gum rosin. There may be cross sensitization between several oxidized rosin acids. The oxidation of rosin acids might be necessary in order to induce immunologic properties (FDA 1994a).

The FDA review also considered that peroxides and hydroperoxides of rosin acids can contribute to the sensitization potential of rosin. Specifically, the test results for nine synthesized oxidation products of abietic acid and other rosin acids indicated that 7-oxodehydroabietic acid; 13,14-epoxy abietic acid; and 8,12-peroxidodihydroabietic acid, (strongest sensitizer of the three) are moderate sensitizers. Furthermore, the sensitization potential of a mixture of oxidation products from the polar fraction was found to be as strong as that of the peroxido compound. Methyl ester, keto, hydroxy, and hydroxylated unsaturated ketone derivatives were weak to poor sensitizers (FDA 1994a).

Phototoxicity

Biosearch, Inc. (1992c) evaluated the phototoxicity of a lipstick containing 1.0% Glyceryl Rosinate, as supplied, using 10 volunteers (17 to 55 years old). All subjects were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Subjects on medication (especially medications suspected of causing photobiological reactions or medications with the potential for modifying the inflammatory response) were excluded. The subjects were classified as Fitzpatrick skin types I, II, and III. The degree of skin pigmentation did not significantly influence responses to UV light or interfere with the scoring of skin reactions. The test substance was applied (approximately 20 mg/site) to two sites on the back of each subject and spread to cover the areas uniformly. One of the test sites was irradiated with 0.5 MED (minimal erythema dose, in seconds) of UVA and UVB light (continuous spectrum in UVA and UVB regions, 290 to 400 nm) between 30 and 60 min after application of the test substance. The MED was defined as the shortest exposure time at which erythema was first observed 20 ± 4 h after exposure. Irradiation with UVA and UVB light was followed by exposure to a total of 14 Joules/cm² of UVA.

A 2 mm thick WG-345 Schott filter was interposed to eliminate UVB (290 to 320 nm) radiation from the ultraviolet source.

Reactions were scored at 24, 48, and 72 h post irradiation according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]). The second site to which the test substance had been applied was not irradiated and served as an irritation control. A third site served as the untreated, irradiated control. Skin irritation was not observed (score = 0) at control or irradiated sites in either of the ten subjects tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a phototoxicity response (Biosearch, Inc. 1992c).

Photoallergenicity

Biosearch, Inc. (1992d) evaluated the photoallergenicity of a lipstick containing 1% Glyceryl Rosinate, as supplied, using 26 volunteers (17 to 55 years old). Four of the original 30 subjects withdrew for personal reasons. All subjects were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Subjects on medication (especially medications suspected of causing photobiological reactions or medications with the potential for modifying the inflammatory response) were excluded. Skin types were variable and the degree of skin pigmentation did not significantly influence responses to UV light or interfere with the scoring of skin reactions. During the induction phase, each of the subjects received six applications of the test substance over a period of 3 weeks. For each application, approximately 0.15 g of the test substance was placed on an occlusive patch that was applied to the back for 24 h. Patches were applied on Tuesdays and Thursdays. After patch removal, each site was exposed to 2.0 MEDs of UVB radiation and 4 Joules/cm² of UVA radiation. The subjects were instructed to keep the back covered throughout the study to avoid exposure to natural or artificial sunlight. The challenge phase was initiated 18 days after the last induction exposure. Challenge patches containing the test substance were applied to two new, adjacent test sites for 24 h. After patch removal, reactions were scored according to the scale indicated in the preceding study.

One of the test sites was then exposed to a combination of 0.5 MED of UVB and 4 Joules/cm² of UVA light. The other site was not exposed to UVA light and served as the irritation control. The UV light control site was defined as an additional site that was not exposed to the test substance but was irradiated with 0.5 MED of UVB and 4 Joules/cm² of UVA light. Challenge sites were scored at 24, 48, and 72 h post-irradiation. No reaction (score = 0) was observed at control or test sites on any of the 26 volunteers tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a photoallergy response (Biosearch, Inc. 1992d).

Case Reports

A strong positive reaction was observed when a 35-year-old female patient with itchy, facial erythema was tested with 0.01% glyceryl monoisostearate. Reportedly, the itchy, facial erythema

resulted from the use of a foundation containing 1.77% glyceryl diisostearate. It is important to note that Glyceryl Monoisostearate was one of the impurities detected in glyceryl diisostearate (Tanaka, Shimizu, and Miyakawa 1993).

Glyceryl Monoisostearate (0.01% in petrolatum) induced ++ reactions (at 48 and 72 h) in an 18-year-old girl with a history of what was described as lip cream dermatitis (Hayakawa et al. 1987).

SAFETY INFORMATION ON ARACHIDONIC ACID

Information from the CIR Final Report on the safety of Arachidonic Acid in cosmetics (Andersen 1993) is summarized below.

Arachidonic Acid is an essential, polyunsaturated, fatty acid that is used as a surfactant-cleansing agent and a surfactant—emulsifying agent in cosmetic formulations. Arachidonic Acid is a liquid at room temperature, is soluble in alcohol, ether, and water, and absorbs in the ultraviolet B (UVB) range. Arachidonic Acid is well absorbed from the gastrointestinal tract and the circulatory system, it distributes rapidly into the lipid compartment of the body, and is rapidly converted to phospholipid by the liver. Arachidonic Acid can be metabolized by three different pathways: the cyclooxygenase, lipoxygenase, and cytochrome P450 systems.

Arachidonic Acid metabolites are involved in the inflammatory process. A chronic cellular imbalance of Arachidonic, γ -linolenic, and eicosapentaenoic acids, and of their respective eicosanoid derivatives, may have major health implications. Arachidonic Acid may alter the cutaneous immune response.

In a study in which Arachidonic Acid was applied to the pinnae of mice, an increase in pinna thickness was observed. Microscopic effects were also observed throughout the study. Application of Arachidonic Acid to mouse skin produced edema and inflammation, with high doses possibly causing ulceration of the skin.

Arachidonic Acid did not produce teratogenic effects. Exogenous Arachidonic Acid appeared to help prevent the teratogenic effects caused by hyperglycemia and phenytoin. Subcutaneous administration to pregnant diabetic rats significantly reduced neural tube defects, cleft palate, and micrognathia. Arachidonic Acid has also dose-dependently reversed antimaskulinization caused by a number of compounds. However, indomethacin has been found to stop the reversal of teratogenic effects by Arachidonic Acid.

Arachidonic Acid has mutagenic potential. Arachidonic Acid has increased the frequency of TG⁺ colonies, phagocyte-induced SCEs, chromosomal aberrations, thioether synthesis, MAL number, and the incorporation of [³H]thymidine/mg cellular DNA.

In 24 h single insult patch tests, a formulation containing 0.04% Arachidonic Acid was not an irritant.

The CIR Expert Panel recognized that dermal absorption data were lacking and that such data were necessary before a deter-

mination of safety can be made. And based on the results of those studies, still further data may be needed. Because Arachidonic Acid may be involved in UV light-induced cutaneous immune suppression, immunomodulatory data may be requested (dependent on the results of the dermal absorption studies). In addition to immunomodulatory data, carcinogenicity, photocarcinogenicity, and human irritation, sensitization, and photosensitization data may also be requested.

Accordingly, the CIR Expert Panel found that the safety of this ingredient has not been documented and substantiated for cosmetic product use. The additional data needed were described as follows:

1. Dermal absorption data

Based on the results of the absorption studies, the Panel indicated there may be a need for the following data:

2. Immunomodulatory data
3. Carcinogenicity and photocarcinogenicity data
4. Human irritation, sensitization, and photosensitization data (Andersen 1993)

SUMMARY

The safety of the following 43 Glyceryl Monoesters in cosmetics is reviewed in this report: Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Iso-stearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate.

According to one source, Glyceryl Monoesters are not pure monoesters, but are mostly mixtures with mono-, di-, and triesters in a ratio of approximately 4:4:2, respectively. Another source indicates that the guaranteed purity of commercial and conventional Monoglyceride (Glyceryl Monoester) is a minimum of 90%, meaning that impurities account for a maximum of 10% of the composition. The results of impurities analyses of 14 Glyceryl Monoesters indicated that only one, Glyceryl Palmitate/Stearate, contained (mono)glycerol diester at a concentration of 1.2%.

UV spectral analyses of 14 Glyceryl Monoesters indicated maximum absorbance at 238 or 239 nm.

Glyceryl Monoesters are used mostly as skin conditioning agents—emollients and/or surfactant—emulsifying agents in cosmetics. Frequency of use data provided by FDA in 1998 indicate that of the 43 ingredients in this safety assessment, the following 16 are used in cosmetics: Glyceryl Laurate, Glyceryl Alginate, Glyceryl Arachidonate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Cocoate, Glyceryl Hydroxystearate, Glyceryl Isostearate, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Palmitate, Glyceryl Myristate, Glyceryl Polyacrylate, Glyceryl Rosinate, and Glyceryl Undecylenate.

Concentration of use data received from the cosmetics industry in 1999 indicate that Glyceryl Monoesters are used at concentrations up to 12% in cosmetic products.

Glyceryl Monoesters have also been approved by FDA for use as direct or indirect food additives. The Food Protection Committee of the National Academy of Sciences National Research Council Food and Nutrition Board concluded that there appears to be no reason to question the safety of mono-, di-, or triglycerides of lauric acid (i.e., Glyceryl Laurate, Glyceryl Dilaurate, or Glyceryl Trilaurate [Trilaurin]) as food additives.

Glyceryl Monoesters (monoglycerides) are metabolized to free fatty acids and glycerol, both of which are available for the resynthesis of triglycerides.

Glyceryl Laurate enhanced the penetration of drugs through cadaverous skin and hairless rat skin *in vitro*.

Lauricin (registered trademark for Glyceryl Laurate) has been described as having a wide spectrum of antimicrobial activity against diverse microbial species (viruses, fungi, molds, yeasts, and bacteria included).

A low-grade irritant response was observed following inhalation of an aerosol containing 10% Glyceryl Laurate by test animals.

An LD₅₀ of >20,000 mg/kg was reported for rats dosed orally with Glyceryl Laurate. In other studies, neither Glyceryl Isostearate nor Glyceryl Citrate/Lactate/Linoleate/Oleate induced toxicity in rats that received a single oral dose of 2000 mg/kg. Similar results were reported in an acute dermal toxicity study in which 2000 mg/kg Glyceryl Citrate/Lactate/Linoleate/Oleate was administered to rats.

Undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was not toxic (LD₅₀ > 5 g/kg) when administered orally to fasted Wistar albino rats (five males, five females; weight range 220 to 292 g). None of the animals died.

A no-effect level of 280 mg/m³ was reported for Glyceryl Laurate in a short-term inhalation toxicity study involving rats. Rats were subjected to 14 1-hour exposures during a 3-week period. Neither gross nor microscopic lesions were noted in rats fed 25% Glyceryl Laurate in another short-term (10 weeks) study.

No test substance-related gross or microscopic changes were observed in albino rats fed a mixture of mono-, di-, and triglycerides containing 40% to 45% Glyceryl Laurate for two years.

Glyceryl Laurate had strong hemolytic activity in an *in vitro* assay using sheep erythrocytes.

Glyceryl Laurate, Glyceryl Isostearate, or Glyceryl Citrate/Lactate/Linoleate/Oleate were not classified as ocular irritants in rabbits. Undiluted, purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) also was not irritating to the eyes of rabbits.

Undiluted Glyceryl Laurate induced minor erythema and edema when applied (occlusive patches, single application) to intact skin of rabbits. In another study, single occlusive patch applications of 20% Glyceryl Laurate emulsion to abraded and intact skin caused moderate skin irritation in rabbits.

Overall, Glyceryl Isostearate was classified as nonirritating to the skin of rabbits in a study in which single, semioclusive patch applications were made to intact skin. The most severe reaction (moderate irritation) did not clear until day 5 post removal. Glyceryl Isostearate was also classified as nonirritating to the skin of rabbits in another study in which single occlusive patch applications were made to intact and abraded skin sites.

A PII of 3.40 (potential for severe irritation—warning label may be considered) was reported in an occlusive patch test evaluating the skin irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) in rabbits. Follicular hyperkeratosis (comedone formation) was not observed in another study in which the same undiluted test substance was applied to the ears of rabbits.

Neither erythema nor edema was observed in rabbits after semioclusive patches containing heated Glyceryl Citrate/Lactate/Linoleate/Oleate (single application) were applied to intact skin. In another study, Glyceryl Citrate/Lactate/Linoleate/Oleate (single application) induced clearly circumscribed erythema and very mild edema when applied to intact skin of rabbits. All reactions had cleared by day 10 post application.

The skin sensitization potential of Glyceryl Laurate was evaluated in the maximization test. Guinea pigs were subjected to four sensitizing injections of 2% Glyceryl Laurate and then challenged with intradermal injections of 0.8% Glyceryl Laurate and topical applications of 25% Glyceryl Laurate. No positive reactions were observed. In another maximization test, skin sensitization was induced in 2 of 10 guinea pigs challenged with a 10% dilution of 20% Glyceryl Laurate emulsion. When a second challenge was initiated 7 days after the first, positive reactions were observed in five animals. Positive reactions were also observed in four animals challenged with a 5% dilution of 20% Glyceryl Laurate emulsion. Because positive reactions were also noted in the control group after the first and second challenge, the results were attributed to skin irritation (but not sensitization) effects of the test substance.

Glyceryl Isostearate was also evaluated in the maximization test. After induction, ten guinea pigs were challenged with 50% Glyceryl Isostearate in polyethylene glycol (PEG) and microcrystalline cellulose (MCC). Two additional challenges were also conducted. The first challenge yielded one and two positive

reactions (all slight reactions) at 24 and 48 h, respectively. These results were confirmed by reactions observed after the third challenge.

The sensitization potential of Glyceryl Citrate/Lactate/Linoleate/Oleate in 20 guinea pigs was evaluated using the Buehler method. Following the dermal application of undiluted test substance during induction and challenge phases, no evidence of irritation or sensitization was observed.

The reaction of rosin with glycerol to form two esterification products (glyceryl triabietate [GTA] and glycerol esterified tall oil rosin [TORG]), in effect, reduced the allergenicity of rosin. GTA results from the esterification of glycerol with abietic acid, the major component of rosin. The incidence of positive challenge reactions in 15 guinea pigs tested was as follows: 1 (8.3% GTA), 2 (10% TORG), 3 (0.93% and 2.8% GTA), and 9 (20% gum rosin). Glyceryl diabietate and glyceryl monoabietate induced either the same incidence or a higher incidence of sensitization in other experiments (similar test groups) in the same study.

No evidence of significant cutaneous reactions, with or without UV irradiation, was found when the phototoxicity and photoallergenicity potential of Glyceryl Isostearate was evaluated using 20 guinea pigs.

In a study (using mice) investigating the effect of Glyceryl Laurate on delayed-type hypersensitivity to sheep erythrocytes, the test substance did not cause significant enhancement of the immunological response. In another study using lymphocytes from murine spleens, Glyceryl Laurate-induced T-cell proliferation was blocked by cyclosporin A (immunosuppressive drug) at concentrations as low as 20 ng/ml. These results suggest that Glyceryl Laurate could be exerting its effect along the calcium-dependent inositol phospholipid, signal transduction pathway.

In Ames plate incorporation and preincubation mutagenicity tests, Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic (with or without metabolic activation) to the following *Salmonella typhimurium* strains: TA 98, TA 100, TA 1535, and TA 1537. In studies on the mutagenicity of resin acids, only neoabietic acid (component of rosin) was mutagenic in the Ames/*Salmonella* assay. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, which is composed of diterpene resin acids.

Marked antitumor activity against two leukemia cell lines in vitro was observed in the presence of Glyceryl Laurate. A follow-up study to the preceding assay indicated that Glyceryl Laurate (i.p. injection, saline suspension) was ineffective in prolonging the lifespan of tumor-bearing BDF₁ mice that had been implanted i.p. with L-1210 leukemia cells. Doses of 30 and 100 mg/kg were injected daily for 5 consecutive days. In other experiments, the antitumor activity of Glyceryl Laurate against Ehrlich ascites tumor cells was demonstrated both in vivo and in vitro. In the two in vivo studies, Glyceryl Laurate (in saline) was injected i.p. into ddY mice that had been implanted i.p. with Ehrlich ascites tumor cells. Doses of 2.5 and 10.0 mg/mouse were injected daily for 5 successive days. Test results (both studies) indicated

no tumor growth and increased survival time (compared to controls) at both doses.

The tumor promoting activity of Glyceryl Stearate on the clipped dorsal skin of Swiss mice was evaluated. One week after a single application of 9,10-dimethylbenz(a)anthracene (DMBA) (1% to 1.5% in mineral oil), 5% Glyceryl Stearate (in acetone) was applied to skin twice weekly. No tumors developed; slight epidermal hyperplasia at the site of application was noted.

Following the administration of hexane extracts of *Pinus ponderosa* needles to mice by stomach tube, increased embryonic resorptions were observed. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, and rosin is obtained from trees of various species of *Pinus*.

Glyceryl Laurate, Glyceryl Linoleate, and Glyceryl Palmate were each tested at a concentration of 50% w/v, in liquid paraffin, in a repeat insult patch test (RIPT) (Finn chambers) involving 91 healthy human subjects. Glyceryl Linoleate did not induce skin irritation or sensitization in the 74 subjects who completed the study. Glyceryl Laurate induced mild, erythematous reactions during induction in most of the subjects and questionable reactions in seven subjects during the challenge phase. Reactions ranged from mild to moderate erythema (score = 2) during induction and challenge phases.

The skin irritation and sensitization potential of Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate was evaluated in a second RIPT (Finn chambers) using 107 healthy subjects, 93 of whom completed the study. Glyceryl Laurate was tested at a concentration of 25% in liquid paraffin oil, whereas Glyceryl Myristate and Glyceryl Oleate were tested at a concentration of 50% in paraffin oil. Glyceryl Laurate induced moderate erythema (score = 2) in eight subjects during induction and in one subject during the challenge phase. Glyceryl Myristate and Glyceryl Oleate did not induce irritation or sensitization. Neither of the three test substances was considered a sensitizer. In another study, Glyceryl Caprylate (15%) did not induce skin irritation or sensitization in an RIPT involving 63 healthy subjects, 58 of whom completed the study.

Two case reports indicated skin reactions to two cosmetic products containing Glyceryl Isostearate, as well as positive patch test reactions to this ingredient.

Skin irritation was not observed in 12 healthy volunteers patch tested (occlusive patches) with a lipstick containing 1.0% Glyceryl Rosinate. Neither skin irritation nor sensitization was observed in 78 healthy volunteers patch tested (occlusive patches) with the same product in a repeated insult patch test.

The contact sensitization potential of three product formulations containing Glyceryl Rosinate was evaluated in three maximization assays (healthy human subjects), respectively. Results were negative for the following three study groups: foundation containing 4.0% Glyceryl Rosinate (25 subjects), blush containing 2.0% Glyceryl Rosinate (27 subjects), and lip gloss containing 2.0% Glyceryl Rosinate (27 subjects).

Skin irritation and sensitization were observed in one of 49 subjects patch tested (RIPT, semiocclusive patches) with a material consisting of 20% Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. PEGMODWP-20). (Because Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Glyceryl Rosinate in the test material is 10%.) The challenge reaction was observed at the original test site, but not at the new site. It was concluded that the positive reaction observed was unique to that individual.

Neither skin irritation nor sensitization was observed in any of the 51 subjects patch tested (semioclusive patches) with a material consisting of 20% Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. Hydrogenated PEGMOD [20]). (Because Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Hydrogenated Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Hydrogenated Glyceryl Rosinate in the test material is 10%.) The subjects were challenged at a new test site, but not at the original site.

Phototoxicity was not induced in a group of 10 healthy volunteers tested with a lipstick containing 1.0% Glyceryl Rosinate. Patches were not applied to test sites. Similarly, photoallergenicity was not induced in a group of 26 healthy volunteers patch tested (occlusive patches) with the same product in a repeat insult patch test.

Data on 12 patients suspected of having gum rosin allergy indicated that sensitization to Portuguese gum rosin exhibited a dose-response relationship (0.001% to 20%). In the same study, the incidence of positive reactions to Portuguese gum rosin in a second group of 12 patients with gum rosin allergy was summarized as follows: 0.001% gum rosin (0 to 1 patient), 0.01% gum rosin (2 to 3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients), and 10% gum rosin (10 to 12 patients). These data were based on patch tests with serial dilutions of Portuguese gum rosin in petrolatum.

The esterification of rosin with glycerol, in effect, reduced the allergenicity of rosin in dermatitis patients. Five of eight patients had positive reactions to 10% tall oil rosin in petrolatum, whereas four of eight patients had positive reactions to 20% glycerol-esterified tall oil rosin in petrolatum. Additionally, seven of eight patients had positive reactions to 5% Portuguese gum rosin in petrolatum and three of eight patients had positive reactions to 20% glycerol-esterified gum rosin in petrolatum.

Glyceryl-1-monoabietate was identified as a contact allergen in another study evaluating the allergenicity of rosin and its esterification products. Abietic acid (esterified to form glyceryl-1-monoabietate) is a main component of rosin, and, furthermore, clinical data indicate that it is easily oxidized to form contact allergens (e.g., 15-hydroperoxyabietic acid and its methyl ester). It is also important to note that oxidation products of abietic acid and dehydroabietic acid (also a main component of

rosin) that can be formed during storage have been found to be allergenic.

FDA concluded that the use of rosin as a substratum in color additive lakes is safe up to rosinated color additive concentrations of 9.0% in cosmetic products. This conclusion was based on the observation that no skin sensitization or photoallergic reactions to cosmetic formulations containing rosinated color additives at concentrations up to 9.0% were noted in human subjects. The human data, submitted by CTFA, included a photoallergy test using 312 subjects and a composite of repeat-insult patch tests on a total of 2381 subjects.

Information from the earlier safety assessment of Arachidonic Acid is considered relevant, in that the concerns raised therein also apply to the safety assessment of Glyceryl Arachidonate. The CIR Expert Panel had concluded that the safety of Arachidonic Acid had not been documented and substantiated for cosmetic product use. Additional safety data that are needed include

1. Dermal absorption data

Based on the results of the absorption studies, the Panel indicated that there may be a need for the following data:

2. Immunomodulatory data
3. Carcinogenicity and photocarcinogenicity data
4. Human irritation, sensitization, and photosensitization data.

DISCUSSION

A primary concern regarding the safety of Glyceryl Monoesters is the possible presence of Glyceryl Diesters, and, specifically, the 1,2 diesters, which are known to have adverse effects. After reviewing impurities data on 14 Glyceryl Monoesters (90% pure), the Panel concluded that the level of 1,2-diacylglycerols (1,2 (mono)glycerol diester) in Glyceryl Monoesters is not sufficient to warrant any concern about effects on signal transduction and resulting effects on cell growth and proliferation that are associated with 1,2-diacylglycerol-induced activation of protein kinase C (PKC). The results of the impurities analysis indicated that only one of the 14 Glyceryl Monoesters, Glyceryl Palmitate/Stearate, contained (mono)glycerol diester.

Of approximately 4% of the (mono)glycerol diester content of Glyceryl Palmitate/Stearate, 29% is actually the 1,2 (mono)glycerol diester. Thus, the concentration of 1,2 (mono)glycerol diester in Glyceryl Palmitate/Stearate is approximately 1.2%. In addition, the Panel noted the absence of tumor promotion activity in a study using Glyceryl Stearate. The Panel noted that if 1.2% represents the maximum concentration of this impurity in cosmetic grade Glyceryl Monoester, then the concentration of 1,2-diacylglycerol in cosmetics would be significantly less, considering that current use concentration data from the cosmetics industry indicate that product concentrations of Glyceryl Monoesters range from 0.1% to 12%.

Given that Glyceryl Laurate is known to enhance the skin penetration of other chemicals, but that data are not available on the

penetration enhancement activity of other Glyceryl Monoesters, the Panel agreed that the manufacturers should consider the skin penetration enhancement potential of all Glyceryl Monoesters when formulating cosmetic products to ensure safety.

The Expert Panel previously stated that the available inhalation toxicity data are insufficient for addressing the Panel's concern over the use of Glyceryl Monoesters in aerosolized products, which relates to the potential surfactant activity of these ingredients on the lungs. After further review of this issue, focusing primarily on the use of Glyceryl Caprylate/Caprates in hair sprays, the Panel determined that Glyceryl Caprylate/Caprates can be used safely in these products, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of anhydrous hair sprays (60 to 80 μm) and pump hair sprays ($>80 \mu\text{m}$) was large compared to the median aerodynamic diameter of $4.25 \pm 1.5 \mu\text{m}$ for a respirable particulate mass.

Though mammalian genotoxicity data on the Glyceryl Monoesters were not available, the Panel concluded that they are not likely genotoxic agents based on the chemical structures of these compounds and negative Ames test data. Limited carcinogenicity data were negative, and data on the Glyceryl Monoester, Glyceryl Stearate indicated that 5% Glyceryl Stearate in acetone was not a tumor promoter in Swiss mice. These data, combined with the observation that maximum use concentrations of Glyceryl Monoesters associated with most (but not all) of the product type categories for cosmetics are $\leq 5\%$, led the Panel to discount any carcinogenic risk.

The Panel expressed specific concerns relating to the safety of Glyceryl Rosinate, Glyceryl Hydrogenated Rosinate, Glyceryl Collagenate, and Glyceryl Arachidonate in cosmetics, based on the specific chemical with which glycerin is esterified.

Glyceryl Rosinate is defined as the monoester of glycerin and mixed long-chain acids derived from rosin, and Glyceryl Hydrogenated Rosinate is defined as the monoester of glycerin and hydrogenated mixed long-chain acids derived from rosin. The Panel recognizes the potential for contamination of cosmetic grade samples of Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate with rosin, a moderate sensitizer. The Panel also noted that abietic acid, the main component of rosin, is easily oxidized to form contact allergens such as 15-hydroperoxyabietic acid and its methyl ester; glyceryl-1-monoabietic acid. Moderating this concern are data indicating that the sensitization potential of rosin is reduced by esterification with glycerol.

The Panel determined that this concern could be adequately addressed by establishing a concentration limit for Glyceryl Rosinate in cosmetic products that is based on the highest test concentration in human skin sensitization studies that did not induce sensitization. Skin irritation and sensitization were observed in 1 of 49 subjects patch tested (semioclusive patches) with a trade mixture containing 10% Glyceryl Rosinate. In the other human study, neither skin irritation nor sensitization was observed in any of the 51 subjects patch tested (semioclusive patches) with a trade mixture containing 10% Glyceryl Hydro-

genated Rosinate. After reviewing these negative data and considering that the highest reported use concentrations of Glyceryl Rosinate at 10% in an eyebrow pencil and up to 12% in a mascara (products applied to the eyebrows or eyelashes), the Panel agreed that Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate could be considered safe as used in cosmetic products. The Panel reasoned that any sensitization potential associated with Glyceryl Rosinate or Glyceryl Hydrogenated Rosinate at a concentration of 10% or 12% in a semioclusive patch test would be significantly reduced in cosmetic products in which the mode of application results in minimal contact with the skin and does not involve any form of occlusion.

After reviewing the positive skin irritation study (rabbits, occlusive patches) on an undiluted trade mixture containing 50% Glyceryl Rosinate and 50% octyldodecyl myristate, the Panel agreed that the irritation potential of this material would be significantly reduced under the conditions of cosmetic use (i.e., dilution to current use concentrations of Glyceryl Rosinate and absence of occlusion).

The Panel noted that the photosensitization potential of Glyceryl Monoesters in cosmetics is not an issue, based on the negative UV absorption data on 14 ingredients and human photoallergenicity data on a cosmetic product containing 1% Glyceryl Rosinate that were provided.

Because protein found in cartilage and other connective tissues in animals is the source of collagen, the Expert Panel stipulates that Glyceryl Collagenate should be free of infectious agents.

The CIR Expert Panel has issued a Final Report with an insufficient data conclusion on Arachidonic Acid. Because it is likely that Glyceryl Arachidonate will be hydrolyzed to Arachidonic Acid, the Panel noted that the data needed for completion of the safety assessment on Arachidonic Acid are also applicable to Glyceryl Arachidonate. Dermal absorption data are needed. Based on the results of the absorption studies, the Panel indicated that there may be a need for the following data: immunomodulatory data; carcinogenicity and photocarcinogenicity data; and human irritation, sensitization, and photosensitization data.

CONCLUSIONS

Based on the available animal and clinical data included in this report, the CIR Expert Panel concludes that the following Glyceryl Monoesters are safe as cosmetic ingredients in the present practices of use and concentration: Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprates, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearamides, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linoleate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl

Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate.

The Panel also concludes that the available data are insufficient to support the safety of Glyceryl Arachidonate in cosmetic formulations.

REFERENCES

- American Conference of Governmental Industrial Hygienists (ACGIH). 1991. Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1990–1991. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.
- Andersen, F. A. 1993. Final report on the safety assessment of arachidonic acid. *J. Am. Coll. Toxicol.* 12(5):481–559.
- Aungst, B. J., N. J. Rogers, and E. Shefter. 1986. Enhancement of naloxone penetration through human skin *in vitro* using fatty acids, fatty alcohols, surfactants, sulfoxides and amides. *Int. J. Pharm.* 33:225–234.
- Biogir, S. A. Conseil Recherche. 1989. Assessment of cutaneous tolerance in the rabbit. Index of primary cutaneous irritation. Extol 2040 glycerol monoistearate No. 82350. (English translation). Report No. IC 88.1516. Unpublished data submitted by CTFA, May 11, 1999 (18 pages).²
- Biosearch, Inc. 1992a. Irritation screening study. Pure Gloss 3402-35 (lipstick, as supplied) containing 1% glyceryl rosinat. Unpublished data submitted by CTFA (14 pages).²
- Biosearch, Inc. 1992b. Modified Draize repeated insult patch test study in human subjects. Pure Gloss 3402-35 (lipstick, as supplied) containing 1% glyceryl rosinat. Unpublished data submitted by CTFA (11 pages).²
- Biosearch, Inc. 1992c. Human phototoxicity test. Pure Gloss 3402-35 (lipstick, as supplied) containing 1% glyceryl rosinat. Unpublished data submitted by CTFA (8 pages).²
- Biosearch, Inc. 1992d. Human photoallergy study. Pure Gloss 3402-35 (lipstick, as supplied) containing 1% glyceryl rosinat. Unpublished data submitted by CTFA (9 pages).²
- Blöbe, G. C., L. M. Obeid, and Y. A. Hannun. 1994. Regulation of protein kinase C and role in cancer biology. *Cancer Metastasis Rev.* 13:411–431.
- Bower, D. 1999. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting.²
- Brooks Industries. 1998. Specification, material safety data sheet, and technical data on Glyceryl Collagenate. Unpublished data submitted by CTFA, May 21, 1999.²
- Budavari, S. 1989. *The Merck index. An encyclopedia of chemicals, drugs, and biologicals*, 983–984, 1530–1531, 1534. Rahway, NJ Merck & Co., Inc.
- Centre de Recherche et d'Élevage des Oncins. 1975. Tests de tolerance chez le lapin: Indices d'irritation primaire. Irritation oculaire. Unpublished data submitted by CTFA, March 10, 1999 (10 pages).²
- Chaibi, A., L. H. Ababouch, and F. F. Busta. 1996a. Inhibition of bacterial spores and vegetative cells by glycerides. *J. Food Protection* 59:716–722.
- Chaibi, A., L. H. Ababouch, and F. F. Busta. 1996b. Inhibition by monoglycerides of L-alanine-triggered *Bacillus cereus*. *J. Food Protection* 59:832–837.
- Consumer Product Testing Company. 1990a. Acute oral toxicity in rats. P.E.G./M.O.D. Purified Ester Gum/M.O.D. (Lot No. 00207). Experiment reference number: 90231-1. Unpublished data submitted by CTFA, June 22, 2000 (2 pages).²
- Consumer Product Testing Company. 1990b. Primary ocular irritation in rabbits. P.E.G./M.O.D. Purified Ester Gum/M.O.D. (Lot No. 00207). Experiment reference number: 90231-1. Unpublished data submitted by CTFA, June 22, 2000 (5 pages).²
- Consumer Product Testing Company. 1990c. Primary dermal irritation in rabbits. P.E.G./M.O.D. Purified Ester Gum/M.O.D. (Lot No. 00207). Experiment reference number: 90231-1. Unpublished data submitted by CTFA, June 22, 2000 (7 pages).²
- Consumer Product Testing Company. 1990d. Comedogenicity assay in rabbits. P.E.G./M.O.D. Purified ester gum/M.O.D. (Lot No. 00207). Experiment reference number: 90231-2. Unpublished data submitted by CTFA, June 22, 2000 (10 pages).²
- Consumer Product Testing Company. 1997. Repeated insult patch test (protocol no. 1.01). PEGMODWP-20 Lot #7045JW01. Unpublished data submitted by CTFA, June 22, 2000 (8 pages).²
- Consumer Product Testing Company. 2000. Repeated insult patch test (protocol no. 1.01). Hydrogenated PEG/MOD (20) (Lot #00124). Experiment reference number: C00-0171.01 (9 pages).² Unpublished data submitted by CTFA June 2000.
- Cosmetic, Toiletry, and Fragrance Association (CTFA). 1975. Guinea pig skin sensitization test no. 75.213. Laurinic monoglyceride. Unpublished data submitted by CTFA, May 11, 1999.²
- CTFA. 1985. Skin sensitization study (test reference SSM85288). Glyceryl isostearate. Unpublished data submitted by CTFA, May 11, 1999.²
- CTFA. 1999. Ingredient use survey—use concentration data. Unpublished data submitted by CTFA, July 26, 1999 (4 pages).²
- Cosmo Trends. no date. Cosmo Trends specialties series. Purified ester gum/M.O.D. = PEGMOD. Unpublished data submitted by CTFA, June 22, 2000 (5 pages).²
- Danisco Ingredients. 1996. A modified Draize repeat insult patch test in healthy volunteers to investigate the irritation and sensitization potential of nine cosmetic ingredients of edible quality and a control (liquid paraffin) following repeated cutaneous patch applications (Report No. DANF001). Unpublished data submitted by Danisco Ingredients. February, 1999 (70 pages).²
- Danisco Ingredients. 1999a. Calculation of the octanol/water partition coefficients. Unpublished data submitted by CTFA, July 15, 1999 (3 pages).²
- Danisco Ingredients. 1999b. Inhalation toxicity data. Unpublished data submitted by CTFA, July 15, 1999 (1 page).²
- Danisco Ingredients. 1999c. Impurity analysis for glycerol monoesters. Unpublished data submitted by CTFA, August 25, 1999 (20 pages).²
- Danisco Ingredients. 1999d. "Impurity analysis" for glycerol monoesters. Unpublished data submitted by CTFA, September 9, 1999 (2 pages).²
- Danisco Ingredients. 1999e. UV-spectra for glycerol monoesters. Unpublished data submitted by CTFA, August 30, 1999 (18 pages).²
- Danisco Ingredients. 1999f. A modified Draize repeat insult patch test in healthy volunteers to investigate the irritation and sensitization potential of nine cosmetic ingredients of edible quality and a control (liquid paraffin) following repeated cutaneous patch applications. Unpublished data submitted by CTFA, July 22, 1999 (108 pages).²
- Eagle, E., and C. E. Poling. 1955. The oral toxicity and pathology of polyoxyethylene derivatives in rats and hamsters. *Food Res.* 21:348–361.
- Elder, R. L., ed. 1982. Final report on the safety assessment of glyceryl stearate and glyceryl stearate/SE. *J. Am. Coll. Toxicol.* 1:169–192.
- Elder, R. L., ed. 1986. Final report on the safety assessment of glyceryl oleate. *J. Am. Coll. Toxicol.* 5:391–413.
- European Economic Community (EEC). 2001. *EEC Cosmetics Directive 76/768/EEC, as amended, Annexes I through VII*. Brussels: EEC.
- Fitzhugh, O. G., P. J. Schouboe, and N. A. Nelson. 1960. Oral toxicities of lauric acid and certain lauric acid derivatives. *Toxicol. Appl. Pharmacol.* 2:59–67.
- Food and Drug Administration (FDA). 1988. Memorandum dated June 27, 1998. Color additive petition no. 7T0130. Safety evaluation of substrata and precursors used in the manufacture of color additive lakes. Washington, DC: FDA.

² Available for review from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC, 20036, USA.

- FDA. 1994a. Memorandum dated July 13, 1994. Safety evaluation of rosin in color additive lakes. Washington, DC: FDA.
- FDA. 1994b. Memorandum dated August 22, 1994. Safety evaluation of dermal sensitization and photosensitization of rosinated lakes of D&C Red No. 6, D&C Red No. 7, and D&C Red No. 34. Washington, DC: FDA.
- FDA. 1998. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.
- Fregert, S. 1981. *Manual of contact dermatitis*, 2nd ed., 71–81. Copenhagen: Munksgaard.
- Gäfvert, E., L. P. Shao, A.-T. Karlberg, U. Nilsson, and J. L. G. Nilsson. 1994. Allergenicity of rosin (colophony) esters. II. Glyceryl monoabietate identified as contact allergen. *Contact Dermatitis* 28:229–234.
- Gattefossé, S. A. 1998. Data sheet. Peceol isostearique (Glyceryl Isostearate). Unpublished data submitted by CTFA, March 10, 1999 (2 pages).²
- Gattefossé, S. A. 1999. Material safety data sheet according to 91/155 EC. Unpublished data submitted by CTFA, March 10, 1999 (4 pages).²
- Gerrard, J. M., and G. Graff. 1980. 1-Arachidonyl-monoglyceride causes platelet aggregation: Indirect evidence for an acylglycerol acylhydrolase involvement in the release of arachidonic acid for prostaglandin synthesis. *Prostaglandins Med.* 4:419–430.
- Giron, D., R. Link, and S. Bouissel. 1992. Analysis of mono-, di- and triglycerides in pharmaceutical excipients by capillary supercritical fluid chromatography. *J. Pharm. Biomed. Anal.* 10:821–830.
- Hayakawa, R., K. Matsunaga, M. Suzuki, Y. Arima, and Y. Ohkido. 1987. Lipstick dermatitis due to C18 aliphatic compounds. *Contact Dermatitis* 16:215–219.
- Henkel KgaA. 1994. Monomuls® 90-L12 (Glyceryl Laurate) Toxicological Evaluation. Unpublished data submitted by CTFA, January 27, 1999 (4 pages).²
- Henkel KgaA. 1996. Monomuls® 90-L12 (Glyceryl Laurate). Quality control and product descriptive data. Unpublished data submitted by CTFA, January 27, 1999 (2 pages).²
- Holland, K. T., D. Taylor, and A. M. Farrell. 1994. The effect of glycerol monolaurate on growth of, and production of toxic shock syndrome toxin-1 and lipase by, *Staphylococcus aureus*. *J. Antimicrob. Chemother.* 33:41–55.
- Huckle, W. R., and H. S. Earp. 1994. Regulation of cell proliferation and growth by angiotensin II. *Prog. Growth Factor Res.* 5:177–194.
- Hüls, A. G. 1996a. Prüfung der akuten oralen Toxizität von Imwitor 375 an der Ratte (Testing of the acute oral toxicity of Imwitor 375 [Glyceryl Citrate/Lactate/Linoleate/Oleate] on rats) (English translation) (Final Report No. AO-96/0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).²
- Hüls, A. G. 1996b. Prüfung der akuten dermalen Toxizität von Imwitor 375 an der Ratte (Testing of the acute dermal toxicity of Imwitor 375 on rats) (English translation) (Final Report No. AD-96/0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).²
- Hüls, A. G. 1996c. Prüfung auf akute augen- und schleimhautreizung von Imwitor 375 am Kaninchen (Testing for acute eye and mucous membrane irritation of Imwitor 375 on rabbits) (English translation) (Final Report No. AA-96/0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).²
- Hüls, A. G. 1996d. Prüfung auf akute hautreizwirkung von Imwitor 375 am Kaninchen (Testing of the acute skin irritation effect of Imwitor 375 on rabbits) (English translation) (Final Report No. AH-96/0182)). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).²
- Hüls, A. G. 1996e. Prüfung auf akute augen- und schleimhautreizung von Imwitor 375 am Kaninchen (Testing for sensitization of the skin of Imwitor 375 on guinea pigs [Buehler method]) (Final Report No. HS-96-0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).²
- Hüls, A. G. 1996f. *S. typhimurium* reverse mutation assay (Ames Test) (Final Report No. AM-96/9). Unpublished data submitted by CTFA, May 5, 1999 (25 pages).²
- Hüls America, Inc. no date. Product information on glyceryl citrate/lactate/linoleate/oleate, glyceryl stearate citrate, glyceryl cocoate, and glyceryl caprylate. Unpublished data submitted by CTFA (15 pages).²
- Informatics, Inc. 1973. *GRAS (Generally Recognized as Safe) Food Ingredients—Glycerine and Glycerides*. NTIS Report No. PB-221 227.
- Institut Français de Recherches et Essais Biologiques [IFREB]. 1977. Indice d'irritation oculaire chez le lapin. Indice d'irritation primaire cutanée chez le lapin. Unpublished data submitted by CTFA, March 10, 1999 (22 pages).²
- International Research Services, Inc. 1995. A study to assess the skin sensitization potential of four (4) test products when applied topically to the skin of healthy humans in a shared panel assay (IRSI 1241 1294PSL). Unpublished data submitted by CTFA (11 pages).²
- Ivy Laboratories. 1990. The determination of the contact-sensitizing potential of four materials by means of the maximization test. Lip gloss 90033-01 containing 2.0% glyceryl rosinate RI9149. Unpublished data submitted by CTFA (12 pages).²
- Ivy Laboratories. 1996. The determination of the contact-sensitizing potential of four materials by means of the maximization assay. Foundation 06636-11 containing 4.0% glyceryl rosinate (RI2326). Unpublished data submitted by CTFA (10 pages).²
- Jensen, P. A., and D. O'Brien. 1993. Industrial hygiene. In *Aerosol measurement. Principles techniques and applications*, eds. K. Willeke and P. A. Baron, 538–540. New York: John Wiley and Sons, Inc.
- Kabara, J. J. 1984. *Cosmetic and drug preservation. Principles and practice*, 305–322, 618, 740. New York: Marcel Dekker.
- Kabara, J. J., M. Ohkawa, T. Ikekawa, T. Katori, and N. Nishikawa. 1985. Examinations on antitumor, immunological, and plant-growth inhibitory effects of monoglycerides of caprylic, capric, and lauric acids and related compounds. *Pharmacol. Eff. Lipids* 13:263–272.
- Karlberg, A. 1988. Contact allergy to colophony. (VII). Sensitizing studies with oxidation products of abietic and related acids. *Acta Dermato-Venereol. Suppl.* 139:1–46.
- Kato, A., K. Ando, S. Suzuki, G. Tamura, and K. Arima. 1969. Antitumor activity of monoglycerides and other esters of fatty acids. *J. Antibiot.* 22:83–84.
- Kato, A., K. Ando, G. Tamura, and K. Arima. 1971. Effects of some fatty acid esters on the viability and transplantability of Ehrlich ascites tumor cells. *Cancer Res.* 31:501–504.
- Kimber, I., G. F. Gerberick, and D. A. Basketter. 1999. Thresholds in contact sensitization: Theoretical and practical considerations. *Food Chem. Toxicol.* 37:553–560.
- Lee, M. W., and D. L. Severson. 1994. Signal transduction in vascular smooth muscle: Diacylglycerol second messengers and PKC action. *Am. J. Physiol.* 267:C659–C678.
- Leo, A., C. Hansch, and D. Elkins. 1971. Partition coefficients and their uses. *Chemical Rev.* 71:525–616.
- Lévy, L., V. Alvaro, C. Dubray, and D. Joubert. 1994. Ca(2+)-dependent protein kinase C isoforms in rat pituitary hyperplasia: effect of *in vivo* treatment with quinagolide. *Eur. J. Pharmacol.* 16:327–334.
- Lewis, R. J., ed. 1993. *Hawley's condensed chemical dictionary*, 12th ed., 568, 1088, 1180. New York: Van Nostrand Reinhold.
- Lide, D. R., and H. P. R. Frederikse, eds. 1993. *CRC handbook of chemistry and physics. A ready reference book of chemical and physical data*, 74th ed., 3-260–3-261, 3-502–3-504. Boca Raton: CRC Press.
- Lyman, W. J., W. F. Reehl, and D. H. Rosenblatt. 1982. *Handbook of chemical property estimation methods*. New York: McGraw-Hill.
- Maruyama, K., and C. Yonese. 1986. Separation and quantitative determination of monoacylglycerol mixtures by reversed phase HPLC. *J. Am. Oil Chem. Soc.* 63:902–905.
- Mattson, F. H., and R. A. Volpenhein. 1964. The digestion and absorption of triglycerides. *J. Biol. Chem.* 239:2772–2777.
- McEwen, G. N., Jr. 2000. Memorandum on glyceryl rosinate and glyceryl hydrogenated rosinate to Dr. F. Alan Andersen, dated June 22, 2000.²
- National Academy of Sciences (NAS). 1960. *The safety of mono- and diglycerides for use as intentional additives in food* (NAS publication no. 251). Washington, DC: NAS.
- Niederpruem, H., H. Schweikert, J. W. Thueroff, and K. S. Zaenker. 1995. Inhibition of steroid 5 alpha-reductase activity by aliphatic fatty acids. Candidates for chemoprevention of prostate cancer. *Ann. N. Y. Acad. Sci.* 768:227–230.

- Nomura, H., A. Katsuhiko, K. Sekiguchi, U. Kikkawa, and Y. Nishizuka. 1986. *Biochem. Biophys. Res. Commun.* 140:1143-1151.
- Oh, D.-H., and D. L. Marshall. 1996. Monolaurin and acetic acid inactivation of *Listeria monocytogenes* attached to stainless steel. *J. Food Protection* 59:249-252.
- Okumura, M., Y. Nakamori, Y. Yoshida, H. Niwa, and Y. Sugibayashi. 1990. Effect of monoglycerides on the percutaneous absorption of papaverine hydrochloride. *Drug Des. Delivery* 6:137-148.
- Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International cosmetic ingredient dictionary and handbook*, 9th ed. Washington, DC: CTFA.
- Petschow, B. W., R. P. Batema, and L. L. Ford. 1996. Susceptibility of *Helicobacter pylori* to bactericidal properties of medium-chain monoglycerides and free fatty acids. *Antimicrob. Agents Chemother.* 40:302-306.
- Procter & Gamble Company. 1950. The comparative nutritive value of certain mono-, di-, and triglycerides. Submitted by FDA in response to an FOI request, 1998 (41 pages).²
- Projan, S. J., S. Brown-Skrobot, P. M. Schlievert, G. Vandenesch, and R. P. Novick. 1994. Glycerol monolaurate inhibits the production of beta-lactamase, toxic shock toxin-1, and other staphylococcal exoproteins by interfering with signal transduction. *J. Bacteriol.* 176:204-209.
- Rempe, J. M., and L. G. Santucci. 1997. *CTFA list of Japanese cosmetic ingredients*, 3rd ed. Washington, DC: CTFA.
- Sánchez-Piñera, P., V. Micol, C. Corbalán-García, and J. C. Gómez-Fernández. 1999. A comparative study of the activation of protein kinase C α by different diacylglycerol isomers. *Biochem. J.* 337:387-395.
- Saffiotti, U., and P. Shubik. 1963. Studies on promoting action in skin carcinogenesis. *Natl. Cancer Inst. Monogr.* 10:489-507.
- Schlievert, P. M., J. R. Deringer, M. H. Kim, S. J. Projan, and R. P. Novick. 1992. Effect of glycerol monolaurate on bacterial growth and toxin production. *Antimicrob. Agents Chemother.* 36:626-631.
- Scientific & Technical Information Network (STN) International. 1997. Properties of esters of glycerin and lauric acid. *Registry database file*. Columbus, OH: STN International.
- Shao, L. P., E. Gäfvert, A.-T. Karlberg, U. Nilsson, and J. L. G. Nilsson. 1993. The allergenicity of glycerol esters and other esters of rosin (colophony). *Contact Dermatitis* 31:11-17.
- Shin-Ei Chemical Company, Ltd. 1998. Material safety data sheet on glyceryl rosinatate, octyldecyl myristate. Unpublished data submitted by CTFA, June 22, 2000 (3 pages).²
- Takano, S., and Y. Kohdoh. 1987. Monoglyceride analysis with reversed phase HPLC. *J. Am. Oil. Chem. Soc.* 64:1001-1003.
- Tanaka, M., S. Shimizu, and S. Miyakawa. 1993. Contact dermatitis from glyceryl di-isostearate. *Contact Dermatitis* 29:41-42.
- Unichema International. 1997a. Isostearate esters of glycerol and polyglycerol: Safety evaluation. Unpublished data submitted by CTFA, May 4, 1998 (8 pages).²
- Unichema International. 1997b. Glyceryl monoesters of fatty acids: Safety evaluation. Unpublished data submitted by CTFA, May 4, 1998 (12 pages).²
- US Cosmetics Corporation. no date. A new product for cosmetics. Purified ester gum-2-octyldodecyl myristate (Purified Ester Gum/M.O.D.). Unpublished data submitted by CTFA, June 22, 2000 (4 pages).²
- US Cosmetics Corporation. 1998. PEG/MOD (Purified Ester Gum/M.O.D.). Unpublished data submitted by CTFA, June 22, 2000 (9 pages).²
- Witcher, K. J., R. P. Novick, and P. M. Schlievert. 1996. Modulation of immune cell proliferation by glycerol monolaurate. *Clin. Diagn. Lab. Immunol.* 3:10-13.

2

Final Report on the Safety Assessment of Glyceryl Ricinoleate

Glyceryl Ricinoleate is the monoester of glycerol and ricinoleic acid. Castor oil contains 87–90% Glycerol Ricinoleate. Ricinoleic acid is metabolized by both β -oxidation and α -oxidation.

Acute oral toxicity tests in mice indicated that Glyceryl Ricinoleate has an LD_{50} greater than 25.0 ml/kg and is, at most, mildly irritating to unrinsed rabbit eyes. This ingredient was not a primary skin irritant.

Castor oil was nonmutagenic by the Ames test. Ricinoleic acid was not a carcinogen when tested in mice.

In human single-insult occlusive patch tests, no indication of skin irritation potential was observed in the two products containing 5.6% Glyceryl Ricinoleate.

The available data on Glyceryl Ricinoleate were insufficient to determine whether this ingredient, under each relevant condition of use, was either safe or not safe. The types of data required before a decision can be made include: (1) 28 day chronic dermal toxicity in guinea pigs, and (2) clinical sensitization and photosensitization studies (or an appropriate ultraviolet spectrum instead of the photosensitization data).

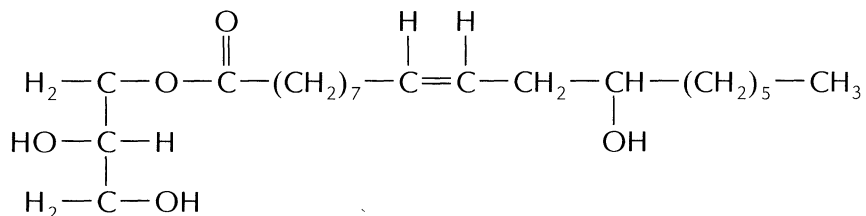
INTRODUCTION

The following report documents all the relevant published and unpublished data available to the Cosmetic Ingredient Review (CIR) on Glyceryl Ricinoleate. The CIR Expert Panel reviewed these data and concluded that additional information is required to substantiate the safety of Glyceryl Ricinoleate for use in cosmetic products. The types of data needed to assess the safety of this cosmetic ingredient are outlined in the Discussion section of this report.

CHEMISTRY

Glyceryl Ricinoleate is a monoglyceride obtained from the glycerolysis of castor oil.

Glyceryl Ricinoleate (CAS No. 141-08-2; 1323-38-2) is a monoester of glycerol and the fatty acid, ricinoleic acid or 12-hydroxy-*cis*-9-octadecenoic acid. The ricinoleic acid moiety is esterified to the α -carbon of glycerol.⁽¹⁾



Glyceryl Ricinoleate

Glyceryl Ricinoleate is a light yellow, oily liquid that has a characteristic odor. It is dispersible in water, slightly soluble in methanol, soluble in ethanol, ether, acetone, benzene, cottonseed oil, and ethyl acetate, and insoluble in mineral oil and aliphatic hydrocarbons.⁽²⁻⁴⁾ Glyceryl Ricinoleate is also known as α -monoricinolein, glyceryl or glycerol 1-monoricinoleate, or 1-mono-12-hydroxy-*cis*-9-octadecenoate.^(1,3)

The molecular weight of Glyceryl Ricinoleate is 372.55. Its density is 1.028 (20/4°C), and its boiling point has not been reported.^(2,3,5) Specifications for its cosmetic use include a minimum pour point of 35°F, a maximum acid value of 8.0, an iodine value between 70 and 90, and a saponification value between 160 and 170.

Analytical Methods

Methods for the analysis of Glyceryl Ricinoleate include gas chromatography of methyl ricinoleate derivatives,⁽⁶⁻⁸⁾ nuclear magnetic resonance spectrometry,^(9,10) high-performance liquid chromatography,⁽¹¹⁾ and infrared spectrometry.⁽⁶⁾ A chemical test for glycerol or its 1-monoglycerides involves periodate or lead tetra-acetate oxidation of primary alcohol groups and colorimetric quantization.^(6,12)

Reactivity

Reactions of Glyceryl Ricinoleate are primarily those of glycerol and ricinoleic acid and the glyceryl ester. Typical reactions include esterification, saponification, reduction and oxidation, hydrogenation, amide formation, epoxidation, halogenation, and dehydration.^(13,14)

Method of Manufacture and Impurities

Monoglycerides occur naturally in fats and oils that have become partially hydrolyzed.^(5,15) They are manufactured by reacting fatty acids or raw or hydrogenated fats and oils with an excess of glycerol or polyglycerols. The latter method, a glycerolysis reaction, depending on the molar ratios of the

reactants, can yield product mixtures containing varying amounts of monoglycerides.

Commercial glycerides, except preparations that have been fractionated, are usually mixtures of mono- and diglycerides and small quantities of triglycerides. These preparations may also contain free fatty acids and glycerol.⁽⁵⁾ Several grades of monoglycerides are available for different uses. A label of "40% monos" or "60% monos" refers to the monoglyceride content of the preparation.⁽¹⁵⁾ A higher monoglyceride content is usually obtained by fractional distillation.

The reported monoglyceride content includes both α - and β -monoglycerides and may also include glyceryl monoesters of other fatty acids, depending on the original fat or oil source used in the manufacturing process. The α -monoglyceride isomer predominates in these preparations; the β -monoglyceride readily isomerizes to form the α -monoglyceride.⁽¹⁵⁾

The commercial manufacture of Glyceryl Ricinoleate involves an alkali-catalyzed glycerolysis of castor oil, followed by distillation to concentrate the monoglyceride. Another method involves refluxing of reactants in a mutual solvent, such as phenol or pyridine and approximately 2.5% sodium bicarbonate. High-purity Glyceryl Ricinoleate can be synthesized by the reaction of isopropylidene glycerol (a product of the condensation of glycerol and acetone) with methyl ricinoleate in the presence of a sodium methoxide catalyst. The methyl ricinoleate is made by alkali-catalyzed methanolysis of castor oil.⁽¹³⁾

Castor oil, obtained from the seeds of the castor plant, *Ricinus communis* L., Euphorbiaceae, is composed of triglycerides of fatty acids, 87% to over 90% of which is ricinoleic acid.^(8,16,17) The quantity of ricinoleic acid may range from 84 to 90% of the fatty acid content in different castor bean varieties.⁽¹⁸⁾ Other fatty acids include oleic (7%), linoleic (3%), palmitic (2%), stearic (1%), and dihydroxystearic (trace) acids.

The cosmetic ingredient description of Glyceryl Ricinoleate did not contain data on the content or the quality of the Glyceryl Ricinoleate used by the cosmetic industry.⁽²⁾

COSMETIC USE

Glyceryl Ricinoleate was contained in 34 cosmetic formulations voluntarily reported in 1986 to the Food and Drug Administration by the cosmetic industry.⁽¹⁹⁾ Reported concentrations of Glyceryl Ricinoleate in these makeup preparations, primarily eye shadows, eyeliners, and lipsticks, ranged from 0.1 to 50% (Table 1). In lipsticks Glyceryl Ricinoleate is used as a base ingredient, and in eye shadows it is used as a pigment binder.⁽²⁰⁾

Voluntary filing of product formulation data with the U.S. Food and Drug Administration (FDA) by cosmetic manufacturers and formulators conforms to the tabular format listing preset ingredient concentration ranges and product categories in accordance with Title 21 Section 720.4 of the Code of Federal Regulations.⁽²¹⁾ Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic

formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration is a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration.

Cosmetic products containing Glyceryl Ricinoleate may be applied to all areas of the skin, including mucous membranes. They are frequently applied to the face and may contact the eyes. Lipstick products may be ingested. Products containing Glyceryl Ricinoleate may be applied up to several times per day and may remain in contact with the skin for as long as 8–12 h.

NONCOSMETIC USE

Monoglycerides of edible fats or oils are generally recognized as safe (GRAS) as emulsifying agents (21 CFR 182.4505)⁽²¹⁾ and as substances migrating to foods from paper and paperboard products (21 CFR 182.90)⁽²¹⁾

Monoglycerides can be indirect food additives as components of adhesives (21 CFR 175.105)⁽²¹⁾ and as components of defoaming agents in paper and paperboard manufacturing (21 CFR 176.210).⁽²¹⁾

Glyceryl Ricinoleate is listed as an allowable component of paper and paperboard contacting aqueous and fatty foods (21 CFR 176.170).⁽²¹⁾ Glycerol ester mixtures of ricinoleic acid containing no more than 50% Glyceryl Ricinoleate can be used as antifogging agents and concentrations not exceeding 1.5% (w/w) of permitted plasticized vinyl chloride polymer concentrations (21 CFR 178.3130).⁽²¹⁾

Castor oil and Glyceryl Ricinoleate were included in the 1982 FDA list of inactive ingredients for approved prescription drug products.⁽²²⁾

Castor oil is also used as an active ingredient in some over-the-counter (OTC) wart-remover drug products.⁽²³⁾ Ricinoleic acid is used in some OTC vaginal contraceptive drug products.⁽²⁴⁾

Other therapeutic applications for castor oil have been reviewed.⁽²⁵⁾ Various cultures have historically used castor oil in the treatment of digestive disorders, bronchitis, and cardiovascular congestion and as an antirheumatic and antiseborrheic. It is also used as an ointment for eye irritation and as a vehicle for ophthalmic solutions.⁽²⁶⁾

BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Absorption

Dietary monoglycerides like Glyceryl Ricinoleate are digested and absorbed as are triglycerides of the diet.⁽²⁷⁾ Following emulsification in the small intestine and hydrolysis of the ester bond, primarily by pancreatic lipase,⁽²⁵⁾

the monoglyceride moieties are absorbed into the intestinal mucosa by passive diffusion.

The enzymatic hydrolysis of Glyceryl Ricinoleate by pancreatic lipase is very rapid and yields glycerol and ricinoleic acid.⁽²⁸⁾ The fate of glycerol, a product of Glyceryl Ricinoleate hydrolysis, in intermediary metabolic pathways is well documented.⁽²⁸⁻³¹⁾ Following phosphorylation and oxidation, glycerol as dihydroxyacetone phosphate may be catabolized via the glycolytic pathway. Alternatively, glycerol may be re-esterified to fatty acids to form glycerides.

Since the glycerides of ricinoleic acid are major components of castor oil, data from studies of castor oil can be used to determine the properties of the absorption, metabolism, distribution, and excretion of ricinoleic acid.

Ricinoleic acid has been used as a marker for the detection of castor oil uptake in animals and humans. Following the intragastric administration of 1 ml of medicinal-grade castor oil, 24.2% ricinoleic acid was recovered in the chyle of four fed Sprague-Dawley rats and 6.8% was recovered in fasted rates.

In two Sprague-Dawley rats that received 0.2 and 0.6 ml castor oil via a cannula to the duodenum, the lower dose resulted in 18.1% ricinoleic acid in the chyle and 6.2% in the lipids of the small intestine, whereas the higher dose resulted in 3.0% ricinoleic acid in the chyle and 3.1% in lipids of the small intestine.⁽³²⁾

Methyl ricinoleate and glyceryl triricinoleate were hydrolyzed in vivo by rats administered 1 ml of these compounds by gavage.⁽³³⁾ Maximum concentrations of 49.9 and 22.7% free ricinoleic acid from respective administrations of methyl ricinoleate and glyceryl triricinoleate were detected 24 h later. Maximum concentrations of ricinoleic acid incorporated into glycerides after 24 h ranged from 18 to 39%.

When castor oil was withdrawn from the diet of rats, the ricinoleic acid accumulated over 4 weeks disappeared linearly with time.⁽³⁴⁾ No ricinoleic acid could be detected in the feces of rats by 48 h.

In humans, the absorption of castor oil was inversely related to the administered dose.⁽²⁸⁾ Medicinal-grade castor oil (90% ricinoleic acid content) containing a trace amount of [¹³¹I]castor oil (~ 6 μ Ci) was orally administered to human subjects at doses ranging from 4 to 61 g. At the 4 g dose, less than 1% of the radioactivity was found in fecal extracts of a treated subject, contrasted with 90% radioactivity in the fecal extracts of subjects given the 61 g dose. Most of the subjects receiving doses of 10 g or more excreted almost all the ingested radioactivity within the first 24 h following administration. The possibility that the addition of iodine to ricinoleic acid altered its pharmacology was noted. The intestinal absorption of castor oil and ricinoleic acid was inversely related to dose.^(28,34)

In a clinical study, the intestinal lumen of healthy human volunteers was perfused with 10 mM ricinoleic acid or oleic acid.⁽³⁵⁾ Oleic acid was absorbed twice as fast as ricinoleic acid (41.9 ± 7.3 versus 21.6 ± 2.6 μ mol/m per 25 cm, respectively).

Distribution

Monoenoic and saturated α -hydroxy fatty acids, primarily those ranging in lengths from 12 to 24 carbon atoms, have been isolated from several mam-

TABLE 1. Product Formulation Data for Glyceryl Ricinoleate

<i>Product category</i>	<i>Total no. of formulations in category</i>	<i>Total no. containing ingredient</i>	<i>No. of product formulations within each concentration range (%)</i>						
			<i>> 25–50</i>	<i>> 10–25</i>	<i>> 5–10</i>	<i>≥ 5</i>	<i>> 1–5</i>	<i>≥ 1</i>	<i>> 0.1–1</i>
Eye makeup preparations	1797	24	1	5	17				1
Hair-coloring preparations	85	1				1			
Lipstick	1552	7			3		4		
Skin-cleansing preparations (cold creams, lotions, liquids, and pads)	729	2						2	
1986 Totals		34	1	5	20	1	4	2	1

Source: From Reference 19.

malian tissues, including brain, spleen, lungs, kidneys, and sciatic nerve, rat skin, and bovine plasma.⁽³⁶⁾ The α -hydroxy fatty acids in mammalian brain tissue are components of cerebrosides, sulfatides, and a minor ganglioside.⁽³⁷⁾ An enzymatic system that converts nonhydroxy long-chain (20–26°C) fatty acids to the corresponding α -hydroxy fatty acids, detected in the brain, was closely integrated with cerebroside synthesis and myelin formation. Small quantities of ricinoleic acid have been isolated from the plasma, kidneys, lungs, and skin samples of the rat.⁽³⁶⁾

Feeding of ricinoleic acid, glyceryl triricinoleate (as castor oil), or methyl ricinoleate (for varying periods of time depending on the exact experiment conducted) to rats resulted in intestinal absorption, activation to form ricinoleoyl CoA,⁽³²⁾ and incorporation into triglycerides primarily of depot fat.^(33,38) Activation of ricinoleic acid by the mucosal thiokinase of the rat was less efficient than that of oleic acid.⁽³²⁾ There were no significant alterations in the general fatty acid composition of lymph lipids, except for the introduction of ricinoleic acid into triglycerides.⁽³³⁾

No ricinoleic acid was found in the liver or brain of rats fed 20% castor oil diets.⁽³²⁾ Ricinoleic acid was not incorporated into phospholipids of the small intestine, liver, or muscle or into glycerides of the liver of rats fed castor oil.^(38,39) The results of in vitro studies with epithelial microsomes of intestinal mucosa⁽³²⁾ and hepatic microsomes⁽⁴⁰⁾ of rats supported the in vivo findings of the preferential incorporation of ricinoleic acid into triglycerides rather than phospholipids.

Radioactivity from [¹²⁵I]castor oil and [¹²⁵I]hydrolyzed castor oil (primarily free [¹²⁵I]ricinoleic acid, but including [¹²⁵I]oleic and [¹²⁵I]linoleic acids) was measured in the blood, heart, liver, and kidneys of Swiss Webster albino mice following intravenous administration.⁽⁴¹⁾ Distinct patterns of uptake and release of radioactivity from the two iodinated preparations were observed in all tissues.

Metabolism

Ricinoleic acid can be a source of calories in some species of animals.^(42,43) After partial degradation of ricinoleic acid via β -oxidation yielding three molecules of acetyl-CoA (per molecule of ricinoleic acid), 6-hydroxy-*cis*-3,7-dodecenoyl-CoA would result. Further β -oxidation, requiring *trans*- α,β unsaturation, cannot continue. Two hypotheses for further degradation of the dodecenoic acid are (1) isomerization of the *cis*- β,γ double bond to the *trans*- α,β double bond and (2) hydration of the double bond followed by oxidation and cleavage.⁽⁴⁴⁾ The first pathway yields 6-hydroxy-*trans*-2,3-dodecenoyl-CoA, which can be further catabolized by β -oxidation to yield two more molecules of acetyl CoA and α -hydroxy-octanoyl-CoA. The second pathway yields a molecule of propionyl-CoA and 3-hydroxy-nonanoyl-CoA, which can be easily degraded by β -oxidation to three molecules of acetyl-CoA and one molecule of propionyl-CoA.

The α -oxidation pathway involving the cleavage of one carbon unit as carbon dioxide from the carbonyl terminus of fatty acids has been demonstrated in young plant leaves, germinating peanuts, bacteria, and hepatic mitochondria and microsomes of the brain of animals.^(29,36,45–47) Intermediates

of the pathway in *Escherichia coli*, in brain microsome cultures from animals, and in leaves of plants are 2-hydroxy fatty acids.^(47–49)

Ricinoleic, hydroxyhexadecenoic, hydroxytetradecenoic, and hydroxydodecenoic acids were isolated from the fat of rats fed ricinoleic acid or castor oil.^(50,51) The hydroxymonoenoic acids of 12-, 14-, and 16-carbon lengths were similar to the metabolites of ricinoleic acid obtained from degradation by *E. coli* cultures, two of which were characterized as 8-D-(+)-hydroxy-*cis*-5-tetradecenoic⁽⁵²⁾ and 6-hydroxy-*cis*-3-dodecenoic acid.⁽⁵³⁾

Excretion

Hydroxystearic acid was found in the feces of humans, rats, and dogs with steatorrhea.^(54–56)

Bacterial hydrogenation of ricinoleic acid in the intestinal lumen was proposed as the explanation for the finding of hydroxystearic acid in the feces of rats fed castor oil in the diet (20% w/w).⁽³²⁾ After synthesis by intestinal bacteria, the hydroxy acids in these systems were absorbed via the portal system and excreted in the bile in an enterohepatic circulation. The proposed reaction forming the hydroxy acids involved hydration of the double bond in unsaturated fatty acids rather than oxidation of saturated fatty acids. Several species of fecal bacteria were able to hydrate unsaturated long-chain fatty acids.⁽⁵⁷⁾

After evaluation by absorption, metabolism, distribution, and toxicity of glycerol and mono- and diglycerides (from edible fats and oils), the select committee on GRAS substances found no evidence that indicated a hazard to the public from these compounds at reported concentrations of use.^(27,58)

Cathartic Properties

The hydrolysis of castor oil and Glyceryl Ricinoleate releases ricinoleic acid, which is the pharmacologically active ingredient responsible for the strong cathartic properties of castor oil.⁽⁵⁹⁾ Catharsis usually occurs 4–8 h following the administration of castor oil.⁽²⁶⁾

Ricinoleic acid inhibited water and electrolyte absorption from the small and large intestine of animals and humans.^(35,60–62) It depressed the contractile activity of intestinal circular smooth muscle.^(63,64) A dose-dependent cytotoxicity for ricinoleic acid ranging from 0.1 to 2.0 mM was observed in vitro in epithelial cells from the small intestine of hamsters.⁽⁶⁵⁾ Furthermore, ricinoleic acid caused erosion of intestinal villi and disorganization of the microvillous surface detected by scanning electron microscopy, indicating the potential malabsorption of nutrients due to its long-term use.⁽⁶⁶⁾ The mechanisms of action of ricinoleic acid involved in catharsis have been studied.^(25,34,67,68)

Several studies have been done to delineate the clinical effects of the use of ricinoleic acid as a laxative. Fluid secretion was increased and intraluminal cell loss was reported in the intestines of human subjects perfused with 5 and 10 ml ricinoleic acid.^(35,69)

The advisory review panel on OTC laxative, antidiarrheal, emetic, and antiemetic drug products concluded that castor oil was safe and effective taken orally as a single dose.⁽⁷⁰⁾ The active ingredient, ricinoleic acid, is

thought to promote bowel movement by inducing the colonic secretion of water and electrolytes. The panel noted that there was "no experimental evidence to support the assumption that the laxative acts to increase peristalsis through a direct irritant effect on the intestinal mucosa." It was concluded that regular peroral use of castor oil may cause excessive loss of water, electrolytes, and unabsorbed nutrients, precluding its repeated administration.

The use of OTC laxatives like castor oil was associated with the development of a dependence on the laxatives to ensure regular bowel movement.⁽⁷¹⁾ The frequent and prolonged use of irritant cathartics may, in turn, result in the development of a "cathartic colon," a poorly functioning large intestine, which radiologically and pathologically resembles chronic ulcerative colitis.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Glyceryl Ricinoleate was evaluated for acute oral toxicity in mice. A preliminary range-finding study was performed using doses of 5.0, 10.0, 20.0, and 25.0 ml/kg, administered by cannula, on groups of two mice each. The mice were observed from the time of dosing until the end of a 7 day period. The results of this test were used to determine doses to be used for the final study. In a preliminary study, none of the mice died. The doses of Glyceryl Ricinoleate used in the final study were 12.5, 20.0, and 25.0 ml/kg. Test groups consisted of 10 mice each. Over the 7 day period, none of the mice at the lowest dose level died. In the 20.0 ml/kg group one mouse died within 24 h of dosing, and two mice died between days 4 and 7 in the 25.0 ml/kg group. The two mice that died in the high-dose group previously had a loss of body weight, as did others of the test animals (especially on day 7). Other signs noted in the test animals were piloerection within 30 minutes after dosing and inactivity within 2 h after dosing. All surviving animals appeared to be asymptomatic after day 7. It was concluded that the LD₅₀ value for Glyceryl Ricinoleate exceeded 25.0 ml/kg.⁽⁷²⁾

The acute oral toxicity of products containing Glyceryl Ricinoleate was tested in rats. In the first test, five rats were dosed by oral intubation with 15.0 g/kg of a product containing 5.6% Glyceryl Ricinoleate. The product was administered in corn oil, with a final Glyceryl Ricinoleate test concentration listed as 33.3%. None of the rats died, and all gained weight over the 7 day observation period.⁽⁷³⁾ The second test was identical to the first, except that a different unspecified product was used. As in the first test, none of the five rats died when dosed with 15.0 g/kg of the product in corn oil, and all gained weight over the 7 day observation period.⁽⁷⁴⁾ The third test was performed in the same manner as the first two, once again the exception being the product type tested. As the previous tests indicated, the product was nontoxic when ingested, and the five rats all gained weight during the study.⁽⁷⁵⁾

Skin and Tissue Irritation

Four New Zealand white rabbits were used in a Draize skin test of Glyceryl Ricinoleate. A 0.5 ml sample of the test substance was placed on the

clipped and intact and clipped and abraded skin of each rabbit. An occlusive patch was then placed over each test site, where it remained for 24 h. The test sites were scored by the method of Draize upon the removal of the patches and 48 h later (24 and 72 h readings). The average of the two scores was the primary irritation index (PII). Two of the rabbits had very slight erythema at both the intact and abraded sites at the 24 h reading, and the reaction of the abraded site of one of these rabbits persisted through the 72 h reading. A third rabbit had well-defined erythema at both sites at the 24 h reading, with the reaction at the abraded site again persisting with the same intensity through the 72 h reading. This same rabbit also had a slight edema at the abraded site at the 72 h reading. The fourth rabbit tested had no reactions. The PII was determined to be 0.75, and it was concluded that the Glyceryl Ricinoleate was mildly irritating.⁽⁷⁶⁾

A primary irritation study with rabbits was performed on Glyceryl Ricinoleate using the solid product, undiluted, as it was supplied by the manufacturer. The Glyceryl Ricinoleate, 5.0 g, was applied to the clipped and intact (left flank) and clipped and abraded (right flank) skin of six albino New Zealand white rabbits. Composite patches were placed over the test sites, remaining in place for 24 h. The sites were graded at 24 h and again at 72 h according to the method of Draize. All rabbits had scores of 0 for both erythema and edema formation, resulting in a group total mean score and a primary irritation score of 0.0. Glyceryl Ricinoleate was thus classified as a nonirritant to the skin.⁽⁷⁷⁾

The primary skin irritation of various unspecified products containing 5.6% Glyceryl Ricinoleate was tested in rabbits using an occlusive patch single-insult test procedure. The maximum obtainable PII was 4. In the first test, the nine rabbits had scores of 0 at 2 and 24 h after removal of the patch, resulting in a group PII score of 0.00.⁽⁷⁸⁾ The results of the second, third, and fourth tests were identical, the group PII being 0.00, indicating that the test products were nonirritating.⁽⁷⁹⁻⁸¹⁾ In another test, rabbit 9 had a score of $\frac{1}{2}$ at the 2 h grading, but this had reduced to 0 by the 24 h grading. The other eight rabbits all had scores of 0 at both grading times. The group PII was 0.06, indicating that the test material was minimally irritating.⁽⁸²⁾ In the final test, all rabbits had scores of 0 at both grading times, resulting in a group PII score of 0.00, indicating that the product tested was nonirritating.⁽⁸³⁾

In a study of tissue irritation, injections of 0.5 ml of Glyceryl Ricinoleate were administered bilaterally into the pectoral muscle of six male Hubbard crossbred chickens weighing 3–4 pounds. On days 1, 3, and 7 postinjection, two chickens were killed and examined for the determination of gross lesions at the injection site. Sites were examined for inflammation and necrosis (scale of 1–5). Scores of 1 (three of six chickens) and 3 (two of six chickens) were reported. The right pectoral muscles of two chickens had necrotic foci (grade 5) on days 1 and 7. Glyceryl Ricinoleate caused moderate irritation and was not absorbed (i.e., the compound was visible at the treatment of sites of all six chickens).⁽⁸⁴⁾

After intravenous administration of a bolus of 0.1 ml/kg technical-grade ricinoleic acid into the inferior venae cavae of eight dogs, five dogs developed tachypnea (increase of at least five breaths per minute over the basal rate) and two dogs died from circulatory arrest.⁽⁸⁵⁾ No other clinical signs, such as

erythema, hives, edema, or defecation, were noted. Ricinoleic acid regularly produced an immediate decrease in blood pressure occasionally followed by a second hypotensive response that was not associated with histamine release. Increased histamine ranging from 0.6 to 15.3 ng/ml in the blood of seven dogs was observed within 2 minutes of administration of ricinoleic acid.

Eye Irritation

A 0.1 ml sample of Glyceryl Ricinoleate was placed into one eye of each of nine New Zealand white rabbits. Three of the rabbits had the test material rinsed from their eyes with 20 ml of lukewarm water 2 s after instillation, three rabbits had their eyes rinsed 4 s after instillation, and 3 rabbits did not have their eyes rinsed. In all the rabbits, the contralateral eye served as an untreated control. The eyes were graded for damage according to the Draize system for scoring ocular lesions at 1, 2, 3, 4, and 7 days after instillation of the test material. No irritation was observed in the eyes that had been rinsed, and only mild irritation of the conjunctiva, lasting no longer than 24 h, was noted in the eyes that were not rinsed.⁽⁷⁶⁾

Into the conjunctival sac of the right eye of each of six albino New Zealand white rabbits was instilled 0.10 g undiluted Glyceryl Ricinoleate. The left eye of each rabbit served as the untreated control. The eyes were examined at 24, 48, and 72 h after instillation of the test material, and irritation was scored according to Draize and the Federal Register 1973. An ophthalmoscope was used to examine the eyes, and ultraviolet light and fluorescein dye were used to determine the incidence of corneal opacities. All test animals had scores of 0 throughout the 3 day observation period, resulting in a group mean 3 day score of 0.0. Glyceryl Ricinoleate was classified as negative for irritation or a nonirritant to the eye.⁽⁸⁶⁾

A group of unspecified products, all but one containing 5.6% Glyceryl Ricinoleate (the exception contained 6.2% Glyceryl Ricinoleate), was tested for eye irritation. In the first six tests, the protocol was the same and is summarized here. The product was applied to 100% concentration to the eyes of six rabbits (per product tested). The product was applied three times, the eyes were not rinsed, and anesthesia was not used. With one exception, the eyes were scored daily for 3 days after application of the test product; in the other case, the eyes were scored for the first 4 days and again on day 7. The irritation was scored by the Draize classification of eye irritation. In test 1, all rabbits scored 0 at all times, the resulting conclusion being that the product tested did not have the potential for eye irritation.⁽⁸⁷⁾ In test 2, rabbit 3 had corneal opacity, iritis, and redness, swelling, and discharge of the conjunctiva (scores of 5, 5, and 4, respectively) on day 1. This resulted in a total score of 3 for the day. On days 2 and 3, all rabbits scored 0, leading to the conclusion that the product tested had a minimal irritation potential.⁽⁸⁸⁾ In test 3, rabbit 3 scored a 2 for conjunctival redness, swelling, and discharge on day 2, resulting in a total score of 1 for the day. On days 1 and 3, the scores were 0, leading to the conclusion that the product tested had a minimal irritation potential.⁽⁸⁹⁾ In test 4, the total score for day 1 was 2, with rabbit 3 having scores of 5 and 6 for corneal opacity and conjunctival redness, swelling, and discharge, respec-

tively. On days 2 and 3 all scores were 0, and it was concluded that the product tested had a minimal irritation potential.⁽⁹⁰⁾ In test 5, the concentration of Glyceryl Ricinoleate in the product tested was 6.2%. On day 1, rabbit 6 scored 2 for conjunctival redness, swelling, and discharge, for a group total score of 1. The same situation occurred with rabbit 2 on day 2, and the condition with this rabbit persisted into day 3. Also on day 3, rabbit 3 scored 5 for corneal opacity and 10 for conjunctival reactions. The group total score for day 3 was 3. On day 4, a conjunctival score of 2 remained for rabbit 3. By day 7, all rabbits were scored as 0. The conclusion reached was that the product tested had a mild irritation potential.⁽⁹¹⁾ In test 6, rabbits 1–3 scored 1 for conjunctival reactions on day 2, resulting in a group total score of 1 for that day. For days 1 and 3 the group total scores were 0, and the conclusion was that the product tested had a minimal eye irritation potential.⁽⁹²⁾ In test 7, the product was tested at a concentration of 50% in corn oil, and all scores for all rabbits were 0, indicating that the product tested did not have a potential for irritation.⁽⁹³⁾ In test 8, the product was also tested at a concentration of 50% in corn oil. On day 1, rabbits 1, 4, and 5 scored 2 for conjunctival reactions, and rabbits 2 and 6 scored 4 for the same category. The group total score for day 1 was 2. On day 2, rabbits 3 and 4 scored 2 for conjunctival reactions, and rabbits 2 and 6 remained in the same condition as the previous day. The group total score for day 2 was 2. On day 3, all rabbits scored 0. The conclusion was that the product tested had a minimal irritation potential.⁽⁹⁴⁾

A final report on the “toxicity testing” of castor oil is expected from the National Toxicology Program.⁽⁹⁵⁾

MUTAGENICITY AND CARCINOGENICITY

Castor oil was negative for mutagenicity when tested by the Ames assay by the National Toxicology Program.⁽⁹⁶⁾

A volume of 0.1 ml of a 2% ricinoleic acid preparation in gum tragacanth was injected intravaginally into 20 BALB/c female mice twice weekly for a total of 100 injections.⁽⁹⁷⁾ No tumors were seen in the 20 treated or in the 30 untreated mice. Of the 20 positive control mice treated with 0.3% 7,12-dimethylbenz(a)anthracene, also in gum tragacanth, 15 developed squamous cell carcinomas of the vagina and/or perineal skin.

Castor oil is currently being evaluated for carcinogenicity by the National Toxicology Program.⁽⁹⁵⁾

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation and Sensitization

The skin irritation potential of Glyceryl Ricinoleate was evaluated in 20 human test subjects. An unspecified product containing 5.6% Glyceryl Ricinoleate was applied at full strength to occlusive patches, which were then applied in a single insult to the test subjects. The PII of the test product was 0.0, indicating that the product containing 5.6% Glyceryl Ricinoleate was not an irritant.⁽⁹⁸⁾

In a second irritation potential test, the PII for an unspecified product containing 5.6% Glyceryl Ricinoleate was also 0.0. In this test, the number of panelists was 19, and as before, the product was applied on an occlusive patch as a single insult. Again the conclusion was that the product containing 5.6% Glyceryl Ricinoleate was not an irritant.⁽⁹⁹⁾

Castor beans, the source of castor oil from which ricinoleic acid is isolated, contain a toxic polypeptide, ricin, at an approximate concentration of 3%.^(100,101) Clinical cases of castor bean skin allergy and asthma have been associated with ricin or "a protein component,"⁽¹⁰²⁻¹⁰⁴⁾ not within the ricinoleic acid component of the castor bean.

A few cases of lipstick dermatitis have been reported. A 3+ positive reaction to castor oil, an ingredient in a makeup remover, was observed upon series testing of cosmetics and their ingredients after a 23-year-old woman reported acute facial dermatitis.⁽¹⁰⁵⁾

After testing with ingredients of lipsticks and lip creams, a 22-year-old woman who had developed dry and painful cracking of the lips reacted with a 2+ response 48 and 72 h after application of castor oil.⁽¹⁰⁶⁾ In follow-up testing, this subject had similar reactions to purified castor oil, ricinoleic acid, and a 3% preparation of ricinoleic acid in petrolatum.⁽¹⁰⁷⁾ Tests with other fatty acids ingredients of castor oil were negative.

A 29-year-old female with a history of dermatitis to deodorant developed an acute edematous dermatitis of the lips and perioral area spreading to the entire face and neck after a few weeks of use of a lipstick product.⁽¹⁰⁸⁾ In a series of three patch tests, the subject had 2+ reactions to a standard test series (20% colophony in petrolatum) and to the lipstick formulation in the first test, 2+ reactions to castor oil and 1% octyl-dimethyl-*p*-aminobenzoic acid in petrolatum, and a 3+ reaction to 0.5% aqueous allantoin in the second test. The third test resulted in a 3+ reaction to castor oil, a severe (3+) spreading reaction to 30% ricinoleic acid in petrolatum, and negative responses to the *p*-aminobenzoic acid derivative and allantoin preparations.

Other cases of dermatitis resulting from the same lipstick formulation were reported previously.⁽¹⁰⁹⁾ A 53-year-old male with no history of skin disease developed periorbital and facial edema with lesions on the lips and in the nose. A 36-year-old male with no history of skin disease developed a severe dermatitis on the lips and around the mouth. A 37-year-old female with a family history of psoriasis and hand eczema developed severe, vesicular dermatitis on the lips and around the mouth. All three subjects had 2+ reactions to the lipstick formulation and to "a microcrystalline wax" ingredient of unknown composition.

SUMMARY

Glyceryl Ricinoleate is the monoester of glycerol and ricinoleic acid. It is an oily liquid with a characteristic odor.

Glyceryl Ricinoleate is most frequently used in cosmetic as a base ingredient in lipsticks and as a pigment binder in eye shadows. Its use in cosmetic

formulations has been reported at concentrations between 0.1 and 50%. In 1986, it was used in a total of 34 cosmetic formulations.

Monoglycerides of edible fats and oils are generally recognized as safe for use as emulsifying agents and food additives. Glyceryl Ricinoleate is listed by the FDA as an inactive ingredient in drug preparations. Castor oil is used as an active ingredient in some OTC wart-removing products, and ricinoleic acid is used in some OTC vaginal contraceptives. Castor oil is also considered a safe and effective laxative when taken orally as a single dose.

Upon ingestion, Glyceryl Ricinoleate is absorbed into the intestinal mucosa. Increased doses of castor oil result in decreased absorption by the intestine.

Ricinoleic acid appears to be preferentially incorporated into the triglycerides rather than the phospholipids.

Metabolically, ricinoleic acid may be degraded by β -oxidation into acetyl-CoA and a dodecanoyl-CoA. This dodecanoic acid may be further metabolized either by hydration followed by oxidation and cleavage or by isomerization of the double bond. Another metabolic pathway involving the α -oxidation of a carbon unit from the carboxyl terminus of the fatty acid has also been observed.

Acute oral toxicity tests indicated that Glyceryl Ricinoleate has an LD₅₀ greater than 25.0 ml/kg in mice and that products containing 5.6% Glyceryl Ricinoleate were not toxic when ingested.

The feeding of castor oil to rats results in the presence of hydroxystearic acid in the feces. The hydroxystearic acid is probably formed by bacterial hydrogenation of ricinoleic acid.

The hydrolysis of castor oil and Glyceryl Ricinoleate in the small intestine releases ricinoleic acid; ricinoleic acid is the active cathartic ingredient in castor oil. The mechanisms of the cathartic action of ricinoleic acid are currently being studied.

Glyceryl Ricinoleate, when evaluated by a Draize skin test, was a mild irritant to rabbits. In a primary skin irritation test in rabbits, Glyceryl Ricinoleate was classified as a nonirritant.

When rabbits were tested with products containing 5.6% Glyceryl Ricinoleate in a single-insult occlusive patch test, the products had either no (four of five tests) or mild (one of five tests) irritation potentials.

Injection of Glyceryl Ricinoleate into the pectoral muscles of chickens caused mild irritation at the site of injection, but no Glyceryl Ricinoleate was absorbed.

Glyceryl Ricinoleate was nonirritating to rabbit eyes in a primary eye irritation test, and in a Draize test, it was mildly irritating to rabbit eyes from which it was not rinsed but nonirritating to rabbit eyes from which it had been rinsed 2 and 4 s after instillation. Various products containing Glyceryl Ricinoleate were tested for irritation potential in rabbit eyes. Of eight tests, two products demonstrated no irritation potential, five products had a minimal irritation potential, and one product had a mild irritation potential.

Castor oil was nonmutagenic by the Ames test. Carcinogenicity testing in female mice using ricinoleic acid, a possible constituent ingredient of spermicidal preparations, yielded negative results.

In human single-insult occlusive patch tests, no indication of skin irritation potential was observed in the two products tested (each contained 5.6% Glyceryl Ricinoleate).

There have been several reported instances of lipstick dermatitis, and castor oil and ricinoleic acid have been implicated in clinical patch test studies on patients experiencing dermatitis, and occasional facial edema, from the use of lipsticks.

DISCUSSION

Section 1 Paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the expert panel informed the public of its decision that the data on Glyceryl Ricinoleate were insufficient to determine that this ingredient, under each relevant condition of use, was either safe or not safe. The panel issued a "Notice of Insufficient Data" on January 29, 1987, outlining the data needed to assess the safety of Glyceryl Ricinoleate. The types of data required included:

1. Guinea pigs 28 day chronic dermal toxicity
2. Clinical sensitization and photosensitization studies (or an appropriate ultraviolet spectrum instead of the photosensitization data)

There has been no response or indication of intent to supply the aforementioned information.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of Glyceryl Ricinoleate as used in cosmetics.

REFERENCES

1. ESTRIN, N.F., CROSLEY, P.A., and HAYNES, C.R. (eds.). (1982). *Cosmetic, Toiletry and Fragrance Association Cosmetic Ingredient Dictionary*, 3rd ed. Washington, D.C.: The Cosmetic, Toiletry and Fragrance Association.
2. ESTRIN, N.F., HAYNES, C.R., and WHELAN, J.M. (eds.). (1982). *CTFA Compendium of Cosmetic Ingredient Compositions. Cosmetic Ingredient Descriptions*. Washington, D.C.: The Cosmetic, Toiletry and Fragrance Association.
3. WEAST, R.C. (1984). *CRC Handbook of Chemistry and Physics*, 65th ed., 1984–1985. Boca Raton, FL: CRC press, p. C-314.
4. GREENBERG, L.A., and LESTER, D. (1954). *Handbook of Cosmetic Materials*. New York: Interscience.
5. GRAYSON, M. (1984). *Kirk-Othmer Encyclopedia of Chemical Technology*, Vol. 11. New York: John Wiley and Sons, p. 931.

6. SENZEL, A.J. (ed.). (1977). *Newburger's Manual of Cosmetic Analysis*, 2nd ed. Washington, D.C.: AOAC.
7. PAULUS, G.L. and CHAMPION, M.H. (1972). Gas-liquid chromatographic determination of castor oil as methyl ricinoleate in lipstick. *J. Soc. Cosmet. Chem.* **23**, 313–9.
8. BINDER, R.G., APPLEWHITE, T.H., KOHLER, G.O., and GOLDBLATT, L.A. (1962). Chromatographic analysis of seed oils. Fatty acid composition of castor oil. *J. Am. Oil Chem. Soc.* **39**, 513–7.
9. KRESZE, G., BEDERKE, K., and SCHAEVFFELHUT, F. (1965). Analysis of mixtures of mono- and diglycerides by gas chromatography and nuclear magnetic resonance. *Z. Anal. Chem.* **209**(2), 329–37.
10. TEUPEL, M., POLLERBERG, J. (1968). Analysis of ricinoleic acid monoglycerides by column chromatography and nuclear magnetic resonance spectroscopy (German abstract). *Tenside* **5**(9–10), 275–8.
11. KING, J.W., ADAMS, E.C., and BIDLINGMEYER, B.A. (1982). Determination of free fatty acids in natural oils and alkyd resins by high-performance liquid chromatography. *J. Liquid Chromatogr.* **5**(2), 275–304.
12. HORWITZ, W. (ed.). (1980). *Official Methods of Analysis of the Association of Official Analytical Chemists (AOAC)*, 13th ed. Washington, D.C.: AOAC.
13. ACHAYA, K.T. (1971). Chemical derivatives of castor oil. *J. Am. Oil Chem. Soc.* **48**(11), 758–63.
14. RONDEAU, R. (1968). La lipochimie de l'huile de ricin. *Rev. Fr. Corps Gras* **15**(8–9), 529–37.
15. SWERN, D. (ed.). (1979). *Bailey's Industrial Oil and Fat Products*, Vol. 1, 4th ed. New York: John Wiley and Sons.
16. WINDHOLZ, M., BUDAVARI, S., BLUMETTI, R.F., and OTTERBEIN, E.S. (eds.). (1983). *The Merck Index*, 10th ed. Rahway, NJ: Merck and Co.
17. HUNTING, A.L.L. (1983). *Encyclopedia of Shampoo Ingredients*. Cranford, NJ: Micelle Press.
18. RAMOS, L.C., TANGO, J.S., SAVI, A., and LEAL, N.R. (1984). Variability for oil and fatty acid composition in castor bean varieties. *J. Am. Oil Chem. Soc.* **61**(12), 1841–3.
19. FOOD AND DRUG ADMINISTRATION (FDA). (1986). Cosmetic product formulation data table.
20. EIERMANN, H.J. (June 12, 1986). Acting Director, Division of Colors and Cosmetics, Food and Drug Administration. Letter to R.L. Elder, of Cosmetic Ingredient Review, on oleic acid group, methylene chloride, and Glyceryl Ricinoleate. Available for review: Director, Cosmetic Ingredient Review, 1110 Vermont Ave., N.W., Suite 810, Washington, D.C. 20005.
21. CODE OF FEDERAL REGULATIONS (CFR). (1984). Title 21. Food and Drugs. Parts 175.105, 176.170, 176.210, 178.3130, 182.90, 182.4505, 720.4.
22. BROWN, J.L. (1983). Incomplete labeling of pharmaceuticals: A list of "inactive" ingredients. *N. Engl. J. Med.* **309**(7), 439–41.
23. FEDERAL REGISTER. (Sept. 3, 1982). Wart remover drug products for OTC human use; tentative final monograph. **47**(172), 39103.
24. FEDERAL REGISTER. (May 24, 1972). Certain OTC vaginal contraceptives. Drugs for human use; drug efficacy study implementation. **37**(101), 10525.
25. SCARPA, A., and GUERCI, A. (1982). Various uses of the castor oil plant (*Ricinus communis* L.). A review. *J. Ethnopharmacol.* **5**(2), 117–37.
26. BLACOW, N.W. (1972). *Martindale. The Extra Pharmacopeia*, 26th ed. London: Pharmaceutical Press, p. 1256.
27. FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY (FASEB), Life Sciences Research Office. (1975). Evaluation of the health aspects of glycerin and glycerides as food ingredients. U.S. Department of Commerce. NTIS PB-254536.
28. WATSON, W.C., GORDON, R.S., Jr., KARMEN, A., and JOYER, A. (1963). The absorption and excretion of castor oil in man. *J. Pharm. Pharmacol.* **15**, 183–8.
29. FLORKIN, M., and STOTZ, E.H. (eds.). (1971). *Lipid Metabolism*, Vol. 18, *Comprehensive Biochemistry*. New York: Elsevier.
30. ELDER, R.L. (ed.). (1982). Final report on the safety assessment of decyl and isodecyl oleates. *J. Am. Coll. Toxicol.* **1**(2), 85–95.
31. COSMETIC INGREDIENT REVIEW. (Nov. 13, 1985). Final report on glyceryl oleate. Available for review: Director, Cosmetic Ingredient Review, 1110 Vermont Ave., N.W., Suite 810, Washington, D.C. 20005.
32. WATSON, W.C., and GORDON, R.S., Jr. (1962). Studies on the digestion, absorption and metabolism of castor oil. *Biochem. Pharmacol.* **11**, 229–36.
33. RAO, M.K.G., RISSER, N., and PERKINS, E.G. (1969). The incorporation of ricinoleic acid into rat lymph lipids. *Proc. Soc. Exp. Biol. Med.* **131**(4), 1369–72.
34. GAGINELLA, T.S., and PHILLIPS, S.F. (1975). Ricinoleic acid: Current view of an ancient oil. *Am. J. Dig. Dis.* **20**(12), 1171–7.

35. AMMON, H.V., THOMAS, P.J., and PHILLIPS, S.F. (1974). Effects of oleic and ricinoleic acid on net jejunal water and electrolyte movement. *J. Clin. Invest.* **53**, 374–9.
36. KISHIMOTO, Y., AND RADIN, N.S. (1963). Occurrence of 2-hydroxy fatty acids in animal tissues. *J. Lipid Res.* **4**(2), 139–43.
37. AKANUMA, H., and KISHIMOTO, Y. (1979). Synthesis of ceramides and cerebroside containing both alpha-hydroxy and non-hydroxy fatty-acids from lignoceroyl-CoA by rat-brain microsomes. *J. Biol. Chem.* **254**(4), 1050–6.
38. STEWART, W.C., and SINCLAIR, R.G. (1945). The absence of ricinoleic acid from phospholipids of rats fed castor oil. *Arch. Biochem.* **89**, 7–11.
39. WATSON, W.C., and MURRAY, E.S. (1965). Triricinolein synthesis in vivo. *Biochim. Biophys. Acta* **106**(2), 311–4.
40. BARBER, E.D., SMITH, W.L., and LANDS, W.E.M. (1971). Incorporation of ricinoleic acid into glycerolipids. *Biochim. Biophys. Acta* **248**(2), 171–9.
41. HALLABA, E., AL-SUHYBANI, A., ABDULLAH, M.E., and ZAKI, F.S. (1985). Labelling of castor oil for myocardial study. *J. Radioanal. Nucl. Chem.* **89**(1), 97–107.
42. PAUL, H., and McCAY, C.M. (1942). The utilization of fats by herbivora. *Arch. Biochem. Biophys.* **1**, 247.
43. PERKINS, E.G., ENDRES, J.G., and KUMMEROW, F.A. (1961). The metabolism of fats. I. Effect of dietary hydroxy acids and their triglycerides on growth, carcass, and fecal fat composition in the rat. *J. Nutr.* **73**, 291.
44. NUTRITION REVIEWS. (1970). Oxidation of unsaturated fatty acids. **28**(6), 165–67.
45. MORRIS, L.J. (1970). Mechanisms and stereochemistry in fatty acid metabolism. *Biochem. J.* **118**(5), 681–93.
46. BOWEN, D.M., and RADIN, N.S. (1968). Hydroxy fatty acid metabolism in the brain. *Adv. Lipid Res.* **6**, 255–72.
47. FULCO, A.J. (1974). Metabolic alterations of fatty acids. *Annu. Rev. Biochem.* **43**, 215–41.
48. LEKAKIS, N.J. (1977). Alpha-oxidation of fatty acids in *Escherichia coli*. *FEMS Microbiol. Lett.* **1**(5), 289–92.
49. GUNSTONE, F.D. (1967). *An Introduction to the Chemistry and Biochemistry of Fatty Acids and Their Glycerides*. Great Britain: Richard Clay (The Chancer Press) Ltd.
50. UCHIYAMA, M., SATO, R., and MIZUGAKI, M. (1963). *Biochim. Biophys. Acta* **70**, 344–6.
51. OKUI, S., UCHIYAMA, M., SATO, R., and MIZUGAKI, M. (1964). *J. Biochem.* **55**, 81–6.
52. OKUI, S., UCHIYAMA, M., and MIZUGAKI, M. (1963). *J. Biochem.* **53**, 265–70.
53. MIZUGAKI, M., FUKUYAMA, H., SAKAMOTO, T., and YAMANAKA, H. (1978). Studies on the metabolism of unsaturated fatty acids. I. Synthesis and identification of 6-hydroxydodec-3-cis-enoic acid, the final metabolite of ricinoleic acid by *Escherichia coli* K-12. *Chem. Pharm. Bull.* **6**(8), 2417–21.
54. JAMES, A.T., WEBB, J.P.W., and KELLOCK, T.D. (1961). The occurrence of unusual fatty acids in fecal lipids from human beings with normal and abnormal fat absorption. *Biochem. J.* **78**, 333–9.
55. SOONG, C.S., THOMPSON, J.B., POLEY, J.R., and HESS, D.R. (1972). Hydroxy fatty acids in human diarrhea. *Gastroenterology* **63**, 748–57.
56. KIM, Y.S., and SPRITZ, N. (1968). Metabolism of hydroxy fatty acids in dogs with steatorrhea secondary to experimentally produced intestinal blind loops. *J. Lipid Res.* **9**, 487–91.
57. THOMAS, P.J. (1972). Identification of some enteric bacteria which convert oleic acid to hydroxystearic acid in vitro. *Gastroenterology* **62**, 430–5.
58. INFORMATICS. (1973). Monograph on glycerine and glycerides. DHEW Contract No. FDA 72-104. NTIS PB-221 227/2.
59. MEYER, H. (1890). Ueber den wirksamen bestandtheil des ricinusols. *Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol.* **28**, 145–521. (Cited in Ref. 67.)
60. BRIGHT-ASARE, P., and BINDER, H.J. (1973). Stimulation of colonic secretion of water and electrolytes by hydroxy fatty acids. *Gastroenterology* **64**, 81–8.
61. AMMON, H.V., and PHILLIPS, S.F. (1973). Inhibition of colonic water and electrolyte absorption by fatty acids in man. *Gastroenterology* **65**, 744–9.
62. AMMON, H.V., and PHILLIPS, S.F. (1974). Inhibition of ileal water absorption by intraluminal fatty acids. *J. Clin. Invest.* **53**, 205–10.
63. STEWART, J.J., GAGINELLA, T.S., OLSEN, W.A., and BASS, P. (1975). Inhibitory actions of laxatives on motility and water and electrolyte transport in the gastrointestinal tract. *J. Pharmacol. Exp. Ther.* **192**, 458–67.

64. STEWART, J.J., GAGINELLA, T.S., and BASS, P. (1975). Actions of ricinoleic acid and structurally related fatty acids on the gastrointestinal tract. I. Effects on smooth muscle contractility in vitro. *J. Pharmacol. Exp. Ther.* **195**(2), 347–54.
65. GAGINELLA, T.S., HADDAD, A.C., GO, V.L., and PHILLIPS, S.F. (1977). Cytotoxicity of ricinoleic acid (castor oil) and other intestinal secretagogues on isolated intestinal epithelial cells. *J. Pharmacol. Exp. Ther.* **201**(1), 259–66.
66. GAGINELLA, T.S., and PHILLIPS, S.F. (1976). Ricinoleic acid (castor oil) alters intestinal surface structure. A scanning electron microscopic study. *Mayo Clin. Proc.* **51**, 6–12.
67. GAGINELLA, T.S., STEWART, J.J., OLSEN, W.A., and BASS, P. (1975). Actions of ricinoleic acid and structurally related fatty acids on the gastrointestinal tract. II. Effects on water and electrolyte absorption in vitro. *J. Pharmacol. Exp. Ther.* **195**(2), 355–61.
68. COHEN, M.M. (1982). The effect of cathartics on prostaglandin synthesis by rat gastrointestinal tract. *Prostaglandins Leukotrienes Med.* **8**(4), 389–97.
69. BRETAGNE, J.F., VIDON, N., L'HIRONDEL, C., BERNIER, J.J., BOVET, M., MAUREL, M., RONGIER, M., and ROUCHETTE, J. (1981). Increased cell loss in the human jejunum induced by laxatives (ricinoleic acid, dioctyl sodium sulphosuccinate, magnesium sulphate, bile salts). *Gut* **22**, 264–9.
70. FEDERAL REGISTER. (March 21, 1975). Proposal to establish monographs for OTC laxative, antidiarrheal, emetic, and antiemetic products. **40**(56), 12909–10.
71. PIETRUSKO, R.G. (1977). Use and abuse of laxatives. *Am. J. Hosp. Pharm.* **34**(3), 291–300.
72. DYNAMIT NOBEL A.G. (1977). Acute oral toxicity evaluation of Softigen 701 in the mouse. Unpublished data submitted to CTFA.
73. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION (CTFA). (1979). Acute oral toxicity of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. 26/63.
74. CTFA. (1979). Acute oral toxicity of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. 26/64.
75. CTFA. (1980). Acute oral toxicity of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. OT29/68.
76. DYNAMIT NOBEL A.G. (1972). Softigen 701: Draize eye test, Draize skin test. Unpublished data submitted to CTFA.
77. DYNAMIT NOBEL A.G. (1980). Primary skin irritation test in the rabbit. Unpublished data submitted to CTFA.
78. CTFA. (1979). Primary skin irritation in rabbits of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. S11/117, product 05C/16813-01.
79. CTFA. (1979). Primary skin irritation in rabbits of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. S11/117, product 05C/16814-01.
80. CTFA. (1979). Primary skin irritation in rabbits of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. S11/117, product 05C/16815-01.
81. CTFA. (1979). Primary skin irritation in rabbits of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. S11/117, product 05C/16816-01.
82. CTFA. (1980). Primary skin irritation in rabbits of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. S12/37.
83. CTFA. (1980). Primary skin irritation in rabbits of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. S12/56.
84. HEM, S.L., BRIGHT, D.R., BANKER, G.S., and POGUE, J.P. (1975). Tissue irritation evaluation of potential parenteral vehicles. *Drug Dev. Commun.* **1**(5), 471–7.
85. LORENZ, W., SCMAL, A., SCHULT, H., LANG, S., OHMANN, C., WEBSTER, D., KAPP, B., LUEBEN, L., and DOENICKE, A. (1982). Histamine release and hypotensive reactions in dogs by solubilizing agents and fatty acids: Analysis of various components in cremophor EL and development of a compound with reduced toxicity. *Agents Actions* **12**, 64–80.
86. DYNAMIT NOBEL A.G. (1980). Primary eye irritation test in the rabbit. Unpublished data submitted to CTFA.
87. CTFA. (1979). Eye irritation of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. E43/71.
88. CTFA. (1979). Eye irritation of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. 43/70.
89. CTFA. (1979). Eye irritation of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. E43/68.

90. CTFA. (1979). Eye irritation of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. E43/69.
91. CTFA. (1979). Eye irritation of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. E43/229.
92. CTFA. (1979). Eye irritation of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. 43/221.
93. CTFA. (1979). Eye irritation of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. E46/5.
94. CTFA. (1980). Eye irritation of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. E44/241.
95. NATIONAL TOXICOLOGY PROGRAM (NTP). (April 28, 1986). Telephone inquiry on status of toxicity testing of castor oil by NTP.
96. NTP. (1985). National Toxicology Program: Fiscal Year 1985 Plan. Chemical test results for mutagenicity in *Salmonella* assays in FY 1984. Washington, D.C.: U.S. Department of Health and Human Services, p. 63.
97. BOYLAND, E., ROE, F.J.C., and MITCHLEY, B.C.V. (1966). Test of certain constituents of spermicides for carcinogenicity in genital tract of female mice. *Br. J. Cancer* **20**(1), 184–9.
98. CTFA. (1979). Skin irritation potential (human patch test) of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. 4527/4.
99. CTFA. (1980). Skin irritation potential (human patch test) of a product containing Glyceryl Ricinoleate. Washington, D.C. Test no. 4527/46.
100. RAMAKRISHNAN, S., BALASUBRAMANIAN, K., and MADHAVAN, M. (1972). Biochemical and pathological studies on castor seed poisoning. *J. Assoc. Physicians India* **20**(10), 781–4.
101. EL MAHOUB, M., KHALIFA, M.M., JASWAL, O.B., and GARRAH, M.S. (1983). "Ricin syndrome." A possible new teratogenic syndrome associated with ingestion of castor oil seed in early pregnancy: A case report. *Ann. Trop. Paediatr.* **3**: 57–61.
102. LEHRER, S.B., KARR, R.M., and SALVAGGIO, J.E. (1981). Analysis of green coffee bean and castor bean allergens using RAST inhibition. *Clin. Allergy* **11**(4), 357–66.
103. DAVISON, A.G., BRITTON, M.G., FORRESTER, J.A. DAVIES, R.J., and HUGHES, D.T.D. (1983). Asthma in merchant seamen and laboratory workers caused by allergy to castor beans (*Ricinus communis*): Analysis of allergens. *Clin. Allergy* **13**(6), 553–62.
104. KEMENY, D.M., FRANKLAND, A.W., FAHKRI, Z.I., and TRULL, A.K. (1981). Allergy to castor bean in the Sudan: Measurement of serum IgE and specific IgE antibodies. *Clin. Allergy* **11**(5), 463–71.
105. BRANDLE, I., BOUJNAH-KHOUDJA, A., and FOUSSEREAU, J. (1983). Allergy to castor oil. *Contact Dermatitis* **9**(5), 424–5.
106. SAI, S. (1983). Lipstick dermatitis caused by castor oil. *Contact Dermatitis* **9**(1), 75.
107. SAI, S. (1983). Lipstick dermatitis caused by ricinoleic acid. *Contact Dermatitis* **9**(6), 524.
108. ANDERSEN, K.E., and NIELSEN, R. (1984). Lipstick dermatitis related to castor oil. *Contact Dermatitis* **11**(4), 253–4.
109. de DARKO, E., and OSMUNDSEN, P.E. (1984). Allergic contact dermatitis to Lipcare® lipstick. *Contact Dermatitis* **11**(1), 46.

Final Report on the Safety Assessment of Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate¹

The oil derived from the seed of the *Ricinus communis* plant and its primary constituent, Ricinoleic Acid, along with certain of its salts and esters function primarily as skin-conditioning agents, emulsion stabilizers, and surfactants in cosmetics, although other functions are described. *Ricinus Communis* (Castor) Seed Oil is the naming convention for castor oil used in cosmetics. It is produced by cold pressing the seeds and subsequent clarification of the oil by heat. Castor oil does not contain ricin because ricin does not partition into the oil. Castor oil and Glyceryl Ricinoleate absorb ultraviolet (UV) light, with a maximum absorbance at 270 nm. Castor oil and Hydrogenated Castor Oil reportedly were used in 769 and 202 cosmetic products, respectively, in 2002; fewer uses were reported for the other ingredients in this group. The highest reported use concentration (81%) for castor oil is associated with lipstick. Castor oil is classified by Food and Drug Administration (FDA) as generally recognized as safe and effective for use as a stimulant laxative. The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives established an acceptable daily castor oil intake (for man) of 0 to 0.7 mg/kg body weight. Castor oil is hydrolyzed in the small intestine by pancreatic enzymes, leading to the release of glycerol and Ricinoleic Acid, although 3,6-epoxyoctanedioic acid, 3,6-epoxydecanedioic acid, and 3,6-epoxydodecanedioic acid also appear to be metabolites. Castor oil and Ricinoleic Acid can enhance the transdermal penetration of other chemicals. Although chemically similar to prostaglandin E₁, Ricinoleic Acid did not have the same physiological properties. These ingredients are not acute toxicants, and a National Toxicology Program (NTP) subchronic oral toxicity study using castor oil at concentrations up to 10% in the diet of rats was not toxic. Other subchronic studies of castor oil produced similar findings. Undiluted castor oil produced minimal ocular toxicity in one study, but none in another. Undiluted castor oil was severely irritating to rabbit skin in one study, only slightly irritating in another, mildly irritating to guinea pig and rat

skin, but not irritating to miniature swine skin. Ricinoleic Acid was nonirritating in mice and in one rabbit study, but produced well-defined erythema at abraded and intact skin sites in another rabbit study. Zinc Ricinoleate was not a sensitizer in guinea pigs. Neither castor oil nor Sodium Ricinoleate was genotoxic in bacterial or mammalian test systems. Ricinoleic Acid produced no neoplasms or hyperplasia in one mouse study and was not a tumor promoter in another mouse study, but did produce epidermal hyperplasia. Castor oil extract had a strong suppressive effect on S₁₈₀ body tumors and ARS ascites cancer in male Kunming mice. No dose-related reproductive toxicity was found in mice fed up to 10% castor oil for 13 weeks. Female rats injected intramuscularly with castor oil on the first day after estrus had suppressed ovarian folliculogenesis and anti-implantation and abortive effects. Castor oil used as a vehicle control in rats receiving subcutaneous injections had no effect on spermatogenesis. A methanol extract of *Ricinus communis* var. *minor* seeds (ether-soluble fraction) produced anti-implantation, anticonceptive, and estrogenic activity in rats and mice. Clinically, castor oil has been used to stimulate labor. Castor oil is not a significant skin irritant, sensitizer, or photosensitizer in human clinical tests, but patients with occupational dermatoses may have a positive reaction to castor oil or Ricinoleic Acid. The instillation of a castor oil solution into the eyes of nine patients resulted in mild and transient discomfort and minor epithelial changes. In another study involving 100 patients, the instillation of castor oil produced corneal epithelial cell death and continuity breaks in the epithelium. Because castor oil contains Ricinoleic Acid as the primary fatty acid group, the Cosmetic Ingredient Review (CIR) Expert Panel considered the safety test data on the oil broadly applicable to this entire group of cosmetic ingredients. The available data demonstrate few toxic effects. Although animal studies indicate no significant irritant or sensitization potential, positive reactions to Ricinoleic Acid in selected populations with identified dermatoses did suggest that sensitization reactions may be higher in that population. Overall, however, the clinical experience suggests that sensitization reactions are seen infrequently. In the absence of inhalation toxicity data on these ingredients, the Panel determined that these ingredients can be used safely in aerosolized cosmetic products because the particle sizes produced are not respirable. Overall, the CIR Expert Panel concluded that these cosmetic ingredients are safe in the practices of use and concentrations as described in this safety assessment.

Received 14 May 2007; accepted 24 August 2007.

Address correspondence to Wilbur Johnson, Jr., Senior Scientific Analyst and Writer, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

¹Reviewed by the Cosmetic Ingredient Review Expert Panel.

INTRODUCTION

The safety of the following ingredients in cosmetics is reviewed in this report: Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate. For the sake of brevity, Ricinus Communis (Castor) Seed Oil will be referred to as castor oil.

Glyceryl Ricinoleate and Glyceryl Ricinoleate SE are esters of glycerin and Ricinoleic Acid (component of castor oil). A Cosmetic Ingredient Review (CIR) safety assessment (Elder 1988) of Glyceryl Ricinoleate in cosmetics was published with the conclusion that the available data are insufficient to support the safety of this ingredient as used in cosmetics. The following data were needed for completion of this safety assessment: (1) 28-day chronic dermal toxicity (guinea pigs) and (2) clinical sensitization and photosensitization studies (or an appropriate ultraviolet spectrum instead of the photosensitization data).

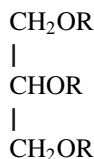
Glyceryl Ricinoleate and Glyceryl Ricinoleate SE are included in the present safety assessment in the expectation that the available data on castor oil, Ricinoleic Acid, salts of Ricinoleic Acid, and other esters of Ricinoleic Acid will contribute to a resolution of the CIR Expert Panel's data needs for Glyceryl Ricinoleate and Glyceryl Ricinoleate SE.

CHEMISTRY

Definition and Structure

Ricinus Communis (Castor) Seed Oil

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Ricinus Communis (Castor) Seed Oil (CAS no. 8001-79-4) is defined as the fixed oil that is obtained from the seeds of *Ricinus communis*. Other names for this oil include: Castor Oil, Castor Oil (Ricinus communis L.), Castor Seed Oil, Ricinus Communis, and Ricinus Communis Oil (Gottschalck and McEwen 2004), and Ricinus Oil (TNO BIBRA International Ltd. 1999). As given by TNO BIBRA International Ltd. (1999), the structural formula is:



where R represents a fatty acyl group [$\text{CH}_3(\text{CH}_2)_5\text{CH}(\text{OH})\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$] that is typically derived from Ricinoleic Acid. Ricinoleic Acid accounts for 87% to 90% of the fatty acyl groups, and the following other fatty acids comprise the remaining fatty acyl groups: oleic acid (2% to 7%), linoleic acid (3% to 5%), palmitic acid (1% to 2%), stearic acid (1%), dihydrostearic acid (1%), and trace amounts of other

fatty acyl groups (not specified) (TNO BIBRA International Ltd. 1999).

According to other sources, Castor Oil contains 2.4% lauric acid (Larsen et al. 2001), 2% to 5% linoleic acid (Maier et al. 1999), and globulin, cholesterol, lipase, vitamin E, and β -sitosterol (Scarpa and Guerri 1982).

Hydrogenated Castor Oil

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Hydrogenated Castor Oil (CAS no. 8001-78-3) is defined as the end product of controlled hydrogenation of Ricinus Communis (Castor) Seed Oil. Castor Oil, Hydrogenated is another technical name for this ingredient, and Castor Wax (trade name) and Montane 481 (trade name mixture) are other names under which Hydrogenated Castor Oil is marketed (Gottschalck and McEwen 2004).

Ricinoleic Acid, Its Salts, and Simple Esters

Table 1 includes the structures, definitions, and cosmetic ingredient functions of Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate.

Chemical and Physical Properties

Properties of castor oil and Hydrogenated Castor Oil are summarized in Table 2 and properties of the following ingredients are summarized in Table 3: Ricinoleic Acid, Ethyl Ricinoleate, Methyl Ricinoleate, Sodium Ricinoleate, Potassium Ricinoleate, and Zinc Ricinoleate.

Composition/Impurities

Castor Oil

The following three peaks were observed in a gas-liquid chromatogram on castor oil: palmitic acid (1.7%), C18 acids (stearic, oleic, and linoleic acids) (15.9%), and Ricinoleic Acid (82.4%) (Kato and Yamaura 1970).

According to the *Food Chemicals Codex* (National Academy of Sciences 1996), the requirements for castor oil are as follows: free fatty acids (passes test), heavy metals, as Pb (not more than 10 mg/kg), hydroxyl value (between 160 and 168), iodine value (between 83 and 88), saponification value (between 176 and 185), and specific gravity (between 0.952 and 0.966). The test for free fatty acids is described as follows: free fatty acids (10 g) are dissolved in 50 ml of a mixture of equal volumes of alcohol and ether (which has been neutralized to phenolphthalein with not more than 7 ml of 0.1 N sodium hydroxide). Phenolphthalein (1 ml) is added, followed by titration with 0.1 N sodium hydroxide until the solution remains pink (after shaking).

Similarly, the United States Pharmacopeia (Committee of Revision of the United States Pharmacopeial Convention 2004a)

TABLE 1

Structures, definitions, and functions of ricinoleic acid, its salts, and esters (Gottschalck and McEwen 2004)

Structure	Definition	Function
$\text{CH}_3(\text{CH}_2)_5\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	Ricinoleic Acid (CAS nos. 141-22-0 and 7431-95-0) is an unsaturated fatty acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid; 9-Octadecenoic Acid, 12-Hydroxy-; Ricinic Acid; and Ricinolic Acid	Surfactant—cleansing agent
$\begin{array}{c} \text{OH} \\ \\ \text{CH}(\text{CH}_2)_5\text{CH}_3 \\ \\ \text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{OH} \end{array}$	Glyceryl Ricinoleate (CAS nos. 141-08-2, 1323-38-2, and 5086-52-2) is the monoester of glycerin and ricinoleic acid. Other names include: Glycerin Monoricinoleate; Glycerol Monoricinoleate; Glyceryl Monoricinoleate, 12-Hydroxy-9-Octadecenoic Acid, Monoester with 1,2,3-Propanediol; Ricinoleic Acid Monoglyceride; and Ricinolein, 1-Mono-	Skin-conditioning agent—emollient and surfactant—emulsifying agent
See above	Glyceryl Ricinoleate SE is a self-emulsifying grade of Glyceryl Ricinoleate containing sodium and/or potassium stearate	Skin-conditioning agent—emollient and surfactant—emulsifying agent
$\text{CH}_3(\text{CH}_2)_5\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOK}$	Potassium Ricinoleate (CAS no. 7492-30-0) is the potassium salt of Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, Monopotassium Salt and 9-Octadecenoic Acid, 12-Hydroxy-, Monopotassium Salt	Surfactant—cleansing agent and surfactant—emulsifying agent
See above, except with Na in place of K	Sodium Ricinoleate (CAS no. 5323-95-5) is the sodium salt of Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, Sodium Salt; 9-Octadecenoic Acid, 12-Hydroxy, Sodium Salt; and Sodium Ricinate	Surfactant—cleansing agent and surfactant—emulsifying agent
$\left[\text{CH}_3(\text{CH}_2)_5\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COO}^- \right]_2 \text{Zn}^{+2}$	Zinc Ricinoleate (CAS no. 13040-19-2) is the zinc salt of Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, Zinc Salt and 9-Octadecenoic Acid, 12-Hydroxy-, Zinc Salt	Anticaking agent, deodorant agent, and opacifying agent
$\begin{array}{c} \text{OH} \\ \\ \text{CH}_3(\text{CH}_2)_5\text{CHCH}_2\text{CH} \\ \\ \text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2(\text{CH}_2)_{14}\text{CH}_3 \end{array}$	Cetyl Ricinoleate (CAS no. 10401-55-5) is the ester of cetyl alcohol and Ricinoleic Acid. Other names include: Hexadecyl 12-Hydroxy-9-Octadecenoate; 12-Hydroxy-9-Octadecenoic Acid, Hexadecyl Ester; 9-Octadecenoic Acid, 12-Hydroxy-, Hexadecyl Ester; and Ricinoleic Acid, Hexadecyl Ester	Skin-conditioning agent—occlusive
$\begin{array}{c} \text{CH}_3(\text{CH}_2)_5\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2\text{CH}_3 \\ \\ \text{OH} \end{array}$ $\begin{array}{c} \text{CH}_3(\text{CH}_2)_5\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2\text{CH}_3 \\ \\ \text{OH} \end{array}$ $\begin{array}{c} \text{CH}_3(\text{CH}_2)_5\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2\text{CH}_3 \\ \\ \text{OH} \end{array}$	Ethyl Ricinoleate (CAS no. 55066-53-0) is the ester of ethyl alcohol and Ricinoleic Acid. Other names include: Ethyl 12-Hydroxy-9-Octadecenoate; 12-Hydroxy-9-Octadecenoic Acid-, Ethyl Ester; 9-Octadecenoic Acid, 12-Hydroxy-, Ethyl Ester; and Ricinoleic Acid, Monoethyl Ester	Fragrance ingredient and skin-conditioning agent—emollient
$\begin{array}{c} \text{OH} \\ \\ \text{CH}(\text{CH}_2)_5\text{CH}_3 \\ \\ \text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2\text{CH}_2\text{OH} \end{array}$	Glycol Ricinoleate (CAS nos. 106-17-2 and 40275-40-9) is the ester of ethylene glycol and Ricinoleic Acid. Other names include: 1,2-Ethanediol Monoricinoleate; Ethylene Glycol Monoricinoleate; Glycol Monoricinoleate; 2-Hydroxyethyl 12-Hydroxy-9-Octadecenoate; 9-Octadecenoic Acid, 12-Hydroxy-, 2-Hydroxyethyl Ester; and Ricinoleic Acid, 2-Hydroxyethyl Ester	Emulsion stabilizer and skin-conditioning agent—emollient

(Continued on next page)

TABLE 1

Structures, definitions, and functions of ricinoleic acid, its salts, and esters (Gottschalck and McEwen 2004) (*Continued*)

Structure	Definition	Function
$\text{CH}_3(\text{CH}_2)_5\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}(\text{CH}_3)_2$	Isopropyl Ricinoleate (CAS no. 71685-99-9) is the ester of isopropyl alcohol and Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, 1-Methylethyl Ester; 1-Methylethyl, 12-Hydroxy-9-Octadecenoate; 9-Octadecenoic Acid, 12-Hydroxy-, 1-Methylethyl Ester; and Ricinoleic Acid, Isopropyl Ester	Skin-conditioning agent—emollient
$\text{CH}_3(\text{CH}_2)_5\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_3$	Methyl Ricinoleate (CAS nos. 141-24-2 and 23224-20-6) is the ester of methyl alcohol and ricinoleic acid. Other names include: Castor Oil Acid, Methyl Ester; 12-Hydroxy-9-Octadecenoic Acid, Methyl Ester; Methyl Castor Oil Fatty Acid; Methyl 12-Hydroxy-9-Octadecenoate; 9-Octadecenoic Acid, 12-Hydroxy-, Methyl Ester; and Ricinoleic Acid, Methyl Ester	Skin-conditioning agent—emollient
$\text{CH}_3(\text{CH}_2)_5\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}(=\text{O})\text{OCH}_2\text{CH}(\text{CH}_2)_9\text{CH}_3$	Octyldodecyl Ricinoleate (CAS nos. 79490-62-3 and 125093-27-8) is the ester of Octyldodecanol and Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, 2-Octyldodecyl Ester; 9-Octadecenoic Acid, 12-Hydroxy-, 2-Octyldodecyl Ester; 2-Octyldodecyl 12-Hydroxy-9-Octadecenoate; and 2-Octyldodecyl Ricinoleate	Skin-conditioning agent—occlusive

has published the following requirements for castor oil: free fatty acids (“the free fatty acids in 10 g require for neutralization not more than 3.5 ml of 0.10 N sodium hydroxide”) heavy metals (0.001%), hydroxyl value (between 160 and 168), iodine value (between 83 and 88), saponification value (between 176 and 182), and specific gravity (between 0.957 and 0.961).

Hydrogenated Castor Oil

According to Nikitakis and McEwen (1990), Hydrogenated Castor Oil consists primarily of glyceryl-tri-hydroxystearate. An earlier source (Binder et al. 1970) indicates that 12-hydroxystearic acid is the principal constituent of Hydrogenated Castor Oil.

The National Formulary (Committee of Revision of the United States Pharmacopeial Convention 2004b) has published the following requirements for Hydrogenated Castor Oil: free fatty acids (free fatty acids in 20 g require for neutralization not more than 11.0 ml of 0.1 N sodium hydroxide), heavy metals (0.001%), hydroxyl value (between 154 and 162), iodine value (not more than 5), and saponification value (between 176 and 182).

Methods of Production

Castor Oil

According to Kathren et al. (1959), castor oil is extracted from the bean of the tropical plant, *Ricinus communis*, by either of the following two methods: (1) use of a solvent [not stated] or (2) mechanical crushing, grinding, and pressing. The former method is more efficient, leaving a more dessicated residue.

This residue, known as pomace, contains ricin and a separate allergen (Ratner and Gruehl 1929). Following extraction from the castor bean, neither of these two fractions is present in castor oil (Ordman 1955).

According to a more recent reference (Cornell University 2001), ricin does not partition into the oil because of its water solubility. Therefore, castor oil does not contain ricin, provided that cross-contamination does not occur during its production.

Other sources indicate that castor oil is produced via the cold pressing of the seeds of *Ricinus communis* (Hui 1996) and by cold expression and subsequent clarification of the oil by heat (Gennaro 1990).

Hydrogenated Castor Oil

According to Nikitakis and McEwen (1990), Hydrogenated Castor Oil is obtained by the controlled hydrogenation of pure Castor Oil. Another source (Campbell & Co. 2002) indicates that Hydrogenated Castor Oil (hard, brittle wax) results from the addition of hydrogen to Castor Oil in the presence of a nickel catalyst.

Ricinoleic Acid

One of the simplest methods for obtaining Ricinoleic Acid is the hydrolysis of castor oil. Ricinoleic acid may then be separated from hydrolyzed castor Oil by successive additions of urea (i.e., urea complexing) (Chakravarty and Bose 1963). According to a more recent source, Ricinoleic Acid results from the saponification of castor oil (Lewis 1997).

TABLE 2
Chemical and physical properties of Castor Oil and Hydrogenated Castor Oil

Property	Value	Reference
Castor Oil		
Color/Form	Colorless to pale-yellow viscous liquid	Lewis 2000
Taste	Slightly acid	National Toxicology Program (NTP) 2003
Specific gravity	0.945 to 0.965 at 25°/25°C; 0.961 to 0.963 at 15.5°/15.5°C	NTP 2003
Density	0.953 to 0.965 g/ml at 20°C	NTP 2003
Viscosity	6 to 8 poises at 25°C 283 cP at 37°C	NTP 2003 Fredholt et al. 2000
Solubility	In water (<1 mg/ml at 20°C); in DMSO (≥100 mg/ml at 20°C); In 95% ethanol (≥ 100 mg/ml at 20°C); in methanol (miscible); In acetone (≥100 mg/ml at 20°C) Miscible in absolute alcohol, glacial acetic acid, chloroform, and ether	NTP 2003 Lewis 2000
Surface tension	39.0 dynes/cm at 20°C; 35.2 dynes/cm at 80°C	NTP 2003
Refractive index	1.4784 at 20°C; 1.473 to 1.477 at 25°C; 1.466 to 1.473 at 40°C	NTP 2003
Optical rotation	Not less than +3.5°	NTP 2003
Flash point	229°C (445°F)	NTP 2003
Autoignition temperature	448°C (840°F)	NTP 2003
Melting point	−12°C	NTP 2003
Boiling point	313°C	NTP 2003
Freezing point	−10°C	NTP 2003
Saponification value	178	NTP 2003
Iodine value	85	NTP 2003
Acid value	<4	NTP 2003
Reichert-Meissl value	<0.5	NTP 2003
Polenske value	<0.5	NTP 2003
Acetyl value	144 to 150	NTP 2003
Hydroxyl value	161 to 169	NTP 2003
Hydrogenated Castor Oil		
Color/Form	White to cream waxy solid	Nikitakis and McEwen 1990
Odor	As specified by the buyer Slight characteristic odor	Nikitakis and McEwen 1990 Allegri et al. 1981
Taste	Tasteless	Allegri et al. 1981
Identification	Positive: Close match to a standard IR spectrum with no indication of foreign materials	Nikitakis and McEwen 1990
Specific gravity	0.98 to 1.04 at 25°/25°C	Nikitakis and McEwen 1990
Melting range	78° to 90°C	Nikitakis and McEwen 1990
Acid value	5.0 maximum	Nikitakis and McEwen 1990
Saponification value	175 to 185	Nikitakis and McEwen 1990
Iodine value	As specified by the buyer <5.0	Nikitakis and McEwen 1990 Budavari 1989
Hydroxyl value	155 max	KIC Chemicals, Inc. 2004

(Continued on next page)

TABLE 2
Chemical and physical properties of Castor Oil and Hydrogenated Castor Oil (*Continued*)

Property	Value	Reference
Density	0.98 g/cm ³	Physical & Theoretical Chemistry Lab 2004
Solubility	Insoluble in water and organic solvents. Soluble in chloroform; very slightly soluble in benzene; virtually insoluble in alcohol, ethyl ether, carbon disulfide, and water	Lewis 1997 Allegri et al. 1981
Drying loss	When dried under vacuum in presence of phosphoric acid anhydride, should lose no more than 0.1% of weight	Allegri et al. 1981
Sulfuric ash	Not more than 0.01%	Allegri et al. 1981

Methyl Ricinoleate

According to Masri et al. (1962), Methyl Ricinoleate has been obtained by alcoholysis of castor oil, followed by fractional distillation of the crude esters and further purification by low temperature crystallization. According to a more recent source, Methyl Ricinoleate is a product of either the esterification of Ricinoleic Acid or the alcoholysis of castor oil; the product is purified by vacuum distillation (Lewis 1997).

Ultraviolet Absorption

Castor Oil

A ultraviolet (UV) absorption spectrum on castor oil indicates maximum absorbance at 270 nm; absorption peaks at 280 and 260 nm were also observed (Sasol North America, Inc. no date).

Glyceryl Ricinoleate

A UV absorption spectrum on Glyceryl Ricinoleate indicates maximum absorbance at 270 nm and an absorption peak at 280 nm (Sasol North America, Inc. no date).

Analytical Methods

Castor Oil

Castor oil has been analyzed using the following methods: mass spectroscopy (Ayorinde et al. 2000), gas-liquid chromatography (Kato and Yamaura 1970; Ramsey et al. 1980), thin-layer chromatography (Srinivasulu and Mahapatra 1973), and nonaqueous reverse-phase high-performance liquid chromatography-mass spectrometry (Stübiger et al. 2003).

Methyl Ricinoleate

Methyl Ricinoleate has been analyzed by nuclear magnetic resonance (NMR) spectroscopy (Wineburg and Swern 1973) and gas-liquid chromatography (Paulus and Champion 1972).

Reactivity

Castor Oil

Castor oil is combustible when exposed to heat, and spontaneous heating may occur (Lewis 2000).

According to Gunstone (1989), Castor Oil is a precursor of octadeca-9,11-dienoic acid (dehydration reaction); 12-hydroxystearic acid (hydrogenation); heptanol and undec-10-enoic acid (pyrolysis); and sebacic acid, 10-hydroxydecanoic acid, octan-2-ol, and octan-2-one (alkaline fusion).

According to Achaya (1971), the hydrogenation of Castor oil produces 12-hydroxystearate, stearate, 12-ketostearate, and ricinoleyl alcohol. Dehydrated castor oil is a dehydration product of castor oil, and contains a fair proportion of conjugated dienes.

Hydrogenated Castor Oil

Hydrogenated Castor Oil is combustible and is incompatible with strong oxidizing agents (Physical and Theoretical Chemistry Lab 2004).

USE

Purpose in Cosmetics

Ricinus Communis (Castor) Seed Oil functions as a fragrance ingredient and a skin-conditioning agent—occlusive in cosmetic products, and Hydrogenated Castor Oil functions as a skin-conditioning agent—occlusive and a viscosity increasing agent—nonaqueous (Gottschalck and McEwen 2004). The cosmetic ingredient functions of Ricinoleic Acid and some of its salts and esters are included in Table 1. Except for the anticaking, deodorant, and opacifying agent functions of Zinc Ricinoleate and the surfactant function of Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Glyceryl Ricinoleate, and Glyceryl Ricinoleate SE, these ingredients function as skin-conditioning agents in cosmetic products. In addition to functioning as a skin-conditioning agent, Ethyl Ricinoleate also functions as a fragrance ingredient. Glycol Ricinoleate also functions as an emulsion stabilizer, and Glyceryl Ricinoleate and Glyceryl Ricinoleate SE also function as surfactants in cosmetics.

Extent of Use in Cosmetics

Frequency of use data based on industry reports to the Food and Drug Administration (FDA) in 2002 indicate that *Ricinus*

TABLE 3
Chemical and physical properties of Ricinoleic Acid, its salts, and esters

Property	Value	Reference
Ricinoleic Acid		
Molecular weight	298.47	Lide and Frederikse 1993
Color/Form	Yellow fatty acid	Grant 1972
	Yellow, viscous liquid	Nikitakis and McEwen 1990
	Colorless to yellow, viscous liquid	Lewis 1997
Odor	As specified by the buyer	Nikitakis and McEwen 1990
Identification	Positive: Close match to a standard IR spectrum with no indication of foreign materials	Nikitakis and McEwen 1990
Specific gravity	0.940 at 25°/25°C	Nikitakis and McEwen 1990
Density	0.9450	Lide and Frederikse 1993
	0.940 at 27.4°/4°C	Lewis 1997
Solubility	Insoluble in water	Grant 1972
	Soluble in alcohol, acetone, ether, and chloroform	Budavari 1989
	Soluble in ethyl alcohol and diethyl ether	Lide and Frederikse 1993
	Soluble in most organic solvents; insoluble in water	Lewis 1997
Refractive index	1.4716 at 20°C	Nikitakis and McEwen 1990
	1.4716	Lide and Frederikse 1993
	1.4697 at 20°C	Lewis 1997
Optical rotation	$[\alpha]^{22/D}$ of +6.67°	Budavari 1989
	+6.67° at 22°C	Nikitakis and McEwen 1990
	$[\alpha]^{12/D}$ of +5.05	Lide and Frederikse 1993
	Dextrorotatory	Lewis 1997
Melting point	5.5°C	Nikitakis and McEwen 1990
	α : 7.7°C; β : 16°C; γ : 5.5°C	Lide and Frederikse 1993
	5.5°C	Lewis 1997
Boiling point	226.8°C	Lide and Frederikse 1993
	226°C at 10 mm Hg	Lewis 1997
Combustibility	Combustible	Lewis 1997
Neutralization value	187.98	Budavari 1989
	188	Nikitakis and McEwen 1990
Iodine value	85.05	Budavari 1989
	85	Nikitakis and McEwen 1990
Potassium Ricinoleate		
Color/Form	White paste	Lewis 1997
Solubility	Soluble in water	Lewis 1997
Combustibility	Combustible	Lewis 1997
Sodium Ricinoleate		
Color/Form	White or slightly yellow powder	Lewis 1997
Odor	Nearly odorless	Lewis 1997
Solubility	Soluble in water or alcohol	Lewis 1997
Combustibility	Combustible	Lewis 1997
Zinc Ricinoleate		
Color/Form	Fine white powder	Lewis 1997
Odor	Faint fatty acid odor	Lewis 1997
Density	1.10 at 25°/25°C	Lewis 1997

(Continued on next page)

TABLE 3
Chemical and physical properties of Ricinoleic Acid, its salts, and esters (*Continued*)

Property	Value	Reference
Melting point	92°C to 95°C	Lewis 1997
Combustibility	Combustible	Lewis 1997
Methyl Ricinoleate		
Color/Form	Colorless liquid	Lewis 1997
Solubility	Insoluble in water; soluble in alcohol and ether	Lewis 1997
Density	0.9236 at 22°/4°C	Lewis 1997
Refractive index	1.4628	Lewis 1997
Boiling point	245°C at 10 mm Hg	Lewis 1997
Flash point	−4.5°C	Lewis 1997
Combustibility	Combustible	Lewis 1997
Ethyl Ricinoleate		
Molecular weight	326.52	Lide and Frederikse 1993
Density	0.9045	Lide and Frederikse 1993
Refractive index	1.4618	Lide and Frederikse 1993
Optical rotation	$[\alpha]^{22/D}$ of +5.3	Lide and Frederikse 1993
Boiling point	258°C	Lide and Frederikse 1993

Communis (Castor) Seed Oil and Hydrogenated Castor Oil are being used in a total of 769 and 202 cosmetic products, respectively. Glyceryl Ricinoleate (16 cosmetic products), Ricinoleic Acid (6 cosmetic products), Sodium Ricinoleate (12 cosmetic products), Zinc Ricinoleate (3 cosmetic products), and Cetyl Ricinoleate (55 cosmetic products) were also reported. These data are given in Table 4 (FDA 2002).

Use concentration data obtained from an industry survey by the Cosmetic, Toiletry, and Fragrance Association (CTFA 2004) indicate that Ricinus Communis (Castor) Seed Oil and Hydrogenated Castor Oil are being used in cosmetics at concentrations up to 81% and 39%, respectively (see Table 4).

Other maximum ingredient use concentrations reported in Table 4 are as follows: Glyceryl Ricinoleate (up to 12%), Zinc Ricinoleate (up to 2%), Cetyl Ricinoleate (up to 10%), and Octyldodecyl Ricinoleate (up to 5%). Of the product categories listed in Table 4, the highest reported use concentration for Ricinus Communis (Castor) Seed Oil is associated with lipsticks. Two other sources indicate that lipstick contains 44% w/w castor oil (Hui 1996) and 10% to 67% castor oil (Smolinske 1992).

Certain ingredients in this group are reportedly used in a given product category, but the concentration of use is not available. For other ingredients in this group, information regarding use concentration for specific product categories is provided, but the number of such products is not known. In still other cases, an ingredient is not in current use, but may be used in the future. For example, Potassium Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, and Methyl Ricinoleate are not currently reported to FDA as in use, nor are there industry survey data indicating a current use concentration.

Cosmetic products containing Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, and Ricinoleic Acid and its salts and esters are applied to most areas of the body, and could come in contact with the oral, ocular, or nasal mucosae. These products may be used on a daily basis, and could be applied frequently over a period of several years.

Product categories for Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, and salts and esters of Ricinoleic Acid include potential aerosol applications. Bower (1999) characterized the typical diameter of anhydrous hair spray particles in the 60- to 80- μm range (typically, <1% are below 10 μm). Pump hair sprays, in contrast, have typical particle diameters of ≥ 80 μm . Johnsen (2004) reported that the mean particle diameter is around 38 μm in a typical aerosol spray. In practice, he stated that aerosols should have at least 99% of particle diameters in the 10- to 110- μm range. For comparison, Jensen and O'Brien (1993) reported a mean aerodynamic diameter of 4.25 ± 1.5 μm for respirable particles, which is smaller than any of the cosmetic product particle sizes given above.

Noncosmetic Use

Castor Oil, Hydrogenated Castor Oil, and Ricinoleic Acid Salts and Esters

According to Aplin and Eiseo (1997), castor oil is used as an industrial lubricant and as a medicinal purgative; the authors noted that medicinal Castor Oil does not contain ricin. McKeon et al. (2000) confirmed lubricant and anti-fungal uses and additional uses in paints, coatings, and plastics.

The following uses have been reported for Hydrogenated Castor Oil (Budavari 1989): in water-repellent coatings, candles,

TABLE 4Current uses and concentrations of *Ricinus Communis* (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
<i>Ricinus Communis</i> (Castor) Seed Oil		
Baby products		
Shampoos (29)	—	—
Lotions, oils, powders, and creams (60)	1	—
Other (34)	2	—
Bath products		
Oils, tablets, and salts (143)	1	22
Soaps and detergents (421)	—	0.008
Bubble baths (215)	—	—
Capsules (2)	—	—
Other (196)	10	—
Eye makeup		
Eyebrow pencils (102)	10	3
Eyeliners (548)	11	4–8
Eye shadow (576)	9	2–5
Eye lotions (25)	—	—
Eye makeup remover (100)	1	—
Mascara (195)	16	0.4–3
Other (152)	11	13
Fragrance products		
Colognes and toilet waters (684)	—	0.1
Perfumes (235)	—	0.3–1
Powders (273)	—	—
Sachets (28)	—	—
Other (173)	—	—
Noncoloring hair care products		
Conditioners (651)	20	0.0002–5
Sprays/aerosol fixatives (275)	1	—
Straighteners (63)	—	—
Permanent waves (207)	—	—
Rinses (42)	5	19
Shampoos (884)	—	0.005
Tonics, dressings, etc. (598)	34	0.005–52
Wave sets (53)	—	16
Other (277)	6	—
Hair—coloring products		
Dyes and colors (1690)	27	2
Tints (49)	—	—
Rinses (20)	—	0.0005
Shampoos (32)	—	—
Color sprays (5)	—	—
Lighteners with color (5)	—	—
Bleaches (120)	1	0.04
Other (55)	—	—
Makeup		
Blushers (245)	10	0.08–45
Face powders (305)	1	1

(Continued on next page)

TABLE 4

Current uses and concentrations of *Ricinus Communis* (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics
(Continued)

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
Foundations (324)	5	0.05–6
Leg and body paints (4)	—	—
Lipsticks (962)	492	15–81
Makeup bases (141)	4	0.002–20
Rouges (28)	1	38–48
Makeup fixatives (20)	—	—
Other (201)	25	40–49
Nail care products		
Basecoats and undercoats (44)	—	—
Cuticle softeners (19)	1	—
Creams and lotions (15)	1	—
Nail extenders (1)	—	—
Nail polishes and enamels (123)	—	69
Nail polish and enamel removers (36)	8	—
Other (55)	3	—
Personal hygiene products		
Bath soaps and detergents (421)	18	≤ 0.008
Underarm deodorants (247)	—	0.01–3
Douches (5)	—	—
Feminine deodorants (4)	—	—
Other (308)	1	0.003
Shaving products		
Aftershave lotions (231)	2	0.004–0.03
Beard softeners (0)	—	—
Mens talcum (7)	—	—
Preshave lotions (14)	—	—
Shaving creams (134)	—	—
Shaving soaps (2)	—	—
Other (63)	1	0.03
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (775)	4	0.004
Depilatories (34)	2	—
Face and neck creams, lotions, powders, and sprays (310)	1	1–7
Body and hand creams, lotions, powders, and sprays (840)	3	0.02–55
Body and hand sprays	—	0.004
Foot powders and sprays (35)	—	—
Moisturizers (905)	8	7
Night creams, lotions, powders, and sprays (200)	—	0.00004
Paste masks/mud packs (271)	2	—
Skin fresheners (184)	—	—
Other (725)	8	—
Suntan products		
Suntan gels, creams, liquids, and sprays (131)	1	6
Indoor tanning preparations (71)	—	—
Other (38)	1	10
Total uses/ranges for <i>Ricinus Communis</i> (Castor) Seed Oil	769	0.00004–81

TABLE 4

Current uses and concentrations of *Ricinus Communis* (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics
(Continued)

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
Hydrogenated Castor Oil		
Baby products		
Other (34)	—	5
Bath products		
Oils, tablets, and salts (143)	1	19
Soaps and detergents (421)	1	0.0003–0.7
Bubble baths (215)	—	4
Other (196)	—	3
Eye makeup		
Eyebrow pencils (102)	11	4–26
Eyeliners (548)	25	3–39
Eye shadow (576)	6	2–19
Eye lotions (25)	—	0.5
Eye makeup		
Eye makeup remover (100)	1	7
Mascara (195)	—	5
Other (152)	14	22–39
Fragrance products		
Colognes and toilet waters (684)	—	0.0003
Perfumes (235)	—	5
Other (173)	—	7
Noncoloring hair care products		
Shampoos (884)	—	0.02
Tonics, dressings, etc. (598)	—	3
Other (277)	1	—
Makeup		
Blushers (245)	2	3
Foundations (324)	4	0.9–5
Leg and body paints (4)	—	1
Lipsticks (962)	20	0.5–33
Makeup fixatives (20)	—	3–7
Other (201)	24	0.04–13
Nail care products		
Creams and lotions (15)	1	—
Oral hygiene products		
Other (6)	—	1–5
Personal hygiene products		
Underarm deodorants (247)	2	2–8
Feminine deodorants (4)	—	2
Other (308)	65	—
Shaving products		
Aftershave lotions (231)	2	—
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (775)	3	1
Face and neck creams, lotions, powders, and sprays (310)	—	1–2
Body and hand creams, lotions, powders, and sprays (840)	3	0.0003–1
Foot powders and sprays (35)	—	8

(Continued on next page)

TABLE 4

Current uses and concentrations of Ricinus Communis (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics
(Continued)

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
Moisturizers (905)	3	1–5
Night creams, lotions, powders, and sprays (200)	1	1–3
Other (725)	9	0.1–1
Suntan products		
Suntan gels, creams, liquids, and sprays (131)	1	0.8–3
Other (38)	2	—
Total uses/ranges for Hydrogenated Castor Oil	202	0.0003–39
Glyceryl Ricinoleate		
Eyebrow pencil (102)	—	11
Eyeliner (548)	1	2
Eyeshadow (576)	5	—
Other eye makeup products (152)	1	2–12
Lipsticks (962)	5	—
Other shaving products (63)	1	—
Body and hand creams, lotions, powders, and sprays (840)	2	—
Night creams, lotions, powders, and sprays (200)	1	—
Total uses/ranges for Glyceryl Ricinoleate	16	12
Ricinoleic Acid		
Bath preparations		
Oils, tablets and salts (143)	1	—
Fragrance preparations		
Colognes and toilet waters (684)	1	—
Other fragrance preparations (173)	4	—
Total uses/ranges for Ricinoleic Acid	6	—
Sodium Ricinoleate		
Baby products		
Other baby products (34)	1	—
Bath Preparations		
Soaps and detergents (421)	10	—
Noncoloring Hair Preparations		
Shampoos (884)	1	—
Total uses/ranges for Sodium Ricinoleate	12	—
Zinc Ricinoleate		
Noncoloring hair preparations		
Hair sprays/aerosol fixatives (275)	—	1
Personal hygiene products		
Underarm deodorants (247)	2	2
Skin care preparations		
Skin cleansing creams, lotions, liquids, and pads (775)	1	—
Body and hand skin care preparations (sprays) (840)	—	1
Total uses/ranges for Zinc Ricinoleate	3	1–2
Cetyl Ricinoleate		
Makeup preparations		
Blushers (245)	—	3

TABLE 4

Current uses and concentrations of *Ricinus Communis* (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics
(Continued)

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
Foundations (324)	3	2–3
Lipsticks (962)	26	0.5–10
Other makeup preparations (201)	1	—
Skin care preparations		
Skin cleansing creams, lotions, liquids, and pads (775)	2	0.1–0.5
Body and hand skin care preparations (840)	1	—
Moisturizers (905)	15	0.1–2
Paste masks (mud packs) (271)	3	—
Other skin care preparations (725)	3	4
Suntan preparations		
Other suntan preparations (38)	1	—
Total uses/ranges for Cetyl Ricinoleate	55	0.1–10
Octyldodecyl Ricinoleate		
Fragrance preparations		
Other fragrance preparations (173)	—	3
Makeup preparations		
Lipsticks (962)	—	3–5
Total uses/ranges for Octyldodecyl Ricinoleate	—	3–5

shoe polish, carbon paper, and ointments; for impregnating paper, wood, and cloth; for electrical condenser impregnation; as a solid lubricant; and as a pressure mold release agent in the manufacture of formed plastics and rubber goods. The use of Hydrogenated Castor Oil in waterproofing fabrics has also been reported (Lewis 1997).

According to FDA's *OTC (Over-the-Counter) Drug Review Ingredient Status Report* (FDA 2003a), castor oil is classified as generally recognized as safe and effective for use as a stimulant laxative, but not generally recognized as safe and effective for use as a wart remover. For use as a stimulant laxative, the single daily dose reported for one product ranges from 15 to 60 ml for adults and children ≥ 12 years (Drugstore.com, Inc. 2004).

FDA had issued a proposed rule in 1982 stating that Castor oil is generally recognized as safe and effective and not misbranded when used as an active ingredient (laxative) in OTC laxative drug products (FDA 1985) and a final rule is pending (FDA 2003a). FDA has concluded that castor oil does not meet monograph conditions and is not generally recognized as safe and effective for use as a wart remover in OTC wart remover drug products (FDA 1990).

Castor oil is included in the list of inactive ingredients (excipients) present in approved oral, intramuscular, and topical drug products or conditionally approved drug products that are currently marketed for human use (FDA 2003b).

FDA-approved direct/indirect food additive uses of Castor oil and the following Ricinoleic Acid salts and esters are summarized in Table 5: Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, and Methyl Ricinoleate.

The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (1980) established an acceptable daily intake (for man) of 0 to 0.7 mg/kg body weight for castor oil. The determination of range was based on consideration of the lack of adequate long-term studies.

Ricinoleic Acid

Noncosmetic uses of Ricinoleic Acid are as follows: turkey red oil, textile finishing, source of sebacic acid and heptanol, ricinoleate salts, and 12-hydroxystearic acid (Lewis 1997).

Zinc Ricinoleate

The following noncosmetic uses of Zinc Ricinoleate have been reported: fungicide, emulsifier, greases, lubricants, waterproofing, lubricating-oil additive, and stabilizer in vinyl compounds (Lewis 1997).

Methyl Ricinoleate

Noncosmetic uses of Methyl Ricinoleate include: plasticizer, lubricant, cutting oil additive, and wetting agent (Lewis 1997).

TABLE 5
Direct/indirect food additive uses of Castor Oil, Hydrogenated Castor Oil, and Ricinoleic acid salts and esters

Use	Specification/listing	Code of Federal Regulations (CFR)
Diluent	Not more than 500 ppm Castor Oil in the finished food may be used safely as a diluent in color additive mixtures for food use that are exempt from certification.	21 CFR 73.1
Release/antisticking agent	Provided that Castor Oil meets the specifications of the United States Pharmacopeia, it is permitted for use as a release agent and antisticking agent, not to exceed 500 ppm in hard candy.	21 CFR 172.876
Natural flavoring substance and adjuvant	Castor Oil is included in the list of natural flavoring substances and natural adjuvants that are permitted for direct addition to food for human consumption.	21 CFR 172.510
Plasticizer	Castor Oil is approved for use as a plasticizer (total not to exceed 30% by weight of rubber product, unless otherwise specified) in rubber articles that have been declared safe for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21 CFR 177.2600
Component of food-contact surface	Hydrogenated Castor Oil may be used safely as a component of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods.	21CFR176.170
Component of food-contact surface	Hydrogenated Castor Oil may be used safely as a component of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding dry food.	21CFR176.180
Component of defoaming agents	Castor Oil, Hydrogenated Castor Oil, Glycol Ricinoleate, Isopropyl Ricinoleate, and Methyl Ricinoleate are among the substances that are permitted for use in the formulation of defoaming agents that have been declared safe for use in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food.	21 CFR 176.210
Component of surface lubricants	Castor Oil is included in the list of substances permitted for use in surface lubricants that have been declared safe for use in the manufacture of metallic articles that contact food. May be used in surface lubricants employed to facilitate the drawing, stamping, or forming of metallic articles from rolled foil or sheet stock by further processing, provided that the total residual lubricant remaining in the metallic article in the form in which it contacts food does not exceed 0.2 mg per square inch of food-contact surface.	21 CFR 178.3910
Component of cellophane	Hydrogenated Castor Oil is included in the list of components of cellophane that may be safely used for packaging food.	21CFR 177.1200

TABLE 5Direct/indirect food additive uses of Castor Oil, Hydrogenated Castor Oil, and Ricinoleic acid salts and esters (*Continued*)

Use	Specification/listing	Code of Federal Regulations (CFR)
Component of closure-sealing gaskets	Hydrogenated Castor Oil may be employed in the manufacture of closure-sealing gaskets that may be safely used on containers intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21CFR177.1210
Component of cross-linked polyester resins	Hydrogenated Castor Oil may be used in the production of or may be added to cross-linked polyester resins that may be safely used as articles or components of articles that are intended for repeated use in contact with food.	21CFR 177.2420
Textiles and textile fiber components derived from Castor Oil	Fats, oils, fatty acids, and fatty alcohols derived from Castor Oil are included in the list of substances that are permitted for use in textiles and textile fibers that have been declared safe for use as articles or components of articles that are intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21 CFR 177.2800
Component of adhesives	Polymeric esters of polyhydric alcohols and polycarboxylic acids prepared from glycerin and phthalic anhydride and modified with Castor Oil are permitted for use in adhesives that have been declared safe for use as components of articles intended for use in packaging, transporting, or holding food. Methyl Ricinoleate is also permitted for use in these adhesives.	21 CFR 175.105
Component of resinous and polymeric coatings	Castor Oil, Hydrogenated Castor Oil, Potassium Ricinoleate, Sodium Ricinoleate, and Zinc Ricinoleate are included in the list of substances employed in the production of resinous and polymeric coatings that have been declared safe for use as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21 CFR 175.300

BIOLOGICAL PROPERTIES**Absorption, Distribution, Metabolism, and Excretion***Castor Oil*

In a study by Paul and McKay (1942), two rabbits (weight = 3 kg) were fed 6% castor oil in the diet for 18 days; fecal collection occurred during the last ten days. The utilization (uncorrected for metabolic fat) of castor oil was 92.1%, which the authors considered to be efficient utilization. For both rabbits, the percentage of fat in the feces was 2.2%.

In a study by Stewart and Sinclair (1945), adult rats (number, weights, and strain not stated) received a diet containing 48.4% castor oil for 4 to 6 weeks. Control rats received stock ration only. Feces were collected from three rats on the castor oil diet. At the end of the feeding period, excised organs/tissues were ground thoroughly and samples of phospholipid fatty acids were

obtained from the liver, small intestine, and muscle; glyceride fatty acids were obtained from the liver and fat depots. There was no evidence of catharsis in any of the animals.

Average percentages of Ricinoleic Acid in the phospholipid fatty acids were as follows: liver (test: $1.3 \pm 0.6\%$ [9 analyses]; controls: $1.7 \pm 1.1\%$ [7 analyses]), small intestine (test: $4.9 \pm 1.7\%$ [8 analyses]; controls: $6.0 \pm 4.4\%$ [4 analyses]), and skeletal muscle (test: $3.6 \pm 2.9\%$ [8 analyses]; controls: $4.0 \pm 1.7\%$ [7 analyses]). The following values are average percentages of Ricinoleic Acid in glycerides and cholesterol esters: fat depots (test: $6.8 \pm 4.2\%$ [11 analyses]; controls: $0.5 \pm 0.5\%$ [7 analyses]) and liver (test: $7.2 \pm 2.4\%$ [8 analyses]; controls: $5.6 \pm 4.1\%$ [5 analyses]).

The authors concluded that the feeding of castor oil did not lead to the appearance of significant amounts of Ricinoleic Acid in phospholipids of the small intestine, liver, and skeletal muscle,

nor in glycerides of the liver. Additionally, they concluded that ricinoleic acid is a component acid of the glycerides in the fat depots, comprising 7% of the total fatty acids. The fatty acids excreted by each of three rats amounted to 2.1%, 2.2%, and 3.6% of those ingested. Total body fat in these three animals was also determined, and it was calculated that 1% to 2% of absorbed Ricinoleic Acid was deposited in the fat depots. The authors concluded that Ricinoleic Acid was rapidly metabolized (Stewart and Sinclair 1945).

Watson and Gordon (1962) studied the digestion, absorption, and metabolism of castor oil (medicinal grade) in eight male Sprague-Dawley rats (weights = 100 to 200 g). The composition of the castor oil was as follows: ricinoleic acid (90.0%), linoleic acid (4.7%), oleic acid (3.2%), stearic acid (1.0%), palmitic acid (1.0%), and palmitoleic acid (0.1%). In the first experiment, four rats were fed rat chow ad libitum, and the remaining four were fasted overnight. On the following morning, castor oil (1.0 ml) was dosed via stomach tube and chyle was collected over a 24-h period. The mean values for percent recovery of Ricinoleic Acid in fasted and fed rats were 6.8% and 24.2%, respectively ($p < .01$).

In the second experiment, seven weanling rats were fed a diet consisting of rat chow that had been mixed with castor oil (20% by weight). The control group was fed an olive oil-supplemented diet. After 4 and 8 weeks of feeding, an epididymal fat pad was removed from each rat in both groups, and fatty acid composition was determined using gas-liquid chromatography. Mean values for Ricinoleic Acid in the fat pad after 4 and 8 weeks of feeding were 9.1 ± 1.7 and $9.7 \pm 1.0\%$, respectively. Ricinoleic Acid was undetectable in the fat pads of control rats fed olive oil. For rats fed castor oil, random analyses of feces indicated a considerable fraction of hydroxystearic acid. However, hydroxystearic acid was undetectable in the feces of rats fed a normal diet. The authors suggested that hydrogenation of Ricinoleic Acid in the gut lumen by intestinal bacteria would be a likely explanation for this finding.

The relationship between dose and absorption of castor oil was studied in the final experiment. Polyethylene cannulae were inserted into the thoracic duct and duodenum of each of two rats, and the animals received 0.5 N saline overnight. On the following morning, one rat received 0.2 ml and one rat received 0.6 ml of castor oil, and the rats were killed 45 min post dosing. Only the high dose induced diarrhea. Intestines (small and large) were excised, homogenized, and tissue lipids were extracted. Chyle was also collected and extracted. Total lipid estimation and gas-liquid chromatography (GLC) analysis of fatty acids were performed on the extracts. For the rat dosed with 0.2 ml castor oil, the percentage of Ricinoleic Acid in the chyle was 18.1% and the percentage detected in the small bowel lipids was 6.2%. For the rat dosed with 0.6 ml Castor Oil, the percentage of Ricinoleic Acid in the chyle was 3.0% and the percentage in the small bowel was 3.1%. Ricinoleic Acid was undetectable in large bowel lipids from the rat with diarrhea. The result indicates a close correlation between the dose administered and the per-

centage of Ricinoleic Acid in the feces, i.e., greater absorption at the lower dose (Watson and Gordon 1962).

Castor oil is metabolized to Ricinoleic Acid by pancreatic lipase in hamsters (Gaginella and Bass 1978). Thompson (1980) reported that Castor Oil is a triglyceride that is hydrolyzed in the small intestine in humans by pancreatic enzymes, leading to the release of glycerol and Ricinoleic Acid.

In a study by Hagenfeldt et al. (1986), castor oil was administered intragastrically to germ-free and conventional rats (number not stated). Urine was collected at intervals over a 24-h period. The following epoxydicarboxylic acids were detected in the urine of both germ-free and conventional rats: 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid. These acids were not detected in urine collected from the rats prior to dosing with castor oil, and they also were not detected in steam-sterilized castor oil. The authors stated that results for the germ-free rat indicate that the cyclization of Ricinoleic Acid (hydroxy fatty acid in castor oil) to form an epoxy compound occurs endogenously and does not require the presence of intestinal bacteria.

In a study by Ihara-Watanabe et al. (1999), two groups of five male Wistar rats (3 weeks old) received 10% castor oil in the diet (cholesterol-enriched and cholesterol-free, respectively) for 20 days. In both dietary groups, a very small quantity of Ricinoleic Acid was present in perirenal adipose tissue, but not in the serum or hepatic tissue. It was also noted that the perirenal fatty acid profiles did not reflect those of the dietary fats, either in the absence or presence of dietary cholesterol. The fecal recovery of Ricinoleic Acid was approximately 0.5% of the total ingested. It was concluded that castor oil was readily absorbed and metabolized.

Hydrogenated Castor Oil

In a study by Binder et al. (1970), groups of 15 male albino rats (Slonaker substrain of Wistar strain, weights = 43 to 83 g) received diets containing the following oils: group 1 (fed 1% Hydrogenated Castor Oil (HCO) + 19% corn oil for 16 weeks), group 2 (1% HCO + 19% corn oil for 8 weeks, then 20% corn oil for 8 weeks), group 3 (10% HCO + 10% corn oil for 16 weeks), and group 4 (10% HCO + 10% corn oil for 8 weeks, then 20% corn oil for 8 weeks). The control group received 20% corn oil in the diet for 16 weeks. The sample of HCO that was incorporated into the diet contained 86.5% 12-hydroxystearic acid, 10.3% nonoxygenated acids, and 3.2% 12-ketostearic acid. Thus, the effective dietary concentrations of Hydrogenated Castor Oil in the 1% and 10% diets were 0.865% and 8.65%, respectively. Results relating to the toxicity of HCO are summarized in the section Subchronic Oral Toxicity later in the report.

After 4 weeks of feeding, some of the animals on the 1% HCO (three rats) and 10% HCO (three rats) diets were necropsied and excised abdominal adipose tissue from each group was pooled. At weeks 4 and 8, sets of three rats on the corn oil diet were used. At the end of the 16-week feeding period, adipose tissue from rats in the various dietary groups was analyzed. Adipose tissue

was not pooled. After 8, 12, and 16 weeks, lipids were extracted from three rats on each diet. Methyl esters were recovered from the extracted lipids and chromatographed.

The deposition of hydroxystearic acid in abdominal fat and other body lipids was reported. In all cases, it was accompanied by hydroxypalmitic acid, hydroxymyristic acid, and hydroxylauric acid (hydroxy-stearic acid metabolites). The percent composition of these HCO-derived hydroxy fatty acids in rat lipids was as follows: 12-hydroxystearic acid ($\approx 81\%$), 10-hydroxypalmitic acid ($\approx 17\%$), 8-hydroxymyristic acid ($\approx 1.6\%$), and 6-hydroxylauric acid ($\approx 0.4\%$). After 4 weeks on the 1% HCO diet, HCO-derived fatty acids accounted for 0.90% (by weight) of the abdominal fat fatty acids. This proportion decreased to $\approx 0.35\%$ over the 8- to 16-week feeding period. Compared to the abdominal fatty acids, the acids obtained from the carcass lipids contained a smaller proportion of HCO-derived hydroxyacids ($\approx 0.28\%$ over the 8- to 16-week feeding period). The period encompassing 4 weeks of feeding on the 10% HCO diet yielded the greatest content of HCO-derived hydroxy acids in the lipids (i.e., 4.4% hydroxy acids in abdominal fat). At 16 weeks, this proportion had decreased to $< 2\%$ (about same as in the carcass lipids).

A rapid decrease in the amount of HCO-derived hydroxy fatty acids in the tissues was noted when the HCO diet was changed to the control diet (Binder et al. 1970).

Ricinoleic Acid and Methyl Ricinoleate

Uchiyama et al. (1963) studied the accumulation of hydroxy acids in depot fat after rats were fed with Ricinoleic Acid in two experiments. In the first experiment, adult male rats (number, strain, and weights not stated) were fed Ricinoleic Acid (5% emulsion, 20 ml) for 7 days. In the second experiment, the animals were fed for 27 days. Lipid extraction from the fat tissue was followed by hydrolysis to yield a fatty acid mixture. A gas-liquid chromatogram indicated appreciable amounts of the following hydroxy fatty acids with shorter chain lengths than Ricinoleic Acid: 10-hydroxyhexadecenoic acid (experiment 1: 0.60% of total fatty acids; experiment 2: 0.33% of total fatty acids), 8-hydroxytetradecenoic acid (experiment 1: 0.03% of total fatty acids; experiment 2: 0.08% of total fatty acids), and 6-hydroxydodecenoic acid (experiment 2: 0.03% of total fatty acids). Ricinoleic Acid comprised 0.51% of total fatty acids in experiment 1 and 3.85% of total fatty acids in experiment 2.

In a study by Okui et al. (1964), the metabolism of hydroxy fatty acids was evaluated using male albino rats (weight = 120 ± 10 g). The rats received 1.5 g Ricinoleic Acid or an emulsion containing 5% (w/v) Ricinoleic Acid by stomach tube three times per day for a desired period. Feces were collected every 24 h until the animals were killed. The animals were killed 20 h after the last dose, and subcutaneous adipose tissue was removed for analyses. Oral dosing with Ricinoleic Acid resulted in a fecal excretion rate (for Ricinoleic Acid) ranging from 1% to 4%. Following oral administration for up to 30 days, the ac-

cumulation of hydroxy acids by 5% of fatty acids in fat tissue was noted. Analyses of adipose tissue indicated an occurrence of shorter chain hydroxy acids other than Ricinoleic Acid.

Ricinoleic Acid was also injected intraperitoneally to determine whether another route of administration would lead to the formation of shorter chain hydroxy acids. After Ricinoleic Acid was injected intraperitoneally daily for 7 days, Ricinoleic Acid accumulated in the adipose tissue; no shorter chain hydroxy acids were reported (Okui et al. 1964).

In a study by Rao et al. (1969), Ricinoleic Acid or Methyl Ricinoleate was administered via gastric intubation to male rats (minimum weight of 400 g) with a cannulated thoracic duct. Lymph was collected for 48 h, and the lipids were then extracted and separated into various lipid classes. Results indicated that Ricinoleic Acid was present in the triglyceride, diglyceride, monoglyceride, and free fatty acid fractions. Peak absorption of Ricinoleic Acid occurred within 30 min post administration. Ricinoleic Acid was not present in the phospholipid or cholesterol ester fractions of the lymph lipids.

Percutaneous Absorption

Ricinoleic Acid

Butcher (1952) evaluated the skin penetration of Ricinoleic Acid in vivo using rats that were 20 to 30 days old. In order to increase the fluorescence of Ricinoleic Acid, either one part of methyl anthranilate or methylcholanthrene was added to 99 parts Ricinoleic Acid. The test substance was either gently rubbed on to skin that had been clipped free of hair. Biopsies were taken at various intervals post application. The preparations were observed using a Spencer microscope with a quartz condenser. Ricinoleic Acid was retained mainly in the outer strata of the epidermis. There was little evidence of deeper penetration in biopsies that were taken at 2 h post application.

In a study by Baynes and Riviere (2004), the percutaneous absorption of a radiolabeled [^3H]Ricinoleic Acid (specific activity = 20.0 mCi/mmol) mixture was evaluated using porcine skin membranes or silastic (polydimethylsiloxane) membranes in the Bronaugh flow-through diffusion cell system. [^3H]Ricinoleic Acid (5%) mixtures were prepared in water containing either 5% mineral oil or 5% PEG 200. Other [^3H]Ricinoleic Acid mixtures were formulated with the following three commonly used cutting fluid additives: triazine, linear alkylbenzene sulfonate, and triethanolamine. At 8 h after topical exposure, Ricinoleic Acid absorption (based on amount recovered in receptor fluid) ranged from 1% to 13% in silastic membranes and 0.1% to 0.3% in porcine skin membranes. For most mixtures, peak absorption of Ricinoleic Acid occurred within 3 h. The greatest Ricinoleic Acid peak concentrations were associated with the control mixtures containing PEG in both membranes.

At the conclusion of the 8-h perfusion experiments, as much as 5% of the dose of Ricinoleic Acid was detected in the dosed skin, and as much as 16% of the dose was detected in the stratum

corneum with mineral oil formulations. With polyethylene glycol (PEG) formulations, the amount of Ricinoleic Acid remaining in the skin tissues was considerably less. The cutting fluid additives significantly decreased Ricinoleic Acid partitioning from the formulation into the stratum corneum in PEG-based mixtures. Additionally, the individual additives or combinations of these additives significantly reduced Ricinoleic Acid permeability in silastic membranes and porcine skin (Baynes and Riviere 2004).

Skin Penetration Enhancement

Ricinoleic Acid

In a study by Song et al. (2001), the effects of *cis*-9-octadecenoic acid (oleic acid) and a group of chemically related *cis*- (Ricinoleic Acid) and *trans*- (ricinelaidic acid) 12-monohydroxylated derivatives and their ethyl and methyl esters on the skin penetration of model hydrophobic (hydrocortisone) and hydrophilic (5-fluorouracil) drugs were evaluated in vitro using hairless mouse skin. Test solutions were prepared by placing either test compound (5-fluorouracil, 5.4 mg; hydrocortisone, 15 mg) with or without an unsaturated fatty acid (50 mg each) or fatty acid ester (50 mg each) in a screw-capped glass vial, and adding propylene glycol (final volume = 1 ml). The mixture was sonicated to effect complete dissolution. Permeation studies were conducted using Vlia-Chien diffusion cells and full thickness abdominal skin from female hairless HRS/J mice (6 weeks old). Ricinoleic Acid enhanced the in vitro transdermal permeation of 5-fluorouracil.

The transdermal penetration rate of hydroquinone from propylene glycol was very slow. However, in the presence of oleic acid, the penetration rate accelerated and was enhanced approximately 1800-fold. In the presence of Ricinoleic Acid, the enhancement of hydroquinone skin penetration was less than 1.5-fold. Regarding the penetration of 5-fluorouracil, fluxes were much higher in the presence of oleic acid (333-fold increase; $p < .001$) than in the presence of Ricinoleic Acid (<5-fold increase) (Song et al. 2001).

Transepidermal Water Loss

Castor Oil

Lieb et al. (1988) evaluated transepidermal water loss (TEWL) using a modification of a flow-through diffusion cell that was originally designed by Bronaugh and Stewart (1985). The membrane was described as full-thickness, cartilage-stripped skin obtained from the ventral ear of the male Syrian golden hamster. Castor oil (10 μ l) was placed on the skin (0.32-cm² area), and a TEWL rate-versus-time study was conducted. Tritiated water (HTO) permeated through the membrane into the diffusion cell's receptor compartment. Flux (TEWL, μ g/cm²/h) was determined (using a scintillation counter) by measuring the HTO that adsorbed to anhydrous calcium chloride in the receptor cell. Castor oil caused a marked decrease in the TEWL rate. For untreated skin, the mean TEWL rate was

approximately 450 μ g/cm²/h at 1 h. Mean values for the TEWL rate were approximately 400 μ g/cm²/h at 1 h and 250 μ g/cm²/h at 24 h. Additionally, castor oil was the only substance that exhibited a burst effect, i.e., initially, the membrane became fully hydrated and swollen and was more permeable, providing an "increased push" effect to pass water through the membrane toward the anhydrous desiccant.

Effect on Smooth Muscle

Castor Oil and Ricinoleic Acid

Mathias et al. (1978) evaluated the effect of Castor Oil and Ricinoleic Acid on smooth muscle of the rabbit small intestine. Anesthetized male New Zealand white rabbits (weights between 1.5 and 3.0 kg) were used in ileal loop studies. Castor oil (dose = 0.85 ml/kg) was administered into the oral end of the ileal loop, and myoelectric recording techniques were used. Ricinoleic Acid was administered by intraluminal infusion (2 μ g/kg/min [6 mM] into the oral end). The term migrating action potential complex (MAPC) was used to describe the myoelectric activity that has been observed in certain abnormal states. MAPC has been defined as action potential discharge activity occurring for longer than 2.5 s, on at least two consecutive electrode sites at 2.5-cm intervals, and having a propagation velocity of ≥ 1.0 cm/s. The myoelectric activity of castor oil and Ricinoleic Acid was similar to the MAPC that was observed in the cholera enterotoxin-infected loops. Castor oil induced an alteration in myoelectric activity.

In experiments that were designed to study the motor response in segments of the duodenum, mid-jejunum, terminal ileum, and sigmoid colon (four experiments, respectively), Ricinoleic Acid was diluted with 0.9% sodium chloride solution to a volume that would deliver 1.14 ml/h. No MAPC activity was observed in control experiments in which 0.9% sodium chloride solution was perfused into the duodenum at a rate of 1.14 ml/h. When compared to control values, there was no statistically significant difference in the slow wave frequency or slow wave propagation velocity in loops exposed to castor oil or Ricinoleic Acid (Mathias et al. 1978).

Lodge (1994) evaluated the potential for Ricinoleic Acid to induce vasoconstriction using tissues from male New Zealand white rabbits. After removal of the thoracic aorta and left and right external jugular veins, the vessels were cleaned and cut into rings. Following removal of the endothelium, the rings were suspended between two wire holders in tissue baths. Ricinoleic Acid was diluted with ethanol to produce final bath concentrations ranging from 0.1 to 30 μ g/ml (molar concentration range of 0.335 to 100.50 μ M). Ricinoleic Acid induced vasoconstriction ($EC_{50} = 0.24 \pm 0.04$ μ g/ml) that was concentration-dependent and sensitive to the inhibitory effect of ifetroban, but not indomethacin. Ricinoleic acid also evoked concentration-dependent force development (constriction) in the aorta ($EC_{50} = 4.7 \pm 0.7$ μ g/ml), and this response was antagonized by ifetroban.

Sodium Ricinoleate, Castor Oil, and Ricinoleic Acid

Stewart and Bass (1976a) evaluated the effects Sodium Ricinoleate, castor oil, and Ricinoleic Acid on the digestive contractility of the canine small bowel using four male, mixed breed dogs (weights between 10 and 15 g). After feeding, each animal received a single bolus infusion of Sodium Ricinoleate (500 mg in 30 ml of saline) into the duodenum. Saline (30-ml volume) served as the control. A duodenal cannula was implanted in each animal, and circular muscle activity was recorded for 1 h. Each animal was dosed with Sodium Ricinoleate in two experiments, and with isotonic saline (30 ml) in two control experiments. In additional experiments, alterations in digestive contractile patterns were monitored after administration (gastric tube) of castor oil or Ricinoleic Acid (volume = 10 ml) one h after feeding. Each treatment was repeated twice in each of two animals.

Intraduodenal administration of Sodium Ricinoleate produced a biphasic response in the proximal and mid-jejunum consisting of brief initial stimulation, followed by inhibition of digestive contractility. Compared to the control experiments, these stimulatory and inhibitory effects on intestinal contractility were described as significant ($p < .05$) changes in the average force per contraction. The changes in mid-jejunal digestive contractility were similar to those observed in the proximal jejunum.

The oral administration of Ricinoleic Acid (10 ml) induced alterations in digestive patterns that were qualitatively similar to those induced by the intraduodenal administration of Sodium Ricinoleate. Brief initial stimulation, followed by an apparent depression of intestinal contractility, was observed after oral dosing with Castor Oil (10 ml) (Stewart and Bass 1976a).

Sodium Ricinoleate and Methyl Ricinoleate

In a study by Stewart et al. (1975), Sodium Ricinoleate depressed the smooth muscle twitch response of the electrically driven guinea-pig ileum preparation at concentrations ranging from 1.25×10^{-5} to 4×10^{-4} M. Methyl Ricinoleate failed to depress the smooth muscle twitch response over this range of test concentrations. Similar results were reported for spontaneously contracting rabbit jejunum.

Antinociceptive Activity

Ricinoleic Acid and Potassium Ricinoleate

Vieira et al. (2000) evaluated the antinociceptive activity of Ricinoleic Acid (in peanut oil), dissolved in a vehicle containing 10% ethanol, 10% Tween 80, and 80% saline, using groups of 5 male albino Dunkin-Hartley guinea pigs (weights = 250 to 350 g) and groups of 8 to 10 male Swiss mice (weights = 20 to 25 g). A series of experiments was performed. In the first experiment, a single topical application of Ricinoleic Acid (900 μ g/mouse) was made to the ventral surface of the right paw of each mouse. Test substance application was followed by intraplantar injection with carrageenan (to induce edema) 30 min later. Ricinoleic acid significantly reduced the reaction time to a heat stimulus, compared to treatment with the vehicle. When

intraplantar injection with carrageenan was preceded by repeated (8 days) topical applications of Ricinoleic Acid (900 μ g/mouse), again, a marked prolongation of paw withdrawal latency to heat, compared to the vehicle control group, was noted.

Another experiment involved the repeated local application (8 days) of Ricinoleic Acid (900 μ g/mouse) or the repeated (4 days) intradermal injection of Potassium Ricinoleate (30 μ g/mouse) on the ventral surface of the right paw. Freund's adjuvant had been injected into the hindpaw on the first day. The paw withdrawal latency to a painful stimulus (heat) after topical application was increased over at least 2 weeks. The intradermal injection of Potassium Ricinoleate induced a significant antinociceptive effect that lasted for at least 3 weeks (Vieira et al. 2000).

Effect on Enzyme Activity

Ricinoleic Acid

In a study by Gaginella et al. (1978), isolated villus cells from the small intestine of the hamster were used to determine whether Ricinoleic Acid stimulates intestinal adenylate cyclase. In the adenylate cyclase assay, activity of the enzyme was determined using a method that is based upon the conversion of [α - ^{32} P]ATP to [^{32} P]cyclic AMP. The cell homogenates (30 to 50 μ g of protein per tube) were incubated for 20 min. Ricinoleic Acid concentrations of 10^{-9} to 5×10^{-3} M did not cause dose-dependent stimulation of adenylate cyclase. Significant ($p < .05$), but slight, stimulation of adenylate cyclase was noted at a concentration of 10^{-5} M, and higher concentrations inhibited basal activity. Prostaglandin E_1 , which is chemically similar to Ricinoleic Acid, was a potent stimulant of adenylate cyclase activity, causing dose-related stimulation ($p < .001$) of adenylate cyclase at concentrations of 10^{-9} to 10^{-4} M.

Simon and Kather (1980) studied the modulation of adenylate cyclase and cAMP-phosphodiesterase, key enzymes of cAMP metabolism, by Ricinoleic Acid in human colonic mucosa. The experiments were performed using histologically normal colonic mucosa obtained from eight patients (five males, three females) who were undergoing hemicolectomy for carcinoma or diverticulosis. Adenylate cyclase activity was determined according to the method of Salomon et al. (1974), and cyclic AMP phosphodiesterase activity was determined according to the method of Pösch (1971). Ricinoleic Acid was tested at concentrations ranging from 1×10^{-8} to 5×10^{-4} mol/l. Basal adenylate cyclase activity in homogenates of human colonic mucosa averaged 250 pmol cAMP/mg protein/15 min. Mean basal cAMP phosphodiesterase activity was 150 ± 15 pmoles per mg protein per minute.

Over the range of concentrations tested, dose-related stimulation of the large bowel adenylate cyclase was not observed. Basal activity of adenylate cyclase was inhibited at concentrations above 1×10^{-5} mol/l. Ricinoleic Acid did not influence soluble cAMP phosphodiesterase activity over the range of concentrations tested. Ricinoleic Acid was an ineffective stimulus of human colonic adenylate cyclase, and also was not a competitive

inhibitor of soluble cAMP phosphodiesterase activity (Simon and Kather 1980).

In a study by Vanderhoek et al. (1980), the effect of Ricinoleic Acid on the oxygenation of [$1\text{-}^{14}\text{C}$]arachidonic acid by platelet cyclooxygenase and lipoxygenase enzymes was monitored using an oxygen electrode and by analysis of the radioactive products formed. The enzymes were obtained from human platelet concentrates (3 to 4 days old). Ricinoleic Acid did not appear to have an effect on either enzyme. The concentration of Ricinoleic Acid that was required for half-maximal inhibition of lipoxygenase or cyclooxygenase activity was $>300\text{ }\mu\text{M}$.

Beubler and Schirgi-Degen (1992) studied the stimulation of enterocyte protein kinase C by laxatives in vitro using intestinal epithelial cell (from female Sprague-Dawley rats) preparations. A protein kinase C assay system was used to determine the activity of protein kinase C. This assay system is based on protein kinase C-catalyzed transfer of the γ -phosphate group of adenosine-5'-triphosphate to a peptide that is specific for protein kinase C. Ricinoleic Acid (dissolved in DMSO) stimulated protein kinase C activity in a concentration-dependent manner within the concentration range of 2 to $200\text{ }\mu\text{g/ml}$.

Effect on Uridine Uptake

At a concentration of $50\text{ }\mu\text{M}$, Ricinoleic Acid suppressed the uptake of uridine into human diploid fibroblasts in culture (Polgar and Taylor 1977).

Effect on Lipid Metabolism

Castor Oil

Ihara-Watanabe et al. (1999) evaluated the effect of the following diets on lipid metabolism using groups of five male Wistar rats (3 weeks old): 10% castor oil, 10% high-oleic safflower oil, and 10% coconut oil. The diets were prepared in the absence or presence of dietary cholesterol, and were fed ad libitum for 20 days. On day 20, blood samples were obtained and liver and perirenal adipose tissues were excised. Serum and hepatic lipids were analyzed for total cholesterol, high-density lipoprotein, triacylglycerols, and phospholipids.

Body weight gain and food intake were lowest for rats fed the castor oil diet enriched with cholesterol, but not for rats fed cholesterol-free diets. Body weight gain to consumption ratios were similar among all of the groups. Compared to rats fed the high-oleic safflower oil diet (enriched with cholesterol), rats fed the castor oil diet enriched with cholesterol had decreased liver weights (g/100 g of body weight). Data on liver weights were not presented in the study.

Values for total cholesterol and phospholipids in the serum were significantly decreased in rats fed castor oil, compared to rats fed high-oleic safflower oil in the absence or presence of cholesterol. For cholesterol-enriched diets, the lowest value for serum high-density lipoproteins was reported for the castor oil dietary group. No significant differences in serum triacylglycerol

occurred between either of the dietary groups (with or without cholesterol in the diet).

Compared to the high-oleic safflower oil dietary group (with or without cholesterol), significantly decreased ($p < .05$) hepatic triacylglycerol concentrations were reported for the castor oil dietary group. For cholesterol-enriched diets, the castor oil and coconut oil dietary groups had significantly increased ($p < .05$) hepatic cholesterol when compared to the high-oleic safflower oil dietary group. It was concluded that castor oil had a hypocholesterolemic effect in rats in this study (Ihara-Watanabe et al. 1999).

Effect on Leukocyte Infiltration and Prostaglandin Synthesis

Castor Oil

Ohia et al. (1992) used castor oil as a vehicle control in a study evaluating the effects of steroids and immunosuppressive drugs on endotoxin-induced uveitis in rabbits. The vehicle control group consisted of four male New Zealand rabbits (weights = 1.5 to 2.0 kg). The animals were injected intramuscularly with castor oil (dose = 2 mg/kg). At 1 h post injection, both eyes of each rabbit were cleansed and anesthetized. This procedure was followed by the intravitreal injection of *Escherichia coli* endotoxin (100 ng). The animals were killed 24 h after injection of the endotoxin. Aqueous humor was obtained and leukocytes were counted. The eyes were then enucleated for microscopic examination. Compared to saline-treated controls, castor oil significantly reduced the infiltration of leukocytes and the prostaglandin E_2 (inflammatory mediator) content of the aqueous humor and iris-ciliary body. The authors concluded that Castor Oil had an anti-inflammatory effect in this study.

Effect on Cytokine-Induced Endothelial Cell Activation

Sodium Ricinoleate

De Caterina and Bernini (1998) evaluated the relationship between structural differences in fatty acids and the inhibition of endothelial activation, taking into consideration that dietary long-chain fatty acids may influence processes that involve endothelial activation (e.g., inflammation and atherosclerosis). To test for a potential stimulatory effect of fatty acids on adhesion molecule expression, sodium salts of saturated, monounsaturated (Sodium Ricinoleate included), and n-6 and n-3 polyunsaturated fatty acids were each incubated alone (test concentration = $25\text{ }\mu\text{M}$) with human saphenous vein endothelial cells (HSVECs) for 72 h. The 72-h incubation period was followed by 16 h of stimulation with the cytokine interleukin (IL)- 1α in the continuous presence of fatty acid salt. At the end of the incubation period, vascular cell adhesion molecule-1 (VCAM-1) expression was assessed using a cell surface enzyme immunoassay (EIA).

Sodium Ricinoleate significantly inhibited (considered modest; $p < .05$) cytokine-induced endothelial adhesion molecule

expression. DHA inhibited VCAM-1 expression ($p < .01$) most potently (De Caterina and Bernini 1998).

De Caterina and Bernini (1998) also conducted an experiment to determine whether the fatty acid sodium salts may induce endothelial activation in the absence of cytokines. The salts were incubated with endothelial cell monolayers for 24 h. Incubation periods prior to detection of adhesion molecule surface expression varied from 0 to 72 h. Neither Sodium Ricinoleate (25 μ M) nor any other fatty acid sodium salt induced adhesion molecule expression, as assessed by EIA.

Ricinoleic Acid

In a study by De Caterina et al. (1995), the effect of Ricinoleic Acid on VCAM-1 expression was evaluated using rabbit coronary artery endothelium in vitro. VCAM-1 (marker for endothelial cell activation) is a surface protein that is not expressed by endothelial cells in vitro, but is inducible by exposure to inflammatory stimuli such as bacterial endotoxin, IL-1, or tumor necrosis factor α (TNF α). Ricinoleic Acid significantly reduced IL-4-induced VCAM-1 expression (50% inhibitory concentration between 10 and 100 μ M). Neither cell number nor viability was increased in this concentration range. Ricinoleic Acid did not inhibit TNF α -induced VCAM-1 expression to any significant extent.

Effect on Prostaglandin Synthesis

Castor Oil

Gao et al. (1999) evaluated the effect of castor oil in the diet on the synthesis of prostaglandin E₂ (PGE₂) and the induction of labor using two groups of eight pregnant Wistar rats (at gestation day 18; test and control groups, respectively). Two milliliters of castor oil-containing diet were administered by gavage daily for a total of four feedings. The diet (labor-inducing diet) consisted of castor oil (30 ml) + one chicken egg, blended and heated to a thick consistency. At 4 h after the fourth feeding, the pregnant females were killed. Compared to the control group, a significant increase in concentrations of PGE₂ in tissues of the intestinal mucosa, placenta, amnion, and amniotic cells was noted in test animals. The authors stated that the increased synthesis of PGE₂ "is a key of" the initiation of labor that is induced by a castor oil diet.

Cytotoxicity

Sodium Ricinoleate

Gaginella et al. (1977b) evaluated the cytotoxicity of Ricinoleic Acid using epithelial cells that were isolated from the small intestines of male Syrian hamsters. Cytotoxicity was assessed by exclusion of trypan blue, the release of intracellular (prelabeled) ⁵¹Cr, and inhibition of the cellular uptake of 3-O-methylglucose. The results produced by all three methods indicated that Sodium Ricinoleate produced a dose-dependent cytotoxicity.

For the trypan blue exclusion method, Sodium Ricinoleate caused dose-related increases in cytotoxicity at concentrations of 0.1 to 5.0 mM. Death of all cells was noted at a concentration of 2.0 mM. Results for control incubation in the ⁵¹Cr release assay indicated that $26.8 \pm 1.7\%$ of ⁵¹Cr, initially within or bound to the cells, was released into the medium. Sodium Ricinoleate induced concentration-dependent (0.1 to 5 mM Sodium Ricinoleate) increases in ⁵¹Cr release, from 4.2% to 54.8% above the control value. In the 3-O-methylglucose uptake assay, Sodium Ricinoleate inhibited the uptake of 3-O-methylglucose over a concentration range of 0.1 to 2.0 mM (Gaginella et al. 1977b).

In a study by De Caterina and Bernini (1998), the cytotoxicity of Sodium Ricinoleate and other fatty acid sodium salts in human saphenous vein endothelial cell cultures was evaluated. Cell count, trypan blue exclusion, and [³H]leucine incorporation into total cell-associated and released proteins were monitored. For the latter of the three, trichloroacetic acid precipitation of total cell extracts and cell supernates was performed. At concentrations ≤ 25 μ M, Sodium Ricinoleate and other fatty acid sodium salts did not induce significant toxicity (based on cell count and trypan blue exclusion) for periods up to 72 h prior to cytokine stimulation.

Antimicrobial Activity

Castor Oil

Morris et al. (1979) evaluated the antimicrobial activity of castor oil on *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* using the Petri plate-paper disc procedure. Paper discs were soaked with 20 μ l of a 10% Castor Oil solution, and the discs were immediately applied to solidified, seeded agar (1 disc per plate). The plates were incubated for 10 to 24 h. Discs containing 95% ethanol (20 μ l) served as negative controls. Castor Oil did not have antimicrobial activity on any of the strains tested.

Sodium Ricinoleate

Whiteside-Carlson et al. (1955) studied the effect of Sodium Ricinoleate on cell division using a laboratory strain of *E. coli*. Sodium Ricinoleate was tested over a concentration range of 1 to 5 mg/ml of medium. The cultivation of *E. coli* on nutrient agar that was saturated with Sodium Ricinoleate caused the development of filamentous forms during the first h of logarithmic growth. By the end of the log phase, organisms of normal morphology were observed. When agar containing Sodium Ricinoleate was adjusted to pH values of 5 to 8, filament formation was more marked and persisted for longer periods at the more alkaline pH value. The utilization of liquid proteose-peptone medium (with periodic readjustment of the pH to a range of 7.6 to 7.8) resulted in maintenance of the cells in filamentous form throughout the entire growth cycle. The tendency toward filament formation was reduced by lowering the incubation temperature to below 37°C. The results of this study indicate

that Sodium Ricinoleate interfered with cell division in *E. coli*, causing the organisms to develop as filaments.

Mordenti et al. (1982) studied the activity of Sodium Ricinoleate against *Streptococcus mutans* strain 6715-13 (plaque) in vitro. The minimum inhibitory concentration of Sodium Ricinoleate against *S. mutans* was 1% (or 3.12×10^{-2} M). During testing for the minimum inhibitory concentration, the following four distinct concentration-dependent cell growth and acid production phenomena were identified: (1) no cell growth, pH > 6.8; (2) cell growth, medium pH > 6.8; (3) cell growth, medium pH of 5.2 to 6.8; and (4) cell growth, medium pH < 5.2. It was concluded that Sodium Ricinoleate had bactericidal activity in this assay. In subsequent experiments, wire-adherent plaque specimens were treated with various concentrations of Sodium Ricinoleate. The intact plaque samples survived in each of these tests. The authors stated that the ability for Sodium Ricinoleate to kill bacteria in suspension, but not in intact plaque, clearly demonstrates the absence of a correlation between antibacterial activity against cells in suspension and antiplaque activity.

Other Biological Effects

Castor Oil

Capasso et al. (1986) evaluated the effect of castor oil on the formation of histamine, 5-hydroxytryptamine (5-HT), and prostaglandin-like material (PG-LM) in the rat intestine using male, fasted Wistar-Nossan rats (number and weights not stated). Castor oil (dose = 2 ml/rat) was administered by gavage. Following the onset of diarrhea, the animals were killed, and sections of colon removed. Untreated rats served as controls. Castor oil induced an approximately fourfold increase in PG-LM ($p < .01$) and a threefold increase in histamine and 5-HT ($p < .01$). A decrease in the Castor oil-induced colonic formation of PG-LM was noted following pretreatment of the animals with indomethacin (inhibitor of prostaglandin biosynthesis) or hydrocortisone. It was concluded that these data support the idea that the laxative effect of castor oil is the result of increased intestinal production of PG-LM, histamine, and 5-HT.

A study was conducted by Pinto et al. (1989) to determine whether oral administration of castor oil leads to changes in the levels of platelet-activating factor (PAF) formed by intestinal tissue, and whether these changes are related to intestinal damage. Fasted, male Wistar-Nossan rats (number not stated; weights = 130 to 140 g) were used. Castor oil (dose = 2 ml/rat) was administered orally, and the animals were killed.

At 3 h post dosing, the formation of PAF by segments of rat intestine was significantly increased (compared to control rats treated with olive oil) in the following intestinal segments: duodenum ($p < .001$), jejunum ($p < .01$), ileum ($p < .2$), and colon ($p < .1$). At macroscopic examination, extensive regions of hyperemia were noted in the entire intestinal mucosa. The duodenum and jejunum regions were the most severely affected. No increase in PAF was noted in control rats dosed with olive oil.

Compared to control rats dosed with olive oil, castor oil also

increased the intraluminal release of acid phosphatase (AP) in the duodenum and jejunum ($p < .01$), and a similar trend was reported for the ileum and colon ($p < 0.2$ to $.1$). A correlation between increased release of AP and intestinal hyperemia was established. The authors noted that the results of this study suggest that PAF is involved in the mechanism underlying castor oil-induced intestinal damage (Pinto et al. 1989).

In a study by Blair et al. (2000), the affinity of castor oil and numerous other chemicals for the estrogen receptor (from uteri of ovariectomized Sprague-Dawley rats) was evaluated using a validated estrogen receptor competitive binding assay. In this assay, the ability for a chemical to compete with [^{3} H]estradiol ([^{3} H]E₂) for the estrogen receptor was determined, based on IC₅₀ (concentration resulting in 50% inhibition of [^{3} H]estradiol binding) values. All assays were replicated a minimum of two times. The mean IC₅₀ for Castor oil was $> 1.0 \times 10^{-4}$ M. Mean IC₅₀ values for 4-heptyloxyphenol and phenophthalein (both classified as moderate estrogen receptor binders) were $6.75 \times 10^{-5} \pm 0.75 \times 10^{-5}$ and $6.73 \times 10^{-6} \pm 1.79 \times 10^{-6}$, respectively. The binding affinity of castor oil for the estrogen receptor was not classified.

Ricinoleic Acid

In a study by Grainger et al. (1982), the effect of Ricinoleic Acid on lymph flow in outperfused segments of cat ileum was evaluated. The cats were anesthetized and a segment of ileum with intact innervation and lymphatic drainage was isolated and perfused by the intact mesenteric artery. A cannula was inserted into a large lymphatic vessel emerging from the mesenteric pedicle, and lymph flow was determined by observing lymph movement in a calibrated pipette that was connected to the lymphatic cannula. The mean control ($\pm$ SE) value for intestinal lymph flow in the experiments was 0.048 ± 0.005 ml/min $\times$ 100 g. Net fluid secretion was stimulated by intraluminal instillation of 5 mM Ricinoleic Acid. The peak increase in intestinal lymph flow produced by Ricinoleic Acid in all experiments was 6.3 ± 1.2 ($n = 5$) times the control. The maximal fluid excretion rate observed with Ricinoleic Acid was 0.43 ± 0.23 ml/min $\times$ 100 g.

Yagaloff et al. (1995) evaluated the inhibitory activity of a series of fatty acids and fatty acid derivatives on [^{3} H]leukotriene B₄ binding (LTB₄) to pig neutrophil membranes using the LTB₄ receptor binding assay. The most potent chemicals were 15-hydroxy-DGLA (20:3; $K_i = 1 \mu$ M), eicosadienoic acid (20:2; $K_i = 3 \mu$ M), and Ricinelaidic Acid (18:1; $K_i = 2 \mu$ M). Ricinoleic Acid (18:1) had a K_i of 9μ M.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Castor Oil

In a study by Capasso et al. (1994), castor oil (2 ml) was administered orally to ten male Wistar rats (weights = 160 to

180 g). The animals were killed and two segments from standardized regions of the duodenum and jejunum were visibly evaluated for macroscopic damage. Mucosal injury was graded according to the following scale: 0 (normal), 1 (hyperemia), 2 (hyperemia with evidence of hemorrhage into the lumen), and 3 (severe hemorrhage into the lumen).

Copious diarrhea was reported for all animals on days 3, 5, and 7 post dosing. Macroscopic damage, characterized mainly by vasocongestion, was observed throughout the duodenum and jejunum. The injury observed ranged from mild (at 1 h) to severe (at 5 h), and was less severe at 7 h. Injury was not observed at 0.5 or 9 h after dosing. Castor oil-induced mucosal damage was associated with statistically significant intraluminal release of acid phosphatase.

In additional experiments (groups of 10 rats), mucosal damage induced by castor oil was exacerbated in the presence of a nitric oxide synthase inhibitor (*N*^ω-nitro-L-arginine methyl ester), suggesting that nitric oxide provides protection against castor oil-induced mucosal damage (Capasso et al. 1994).

In a study involving male Crl:CD BR rats, the findings suggested that castor oil-induced diarrhea is the result of activation of NK₁ and NK₂ receptors by endogenous tachykinins (Crocini et al. 1997).

In a study by Johnson et al. (1993), castor oil was administered orally to 12 ponies (17 months to 20 years old; weights = 160 to 250 kg). The ponies were randomly assigned to two treatment groups and one control group (four ponies per group). Each animal received a single 2.5 ml/kg body weight dose of castor oil via nasogastric tube. Diarrhea occurred within 24 h of dosing. The animals were killed and necropsied at 24, 48, and 72 h post dosing. Intestinal tissues were removed and subjected to gross and microscopic examination.

In ponies killed at 24 or 48 h, gross lesions were most severe in the cecum and ventral colon. At 24 h, the mucosa of the distal jejunum, ileum, cecum, and ventral colon was diffusely red. Most of the ponies dosed with castor oil had generalized hyperemia of the intestinal mucosa at 24, 48, and 72 h post dosing, and mesenteric, cecal, and colonic lymph nodes were edematous. Mucosal and submucosal edema of the ileum, cecum, and ventral colon was noted in all ponies dosed with castor oil. At 72 h post dosing, focal acute ulceration and intense mucosal hyperemia of the glandular stomach was observed in three of four ponies dosed with castor oil.

Microscopic changes in the superficial enterocytes of the cecum and ventral colon that were characterized as follows: loss of microvilli; distortion of the cytoplasmic terminal web; expansion of the cytoplasmic matrix, with formation of precipitates; and widening of intracellular spaces between junctional complexes. Castor oil induced acute superficial enterocolitis in ponies. Dosing was associated with transient diarrhea, neutrophilic inflammation, and mucosal erosion in the cecum and ventral colon (Johnson et al. 1993).

Hydrogenated Castor Oil

The acute oral toxicity of a 25% solution of Hydrogenated castor oil in olive oil was evaluated in a study involving ten male Wistar rats (average body weight = 155 g). The test solution (dose = 10 g/kg) was administered via a gastric probe. Toxic signs were not observed in any of the animals, indicating that the test substance was well tolerated. The LD₅₀ was >10 g/kg (Allegrini et al. 1981).

Ricinoleic Acid

In a study by Okui et al. (1964), male albino rats (number not stated; weight = 120 ± 10 g) were injected intraperitoneally (i.p.) with 100 mg Ricinoleic Acid. All of the animals were dead within 24 h. The i.p. injection of a 5% Ricinoleic Acid emulsion (1 ml) was tolerable, but caused an increase in the following: amount of ascites, conglutination of peritoneal organs, and swelling of the liver. However, histological changes were not observed in liver specimens.

Cetyl Ricinoleate

In an acute oral toxicity test performed by Laboratoire de Recherche et d'Experimentation (1994), Cetyl Ricinoleate was evaluated using five female NMRI EOPS mice (weights = 19 to 22 g). Oral dosing (single dose 2000 mg/kg) was followed by a 6-day observation period. None of the animals died, and clinical and behavioral evaluations were normal. Weight gain was considered satisfactory. The authors stated that Cetyl Ricinoleate was non-toxic in this study.

Ethyl Ricinoleate

The acute oral toxicity of Ethyl Ricinoleate was evaluated using 10 rats (weights and strain not stated). The acute oral LD₅₀ exceeded 5.0 g/kg; one animal receiving this dose died. The following clinical signs were observed during the study: isolated instances of diarrhea, chromorhinorrhea, ptosis, and chromodacryorrhea. At necropsy, gross observations were normal for eight animals. Necropsy of the remaining two animals revealed the following changes in either one or both animals: red and/or yellow areas in the intestines, red areas in the stomach, mottled liver, mottled spleen, mottled kidneys, dark lungs, red exudate in the anogenital area, and a large amount of blood in the bladder (Research Institute for Fragrance Materials [RIFM] 2000).

Acute Dermal Toxicity

Ethyl Ricinoleate

The acute dermal toxicity of Ethyl Ricinoleate was evaluated using six rabbits (weights and strain not stated). The acute dermal LD₅₀ exceeded 5.0 g/kg; one animal receiving this dose died. The following clinical signs were observed during the study: isolated instances of lethargy, diarrhea, ptosis, and yellow nasal discharge, and moderate erythema (six rabbits), slight edema (one rabbit), and moderate edema (five rabbits). At necropsy,

gross observations were normal for three animals. Necropsy of the remaining animals revealed the following changes: red areas in the intestines, mottled liver, white nodules in the liver, dark areas in the lungs, mottled kidneys, pale kidneys, dark spleen, and dark areas in the stomach (RIFM 2000).

Acute Intravenous Toxicity

Castor Oil

In a study by Lorenz et al. (1982), castor oil was administered intravenously (single bolus dose = 0.1 ml/kg) to each of eight anesthetized adult mongrel dogs (four males, four females; mean weight = 20.5 kg). Blood for histamine assays was obtained at 2, 5, 10, 15, and 20 min post dosing. The incidence of the following signs was determined: erythema, hives (papules and wheals), edema, defecation, tachypnea, hypotension, and death (circulatory arrest). None of the animals died, and erythema (one animal; score not stated) was the only clinical sign that was reported. An increase in blood histamine occurred in one of the eight animals. At 2 min post dosing, the increase was 0.6 ng/ml of whole blood (maximum response) in this animal. The authors concluded that castor oil was ineffective in terms of its ability to cause histamine release.

Short-Term Oral Toxicity

Castor Oil

Masri et al. (1962) conducted an experiment in which ten male weanling rats (4 weeks old; mean weight = 42.2 ± 0.6 g) were fed (ad libitum) 10% castor oil for approximately 5 weeks. A similar control group (mean weight = 42.2 ± 0.5 g) received corn oil in the diet. The animals were observed for growth and catharsis throughout the duration of the study. Castor oil in the diet did not induce catharsis in any of the 10 rats, and growth of these animals was comparable to that observed in the control group. At the end of the experiment, mean weights for test and control rats were 155.6 ± 4.6 and 160.5 ± 4.1 g, respectively. Grossly, there were no abnormalities. Additionally, no abnormalities of the perirenal fat were noted.

Short-Term Subcutaneous Toxicity

Castor Oil

In a study by Migally (1979), the morphology of the adrenal cortex was examined after injection of a commonly used vehicle consisting of castor oil and benzyl benzoate. Twenty-five adult C57 BL/6J mice (weights not stated) were divided into the following groups: group I (five intact control mice); group II (five sham-injected mice); group III (five mice each injected with 0.1 ml castor oil); group IV (five mice each injected with 0.1 ml benzyl benzoate; and group V (five mice each injected with 0.1 ml castor oil and benzyl benzoate [4:1]). The mice were injected subcutaneously daily for four weeks and then killed. Necropsy was then performed and tissues prepared for light and electron microscopic examination.

Using electron microscopy, parenchymal cells containing electron-dense lipid inclusions were observed in the zona fasciculata of adrenal glands from mice injected with castor oil. By light microscopy, there was no difference between adrenal glands from control mice and mice injected with the vehicle consisting of castor oil and benzyl benzoate; however, by electron microscopy, the following variations were observed: profound disruption of parenchymal mitochondria in the zona fasciculata and a noticeable increase in size for some of the mitochondria. The vesicular orientation of the inner mitochondrial membrane was lost (i.e., random orientation), and diminution of the mitochondrial matrix was also observed.

Unlike the controls, the macrophages of exposed animals had large vacuoles filled with globular material. In the zona reticularis and inner zona fasciculata, parenchymal mitochondria with circular orientation of the inner membrane (normally few) were noticeably increased in number. The authors noted the appearance of similar mitochondria following adrenocorticotrophic hormone (ACTH) stimulation, and that the alteration of ACTH release has been shown to result from stress. The author concluded that subcutaneous injection of the castor oil–benzyl benzoate vehicle caused morphological alterations that are suggestive of stress-induced changes (Migally 1979).

Subchronic Oral Toxicity

Castor Oil

In a study by the National Toxicology Program (NTP) (1992), the subchronic oral toxicity of castor oil was evaluated using groups of 10 male and 10 female F344/N rats (mean body weights = 126 to 132 g [males]; 107 to 110 g [females]) and groups of 10 male and 10 female B6C3F₁ mice (mean body weights = 22.6 to 23.0 [males]; 17.2 to 17.7 [females]). In the core study, five groups of test animals (mice or rats) received diets containing 0.62%, 1.25%, 2.5%, 5.0%, or 10% castor oil continuously for 13 weeks. Two control groups of 20 rats and 20 mice received diets that did not contain castor oil.

Ten additional rats/sex were included at each dose level for evaluation of hematological and clinical chemistry parameters. On days 5 and 21, these animals were anesthetized with CO₂ and blood samples were obtained. These animals were killed following blood collection on day 21. Blood samples for hematology and clinical chemistry were also collected from core-study rats at the end of the study. Also, at the end of the 13-week study, all core-study animals were killed and complete necropsies were performed, including complete microscopic examination on tissues, on all test and control animals.

No effect on survival or significant differences in average food consumption were noted in any of the five groups of male and female rats fed castor oil. There were no significant differences in mean body weights between test and control groups.

The following hematological effects were reported for male rats: a slight decrease in mean corpuscular hemoglobin

concentration (MCHC) (10% castor oil diet), a statistically significant decrease ($p < .05$) in mean corpuscular volume (MCV) (10% castor oil diet), a decrease in mean corpuscular hemoglobin (MCH) (5% and 10% castor oil diets), and an increase in platelets (1.25%, 5%, and 10% castor oil diets). The only hematological abnormality reported for female rats was a statistically significant ($p < .05$) decrease in reticulocyte counts (0.62% or 10% castor oil diets). The authors did not consider the hematological effects to be biologically significant. A dose-related increase (treatment-related) in the activity of serum alkaline phosphatase was noted in male and female rats at days 5 and 21, and at the end of the study.

Increased heart-to-body weight ratios were reported for male rats that received 0.62%, 2.5%, and 10.0% castor oil diets; however, no increase in absolute heart weight was noted. The observed differences in organ-to-body weight ratios were not considered treatment related. Microscopically, no morphologic changes were associated with the slight differences in organ weights between the dietary groups.

Compared to controls, liver weights were increased in male and female mice receiving diets containing 5% or 10% castor oil. Increased kidney weights were reported for female mice that received 5% or 10% castor oil in the diet. Microscopically, there was no evidence of morphologic changes that could be associated with the slight differences in organ weights between the groups tested. Additionally, there was no evidence of treatment-related lesions in any of the tissues or organs that were examined (all dietary groups).

The authors concluded that diets containing up to 10% castor oil to B6C3F₁ mice and F344/N rats was not associated with toxicity to any specific organ, organ system, or tissue in this study (NTP 1992).

Hydrogenated Castor Oil

In a preliminary feeding trial (preparatory to the 16-week feeding study reported below) by Binder et al. (1970), the subchronic oral toxicity of 5%, 10%, and 20% Hydrogenated Castor Oil [HCO] (effective concentrations of 4.33%, 8.65%, and 17.3%, respectively) in the diet was evaluated using groups of three weanling female rats (Slonaker substrain of Wistar strain). The sample of HCO that was incorporated into the diet contained 86.5% 12-hydroxystearic acid, 10.3% nonoxygenated acids, and 3.2% 12-ketostearic acid. The three groups were fed for 90 days, and the control group received diet only. At necropsy, organ weights were recorded and numerous tissues were prepared for microscopic examination. Prior to necropsy, blood samples were obtained for hematological evaluation.

A reduced growth rate in rats fed 8.65% and 17.3% Hydrogenated Castor Oil, respectively, was the only abnormality that was noted. The authors stated that it is likely that Hydrogenated Castor Oil was poorly digested because of its high melting point. Therefore, the poor body weight gains may have been due to the lower caloric density of the diets containing Hydrogenated Castor Oil at concentrations $\geq 8.65\%$.

To confirm the authors' explanation of the results, the experimental trial was repeated with Hydrogenated Castor Oil at concentrations of 1%, 5%, and 10% in corn oil (effective concentrations of 0.865%, 4.33%, and 8.65%, respectively). The amount of corn oil added to the individual diets was 9%, 15%, and 10%. Corn oil (20%) was present in the control diet. Necropsy was performed at the end of the 90-day feeding period. The growth rate for rats fed 8.65% Hydrogenated Castor Oil in the diet was equivalent to that of the other dietary groups. Based on organ weight determinations and the results of hematological and microscopic evaluations, no adverse effects were observed (Binder et al. 1970).

In the 16-week feeding study (Binder et al. 1970), groups of 15 male albino rats (Slonaker substrain of Wistar strain, weights = 43 to 83 g) received diets containing the following oils: group 1 (fed 0.865% HCO + 19% corn oil for 16 weeks), group 2 (0.865% HCO + 19% corn oil for 8 weeks, then 20% corn oil for 8 weeks), group 3 (8.65% HCO + 10% corn oil for 16 weeks), and group 4 (8.65% HCO + 10% corn oil for 8 weeks, then 20% corn oil for 8 weeks).

The effective dietary concentrations of Hydrogenated Castor Oil in the 0.865% and 8.65% diets were 0.865% and 8.65%, respectively. The control group received 20% corn oil in the diet for 16 weeks.

At 4, 8, 12, and 16 weeks, the number of animals on the HCO diets that were alive was 33, 30, 12, and 6 rats, respectively. The corresponding number of rats remaining on the control diet was 15, 15, 12, and 6.

Weight differences due to the different diets at 4 and 8 weeks were not statistically significant at the 95% level. However, at 12 weeks, rats on the 8.65% HCO diet weighed significantly less than rats on the control diet or 0.865% HCO diet. At 16 weeks, the weight gain of rats on the control diet was significantly greater than that of rats on the 8.65% HCO diet for 16 weeks or on the 8.65% HCO diet for 8 weeks + control diet for the remaining 8 weeks. The weight gain of rats on the 0.865% HCO diet was not significantly different from that of rats on the control diet. Except for the reduced growth rate in rats receiving the 8.65% HCO diet, no adverse effects were observed (Binder et al. 1970).

Ocular Irritation/Toxicity

Castor Oil

Carpenter and Smyth (1946) evaluated the ocular irritation potential of castor oil using albino rabbits. The eyelids were retracted, and undiluted castor oil (0.5 ml) was applied to the center of the cornea. At approximately 1 min post instillation, the eyelids were released. Reactions were scored 18 to 24 h later. To determine the score for ocular injury, the individual numerical scores for each eye were added together and then divided by the number of eyes (usually 5). An ocular injury score of 5.0 represents severe injury, and corresponds to necrosis (covering approximately three-fourths of the corneal surface) that is visible only after staining or a more severe necrosis covering a smaller

area. An injury grade of 1 (maximum score possible = 20) was reported for castor oil.

In a study by Guillot et al. (1979), the effects of various oils (used in cosmetics) on the rabbit eye were assessed according to the official French methods. Following the instillation of undiluted castor oil (no ocular rinsing), no corneal involvement was found. However, slight congestion of the iris and conjunctiva was observed.

Castor oil served as one of the vehicle controls in a study by Behrens-Baumann et al. (1986) investigating the effect of topical cyclosporin A on the abraded and intact rabbit cornea. Two castor oil vehicle control groups of outbred male rabbits were used. In both groups (10 eyes/group), 10 drops of castor oil were instilled daily for 3 weeks, and all eyes were examined using a slit-lamp. At the end of the 3-week period, the animals were killed and their corneas were excised and prepared for scanning and transmission electron microscopy. For eyes (no corneal abrasion) treated with Castor oil and examined by scanning electron microscopy, there were increased numbers of medium dark and dark epithelial cells (compared to the normal epithelium). The cell borders were intact and the number of holes was reduced. By transmission electron microscopy, corneal endothelial cells were intact. By scanning electron microscopy, an intact cell pattern, with more cell microstructures than normal, for the corneal endothelium was reported. Ultrathin sections appeared normal. The authors concluded that castor oil did not damage the rabbit corneal epithelium or endothelium (Behrens-Baumann et al. 1986).

Skin Irritation

Castor Oil

Butcher (1951) evaluated the effect of castor oil and other substances on rat epidermis using, primarily, 22-day-old albino or Long-Evans rats or rats of either strain in which the hair follicles were in the resting stage; older animals were also used. A total of 216 rats were used in the experiments. Using dry cotton, castor oil was gently swabbed onto a large area of the dorsum (clipped free of hair) daily for 5 days to 2 weeks. At the end of the application period, small areas of skin were obtained from the backs of treated and control (one rat/litter) rats and examined microscopically. Castor oil was described as having a mild effect on the epidermis. The alteration was mainly confined to the stratum granulosum, where the cells were more numerous and the granules were more evident, compared to the litter-mate controls.

In a study by Meyer et al. (1976), castor oil (undiluted, 4 drops) was rubbed onto either side of the shaved left flank of each of six albino guinea pigs (weights = 300 to 400 g) and six young pigs (weights = 10 to 12 kg) within 30 s on 10 successive days. The opposite side served as the control field, and was massaged only. The animals were killed on day 11. A tissue section (1 × 1 cm) was excised from the center of the test fields and prepared for microscopic examination. Five to eight sections of 7 μ m thickness per test area were used for evaluation.

A micrometer eyepiece was inserted into the microscope, and epidermal width measurements (25 per individual field; 400× magnification) were made. Castor oil induced slight reddening at the application site.

Microscopically (pigs and guinea pigs), hyperplasia, with an increase in the cell and nuclear density of the basal cell layers, was observed. Additionally, widening of the granular layer and thick keratohyalin granules were observed. Average epidermal widths (25 measurements) were as follows at the end of the 10-day application period: guinea pigs (control, 27.9 μ m; test, 94.3 μ m) and pigs (control, 26.5 μ m; test, 32.3 m) (Meyer et al. 1976).

Rantuccio et al. (1981) evaluated the effect of undiluted castor oil on the skin of five female albino rabbits (6 months old; mean weight = 2500 g). The test substance (0.5 ml) was gently massaged into depilated skin of the right flank of each rabbit daily for 30 days. Following each daily application, the test site was covered with a simple protective dressing. Two small skin punch biopsies were obtained from the right and left (control) flank on days 10, 20, and 30. Macroscopic skin changes included slight erythema and slight edema. Microscopic examination of punch biopsies obtained at day 10 revealed "clear-cut" acanthosis with vacuolization and disorganization of the basal layer. These changes were associated with some infiltration of the dermis by mononuclear cells and fibrocytes. After days 20 and 30, the epithelial changes became progressively more evident. However, the appearance of the infiltrate remained unchanged.

In a study by Guillot et al. (1979), the effect of various oils that are used in cosmetics on rabbit skin was assessed according to the official French methods. An open skin irritation test and repeated application test (8 weeks) were performed. The authors stated that the two samples of undiluted castor oil, as well as 10% aqueous castor oil, were well tolerated.

In a study by Motoyoshi et al. (1979), the skin irritation potential of castor oil (undiluted) was evaluated using six albino angora rabbits (average weight = 2.6 kg). The test substance (0.1 g of liquid or semisolid) was applied for 24 h to two test areas (clipped free of hair) on the dorsal surface of each animal. A plastic collar was wrapped around the neck of each animal and remained throughout the application period, after which reactions were scored according to the following scale: – (no reddening) to + + + (severe reddening, beet redness). At 30 min, after reactions were scored, the test areas were clipped free of hair and castor oil was reapplied according to the same procedure. A third application of Castor Oil occurred 48 h later, and reactions were scored. Reactions were scored again at 72 h. Castor oil was severely irritating to the skin of rabbits (score = 3).

The skin irritation potential of Castor oil was also evaluated using guinea pigs, rats, and miniature swine in this study.

Undiluted castor oil (0.1 g) was applied daily to dorsal skin (clipped free of hair) in the mid-lumbar region of six male Hartley guinea pigs (weights = 350 to 500 g) and six male Wistar rats (weights = 250 to 350 g). The period of testing, the frequency of application, and the method of evaluation of skin reactions were

the same as those in the preceding test involving albino angora rabbits. Castor oil was mildly irritating to the skin of guinea pigs and rats.

The skin irritation potential of undiluted castor oil was evaluated using six miniature swine of the Pitman-Moore strain (1 month old). The test substance (0.05 g) was introduced under a 15-mm-diameter patch that was secured with adhesive tape. The entire trunk was wrapped with rubberized cloth during the 48-h exposure period. Reactions were scored after patch removal. The grading scale was the same as that used in the experiment involving albino angora rabbits that is summarized above. Castor oil was not irritating to the skin of miniature swine (Motoyoshi et al. 1979).

Ricinoleic Acid

In a study by Vieira et al. (2000), 8 to 10 male Swiss mice received a single topical application of Ricinoleic Acid (in peanut oil, 10 mg/mouse) on the ventral surface of the paw. Neither erythema nor edema of the paw was observed.

Vieira et al. (2001) presented results on the skin irritation potential of Ricinoleic Acid, using groups of six male albino Dunkin-Hartley guinea pigs, in a study evaluating pro- and anti-inflammatory effects of Ricinoleic Acid (concentration not stated). Ricinoleic Acid (0.1 ml, in peanut oil) was administered topically to the entire eyelid surface. The thickness of the eyelid was measured in mm using ophthalmic microcallipers. Topical treatment with Ricinoleic Acid (10, 30, or 100 mg/guinea pig) caused eyelid reddening and edema. A moderate, dose-dependent eyelid edema was reported as follows: 0.12 ± 0.05 mm (10 mg Ricinoleic Acid), 0.18 ± 0.02 mm (30 mg), and 0.23 ± 0.1 mm (100 mg). Maximal edema was achieved at 2 h post-application. The application of Ricinoleic acid vehicle did not cause any appreciable edema.

Cetyl Ricinoleate

In a skin irritation study conducted by the Laboratoire de Recherche et d'Experimentation (1994), Cetyl Ricinoleate (test concentration not stated) was evaluated using three male New Zealand albino rabbits. Erythema and edema were observed in three and two rabbits, respectively, up to 72 h post application. At 72 h, one rabbit had an erythema score of 2 and the remaining two had an erythema score of 1. Edema (score = 1) was observed in two rabbits at 72 h. All reactions were totally reversible at 7 days post application. Cetyl Ricinoleate was a nonirritant in this study.

Zinc Ricinoleate

In a study by International Bio-Research, Inc. (1977a), the skin irritation potential of 10% Griillocin HY 77 (now TEGODEO HY 77) in soybean oil was evaluated using six New Zealand albino rabbits (weight range = 2.4 to 2.6 kg). TEGODEO HY 77 (trade name mixture for Zinc Ricinoleate) has the following composition: Zinc Ricinoleate (more than 50%), triethanolamine (10% to 25%), dipropylene glycol (1%

to 5%), and lactic acid (1% to 5%). The diluted test substance (concentration after dilution not stated) was applied to clipped skin on two areas of the back of each animal; one of the areas was abraded. The test sites were covered with occlusive patches (secured with adhesive tape) and the entire trunk was wrapped in a rubber sleeve. The patches remained in place for 24 h and reactions were scored at 24 and 72 h post application as follows according the Draize scale: 0 (no erythema) to 4 (severe erythema [beet redness] to slight eschar formation [injuries in depth] and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond area of exposure).

At 24 h post application, well-defined erythema was observed at the abraded test sites of all six rabbits and slight erythema was observed at the intact sites of four rabbits. Well-defined erythema was observed at the intact sites of two rabbits during the 24-h reading. At 72 h post application, five rabbits had mild erythema at the abraded site and two rabbits had the same reaction at the intact site. Using the data for abraded and intact test sites, a total primary irritation index of 1.1 was calculated (International Bio-Research, Inc. 1977a).

Effect on Intestinal Membranes

Ricinoleic Acid

In a study by Morehouse et al. (1986), a single 0.1 ml dose of Ricinoleic Acid (100 mg/ml) was administered intragastrically to fasted, specific pathogen-free mice (strain CD-1, number not stated). This dosage of Ricinoleic Acid was determined, on a weight basis, to be approximately the dosage that is used therapeutically in humans. Groups of mice were killed at various intervals, and light microscopy and transmission and scanning electron microscopy were used to identify structural alterations. At 2 h post dosing, the duodenal villi were markedly shortened when compared to control duodenal villi. This erosion of the villi throughout the duodenum caused massive exfoliation of columnar and goblet cells, filling the lumen with cellular debris and mucus. Disruption of the mucosal barrier resulted in continuity between the intestinal lumen and lamina propria of the villi, with the loss of formed blood elements and lamina propria constituents into the intestinal lumen. The mucosal damage was much more localized at 4 h post dosing, and the erosion of the villi had been largely repaired. Repair was complete at 6 h post dosing.

Sodium Ricinoleate

Gaginella et al. (1977a) studied the morphology of the colon after perfusion of the organ with Sodium Ricinoleate solution, using 25 male New Zealand white rabbits. A Foley catheter was inserted and the colon was perfused with control solution (1.25 ml per minute) for 20 min. The colon was then flushed and perfused with the test solutions. Ten rabbits were perfused with 10 mM Sodium Ricinoleate and the remaining three groups of five were perfused with 2.5, 5.0, and 7.5 mM, respectively. The animals were killed and full thickness samples of colon

were obtained and prepared for light or scanning electron microscopy. In additional experiments, tissue was obtained from animals that were not perfused and those perfused with control buffer (contained PEG 400) for 60 or 160 min.

Using scanning electron microscopy, mucous membranes of colons perfused with control buffer for 60 min and unperfused colons appeared normal. After 1 h of perfusion with 10 mM Sodium Ricinoleate, patchy loss of epithelial cells was apparent. The loss of epithelial cells was confirmed using light microscopy. A dose response-relationship for mucosal damage was noted. The most severe damage resulted from perfusion with 10 mM Sodium Ricinoleate. Lesser degrees of change and lesser areas of mucosal surface affected were associated with lower concentrations. Small amounts of DNA (due to loss of DNA into the lumen) accumulated in the control buffer, and perfusion with 2.5 mM Sodium Ricinoleate did not cause a significant increase in these amounts. However, DNA accumulation increased significantly after perfusion with 5.0, 7.5, and 10 mM Sodium Ricinoleate, and a plateau was reached with 7.5 mM solutions.

The control perfusate that was used contained low (PEG 400) and high-molecular-weight (PEG 4000) polyethylene glycols. The absorption of PEG 400 increased progressively with increases in the concentration of Sodium Ricinoleate (above 2.5 mM) perfused. Sodium Ricinoleate (2.5 mM) did not increase absorption of the individual polymers that comprise PEG 400 (molecular weight 242 to 594). The absorption of lower molecular weight polymers (242 to 462) increased significantly ($p < .005$) in the presence of 5, 7.5, and 10 mM Sodium Ricinoleate. For higher molecular weight polymers (506 to 594), increased absorption in the presence of 5 mM Sodium Ricinoleate was not observed. However, significantly increased absorption ($p < .05$) of the higher molecular weight polymers was observed during perfusion with 7.5 and 10 mM Sodium Ricinoleate (Gaginella et al. 1977a).

Comedogenicity

Castor Oil

Fulton et al. (1976) evaluated the comedogenicity of cosmetics and cosmetic ingredients. Castor oil was applied to the base of the internal right ear of each of three white albino rabbits on Monday through Friday for 2 weeks. The left ear served as the control. Comedogenicity was clinically evaluated on the following Monday using the scale: 0 (no increase in visible hyperkeratosis) to 5 (severe lesions, such as those seen following the application of coal tar). Six-millimeter punch biopsies (right ear) were obtained for microscopic examination, and comedogenicity was evaluated according to the same scale. A score of 1 (increase in visible hyperkeratosis extending to the possible presence of comedones) was reported for castor oil, which was considered nonsignificant because repeated testing in different rabbits often failed to produce identical effects.

In a study by Morris and Kwan (1983), the comedogenicity of castor oil was evaluated using three New Zealand rabbits.

Castor oil was applied to the external ear five times weekly (one application per day). The actual amount applied ranged from 5 to 10 mg/cm². The animals were killed after the 14th application and several full-thickness sections of the test site and contralateral untreated ear were prepared for microscopic examination. Comedogenic activity was based on the degree of follicular hyperkeratosis and other morphologic changes in the majority of pilosebaceous units, when compared to control sections. Comedogenicity was graded according to the following scale: 0 (negative: pilosebaceous unit normal in appearance when compared to control [untreated] ear section) to 5 (severe: widely dilated follicles, filled with packed keratin; follicular epithelial hyperplasia causing partial or total involution of sebaceous glands and ducts; possible inflammatory changes). Comedogenicity scores for castor oil were 0 to 1, corresponding to a slight increase in keratin content within the follicle, with essentially no change in follicular epithelium.

Fulton (1989) evaluated the comedogenicity of castor oil (mixed in propylene glycol at 9:1 dilution; test concentration = 10%) using three New Zealand albino rabbits. The test substance (1 ml) was applied onto the entire inner surface of one ear 5 days per week for 2 weeks. Untreated ears served as controls. Follicular keratosis was evaluated both macroscopically (visually) and microscopically, using a micrometer to measure the width of the follicular keratosis. Follicular keratosis was evaluated according to the following scale: 0 or 1 (no significant increase in follicular keratosis) to 4 or 5 (an extensive increase in follicular keratosis). The following scale was used to evaluate skin irritation that resulted from repeated application of the test substance: 0 (no irritation) to 5 (epidermal necrosis and slough). A follicular keratosis score of 1 and an irritation score of 0 was reported for castor oil.

Skin Sensitization

Zinc Ricinoleate

International Bio-Research, Inc (1977b) conducted a skin sensitization study on Grillocin HY 77 (now TEGODEO HY 77) using 30 white guinea pigs (average weight = 300 g). TEGODEO HY 77 (trade name mixture for Zinc Ricinoleate) has the following composition: Zinc Ricinoleate (more than 50%), triethanolamine (10% to 25%), dipropylene glycol (1% to 5%), and lactic acid (1% to 5%) (Degussa 2001). Test and control groups consisted of 20 and 10 guinea pigs, respectively. A closed patch containing the trade mixture (0.5 ml, undiluted) was placed on the left shoulder, clipped free of hair, of each animal and remained in place for 6 h. Treatments were repeated once weekly for 3 weeks.

At two weeks after the last exposure, test and control guinea pigs were challenged (same procedure, right side) with duplicate closed patches. At 24 h post removal of the patches, the test site on each animal was treated with a depilatory. Sites were then rinsed and reactions were graded 2, 24, and 48 h later according to the method of Draize. Clinical observations were

normal throughout the study. Erythema and eschar formation were graded according to the following scale: 0 (no erythema) to 4 (severe erythema [beet redness] to slight eschar formation [injuries in depth]). The following scale for edema formation was used: 0 (no edema) to 4 (severe edema [raised more than 1 mm and extending beyond area of exposure]). A score of 0 (erythema and edema) was reported for each test and control animal during each of the three grading periods. Grillo cyn HY 77 did not produce a positive reaction in any of the test animals (International Bio-Research, Inc. 1977b).

Allergenicity

Hydrogenated Castor Oil

Lehrer et al. (1980) investigated the presence of castor bean allergens in Castor Wax (Hydrogenated Castor Oil) using both in vitro and in vivo analyses. The experiments in this study involving human subjects are summarized under the subsection Allergenicity in the Clinical Assessment of Safety section of this report. The following solvents were used to prepare aqueous extracts of Castor Wax: phosphate buffered saline (PBS), urea-NaCl, Triton X-100, or sodium lauryl sulfate (SLS). The aqueous extracts prepared were analyzed for total organic matter and protein (expressed as percent of total organic matter or dry weight). Results from assays for protein in the aqueous extracts of Castor Wax were as follows: 100% protein (urea-NaCl extract), 17.0% (SLS extract), 12.9% (PBS extract), and 0.34% (Triton X-100 extract) protein.

In a qualitative precipitation analysis, Castor Wax aqueous extracts were analyzed for castor bean antigens using an immunodiffusion procedure involving rabbit antiserum (50 μ l of antigen or antiserum in each well). The antiserum was produced in rabbits that had been immunized with extracts of castor bean in Freund's complete adjuvant. Of the aqueous extracts tested, only the SLS Castor Wax extract reacted with the rabbit antiserum. No reactivity with the antiserum was observed when the SLS solution alone was tested. Because the reaction was unusually strong, suggesting a false-positive reaction, the extract was tested with normal rabbit serum. However, the same precipitin line was observed. It was concluded that the reaction of the SLS Castor Wax extract with rabbit serum proteins was probably a nonspecific reaction.

The aqueous extracts of Castor Wax were also analyzed for allergens by determining their reactivity (48-h passive cutaneous anaphylaxis [PCA] reaction) with mouse anticastor reaginic (immunoglobulin E [IgE]) antibody. CFW female mice were sensitized with reaginic antibody that was produced in BDF mice that had been immunized with heated castor bean extracts and *Bordetella pertussis* adjuvant. The mice were challenged 48 h later by intravenous injection of extracts of Castor Wax in 0.5% Evans blue solution and killed at 30 min post injection. Nonsensitized mice challenged with Castor Wax extracts served as controls. The reactions in control mice were always classified as negative. The antiserum did not react with PBS, urea-NaCl,

or Triton X-100 extracts of Castor Wax, but a positive response (positive PCA titer of 40, mean of three determinations) resulted from the reaction of the antiserum with the SLS extract of Castor Wax.

The radioallergosorbent test (RAST) inhibition assay was used for further analysis of allergens in the extracts of Castor Wax. This assay was capable of detecting up to 7.5 μ g castor allergen. Patient serum (100 μ l) and Castor Wax extract (100 μ l) were incubated with antigen-coated discs. Incubation was followed by the addition of radioiodinated anti-IgE and another incubation period. Normal serum incubated with antigen coated discs and test serum incubated with discs coated with a non-cross-reacting antigen served as controls. Assay results were expressed as percent inhibition of the patients' RAS test. Neither the PBS nor Triton X-100 extract of Castor Wax had an inhibitory effect on the RAS test, whereas the urea-NaCl extract induced a small degree (13.4%) of inhibition. However, the SLS Castor Wax extract induced significant inhibition (40.1%) of the RAS reaction.

Based on the nonspecific reaction of the SLS Castor Wax extract with rabbit serum proteins in the first experiment of this study, the authors examined the possibility that this extract may inhibit the RAST nonspecifically using a heterologous RAST inhibition assay. An SLS or Triton X-100 extract of Castor Wax was incubated with reaginic antisera from a patient who was sensitive to peanuts, and then assayed in the peanut RAST. The SLS extract of Castor Wax inhibited the peanut RAST by 37%, suggesting that the results for the RAST inhibition assay in the preceding paragraph may be due entirely or, in part, to a nonspecific inhibition of the RAST reaction, rather than indicating that the SLS extract of Castor Wax contains specific castor allergens.

The results of these experiments (both in vitro and in vivo) indicate that allergens are present at low concentrations in Castor Wax, because the SLS Castor Wax extract induced positive PCA reactions in mice and a positive direct RAS test for reaginic castor allergens (Lehrer et al. 1980).

NEUROTOXICITY

Sodium Ricinoleate

Fox et al. (1983) applied Sodium Ricinoleate (0.01% to 1.0%) to the serosal surface of the rat (anesthetized male Sprague-Dawley rats, weights = 200 to 225 g) jejunum every 5 min for 0.5 h. At 30 days post application, treated and untreated jejunal segments were removed and examined microscopically. At a concentration of 0.1%, Sodium Ricinoleate significantly reduced ($p < .02$) the number of ganglion cells in the myenteric plexus. The highest test concentration (1% Sodium Ricinoleate) significantly reduced the number of cells in the myenteric plexus ($p < .01$) and the submucosal plexus ($p < .02$). The lowest test concentration (0.01%) did not significantly reduce the number of ganglion cells in the myenteric or submucosal plexus.

Renal Toxicity

Castor Oil

Langer et al. (1968) evaluated effects of castor oil on the rat kidney, following intraluminal injection, using five male white albino rats (weights = 180 to 220 g). The kidney was exposed and proximal tubuli were punctured (using Leitz stereomicroscope) and filled with castor oil. At 15 to 60 min, the proximal tubular segments (filled with oil) were fixed in situ. The kidney was excised and prepared for both light and electron microscopic examination. The injection of castor oil resulted in dilatation of the proximal convoluted tubular lumen and compression of the brush border of proximal tubular cells, although a cessation of the normal pinocytosis was induced in the presence of tubular fluid. A toxic effect of castor oil on the tubular epithelium was not observed.

In a study by Racusen et al. (1986) evaluating the nephrotoxicity of cyclosporine, castor oil served as the vehicle control. Two control groups of eight adult male Munich-Wistar rats (weights = 220 to 270 g) were used. Group 1 vehicle controls (vehicle-ischemia group) underwent bilateral renal artery clamping, and were then dosed intraperitoneally (i.p.) daily (4-day period) with a volume of castor oil vehicle that was equivalent to the i.p. dose of cyclosporine (dose = 60 mg/kg). Group 2 vehicle controls (vehicle-sham group) underwent sham surgery. The incisions were closed prior to daily i.p. dosing with castor oil. On postoperative day 3, feed was withdrawn and urine was collected over a period of 12 h for clearance studies. On postoperative day 4, the animals were killed and tissues prepared for light and electron microscopy (confined to cortical proximal convoluted tubules).

In separate studies, renal blood flow and the glomerular filtration rate were determined. Two groups of eight saline control groups (saline-ischemia and saline-sham groups, respectively) were treated according to the same procedure.

Tubular vacuolization was a prominent feature in vehicle-ischemia control rats, and was observed to a minor degree in the vehicle-sham control rats. The clear vacuoles observed using light microscopy probably corresponded to two ultrastructural changes, dilated endoplasmic reticulum and lipid droplets. With the exception of the saline-sham group, dilated endoplasmic reticulum was observed in all control animals. However, lipid droplets were not observed in any of the control animals. The presence of eosinophilic cytoplasmic inclusions was reported for two of eight vehicle-ischemia rats and four of eight vehicle-sham rats, but not for saline-control rats. Tubular necrosis (confined entirely to outer medullary pars recta) was observed in half of the vehicle-ischemia rats and in all saline-ischemia rats, but was not observed in saline-sham or vehicle-sham control groups. Tubular regeneration was noted in vehicle-ischemia and saline-ischemia control rats.

The renal clearance study involved two control groups that were dosed with castor oil (five rats) or mineral oil (six rats). Two 20-min inulin clearance determinations were made, and the vehicle was then administered i.p. (at dose volume comparable to 60

mg/kg cyclosporine dose; administered to test group of seven) in a region of the upper right abdomen. Dosing was followed by five 20-min clearance periods. Compared to the mineral oil control group (six rats), a significant decrease (25% decrease; $p < .05$) in renal blood flow was noted in rats (group of five) dosed i.p. with castor oil. Renal vascular resistance was also significantly higher ($p < .05$). No significant changes in inulin clearance were reported. A significant decrease in blood pressure was noted in all groups; however, blood pressure remained within the physiologic and autoregulatory range (Racusen et al. 1986).

GENOTOXICITY

Castor Oil

Zeiger et al. (1988) evaluated the mutagenicity of castor oil (United States Pharmacopeia purity grade; in dimethylsulfoxide [DMSO]) in the preincubation assay using *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537. The assay was conducted, with and without metabolic activation, according to a modification of the procedure by Haworth et al. (1983). Castor oil was tested at doses up to 10,000 $\mu\text{g}/\text{plate}$ and classified as nonmutagenic (all strains, with and without metabolic activation) over the range of doses tested in this assay.

Hachiya (1987) evaluated the mutagenicity of castor oil using *S. typhimurium* strains TA97, TA98, TA100, TA102, TA1537 and strain WP2/pKM102 of *Escherichia coli*. In each strain, castor oil was tested at doses ranging from 100 to 5000 $\mu\text{g}/\text{plate}$ with and without metabolic activation. Results were negative for all strains tested, both with and without metabolic activation. Cytotoxicity (at doses of 100 to 5000 $\mu\text{g}/\text{plate}$) was noted only in strain WP2/pKM102, with and without metabolic activation.

NTP (1992) reported a study in which groups of male and female B6C3F₁ mice received diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10% castor oil (in DMSO) for 13 weeks. Blood samples were obtained at the end of the 13-week study. There was no evidence of induction of micronuclei in peripheral erythrocytes.

NTP (1992) also evaluated the induction of sister chromatid changes by castor oil (in DMSO) in Chinese hamster ovary cells. The cells were incubated with castor oil at concentrations up to 5000 $\mu\text{g}/\text{ml}$ with and without metabolic activation. Mitomycin-C and cyclophosphamide served as positive controls without and with metabolic activation, respectively. DMSO served as the solvent control. Castor oil did not induce sister chromatid exchanges either with or without metabolic activation.

Sodium Ricinoleate

In a study by Haworth et al. (1983), the mutagenicity of Sodium Ricinoleate was evaluated according to the preincubation procedure of the *Salmonella* assay (Ames et al. 1975) as described by Yahagi et al. (1975). Sodium Ricinoleate (in distilled water) was tested at concentrations up to 33 $\mu\text{g}/\text{plate}$

at one testing laboratory, and up to 333.3 $\mu\text{g}/\text{plate}$ at another laboratory. The following *S. typhimurium* strains were used with and without metabolic activation: TA98, TA100, TA1535, and TA1537. Distilled water served as the vehicle control. The positive controls were as follows: 2-aminoanthracene, 4-nitro-*o*-phenylenediamine, sodium azide, and 9-aminoacridine. Results for Sodium Ricinoleate were negative with and without metabolic activation.

DNA Binding of Reaction Product

Methyl Ricinoleate

Frankel et al. (1987) evaluated the fluorescence formed by the interaction of DNA with lipid oxidation products. The keto ester, methyl ketoricinoleate, was prepared from Methyl Ricinoleate by allylic oxidation with a CrO_3 -pyridine complex in methylene chloride. Results from this assay indicated that methyl ketoricinoleate (relative concentration = 1 mM/3 ml) produced very little fluorescence (mean = 29 ± 2 units) with DNA in the presence of ferric chloride-ascorbic acid. The mean value for methyl linolenate hydroperoxides (used as reference) was 362 ± 9 units. Mean values were given as the fluorescence intensity of DNA after 72 h (excitation: 315 nm; emission: 420 nm).

CARCINOGENICITY

Ricinoleic Acid

In a study by Boyland et al. (1966), 2% Ricinoleic Acid, in gum tragacanth, was injected intravaginally into each of 20 BALB/c female mice (5 to 6 weeks old). Injections were made twice per week, and each animal received a total of 100 injections. According to the same dosing schedule, each of 20 positive control and 30 vehicle control mice received 62 injections of 0.3% dimethylbenz(*a*)anthracene and 100 injections of gum tragacanth, respectively. An additional 30 mice served as the untreated control group.

None of the 20 mice injected with Ricinoleic Acid had neoplasms or hyperplastic lesions of the corpus uteri, cervix uteri, vagina, or perineal skin. However, benign lung adenomas were observed in ten of the 13 mice dosed with Ricinoleic Acid and in 6 of the 24 vehicle control mice that were killed after the 14th month of dosing. Benign lung adenomas were also observed in 9 of the 20 untreated control mice that were killed after the 14th month. The difference in benign adenoma incidence between Ricinoleic Acid-treated and untreated control mice was not statistically significant ($p > .1$). Additionally, compared to controls, there was no tendency for Ricinoleic Acid-treated mice with adenomas to have a higher average number of tumor nodules per mouse. Malignant tumors of the vagina and perineal skin were observed in 15 of the 20 (75%) positive control mice. The authors stated that the results of this study do not provide any definite evidence of the carcinogenicity of Ricinoleic Acid (Boyland et al. 1966).

Tumor Promotion Activity

Castor Oil, Ricinoleic Acid, and Glyceryl Ricinoleate

Shubik (1950) evaluated the tumor promotion activity of castor oil, Ricinoleic Acid, Glyceryl Ricinoleate and the following other chemicals using groups of mice (strain and weights not stated): 20% turpentine in liquid paraffin, 0.3% acridine in liquid paraffin, 0.5% fluorene in liquid paraffin, 1% phenanthrene in liquid paraffin, silver nitrate (10% aqueous), and oleic acid. Castor oil, Ricinoleic Acid, Glyceryl Ricinoleate, and oleic acid were not diluted prior to testing.

Initially, the nine substances were tested using groups of three mice (one group per substance). The test substances were applied to a small area of skin in the interscapular region (clipped free of hair). Four applications per mouse, spaced over a period of 2 weeks, were made. At the end of the application period, the animals were killed and tissues were obtained for microscopic examination. The following substances induced slight epidermal hyperplasia: castor oil, Ricinoleic Acid, Glyceryl Ricinoleate, oleic acid, fluorene, and phenanthrene. Turpentine induced minimal histologic change, and acridine induced marked epidermal hyperplasia. Silver nitrate induced hyperplasia most marked in the hair follicles.

In the tumor promotion experiment (groups of 10 mice; strain and weights not stated), each mouse received a single application of 9,10-dimethyl-1,2-benzanthracene in liquid paraffin. The nine test substances (one per group) were then applied semiweekly for 20 weeks. For all groups of mice tested, no tumors were recorded. Castor oil, Ricinoleic Acid, and Glyceryl Ricinoleate, as well as the other test substances that were evaluated, were not tumor promoters in this study (Shubik 1950).

Ricinoleic Acid

Bull et al. (1988) investigated the effect of Ricinoleic Acid (unoxidized) on DNA synthesis and the induction of ornithine decarboxylase activity. The authors noted that unsaturated fatty acids are readily oxidized to a variety of biologically active derivatives, and have suggested that autooxidation products of polyunsaturated fatty acids may also play a role in the enhancement of tumorigenesis. They noted that this suggestion is based on published results (Bull et al. 1984) indicating that hydroperoxy and hydroxy derivatives of arachidonic acid and linoleic acids, the primary autooxidation products of major dietary unsaturated fatty acids, induce ornithine decarboxylase (ODC) and stimulate DNA synthesis (two components of mitogenesis) in colonic mucosa in vivo.

Male Sprague-Dawley rats (weights = 100 to 125 g) fed the following semisynthetic diet (weight percentages indicated) were starved for 24 h prior to intrarectal (i.r.) instillation of Ricinoleic Acid (vehicle: 5% ethanol in 50 mM NaHCO_3 , pH 8.0): casein (20%), DL-methionine (0.2%), salt mix (3.6%), vitamin mix (2%), beef fat (5%), dextrose (45.2%), cellulose (5%), and cornstarch (19%). Two experiments were performed using Ricinoleic Acid test concentrations of 5 and 10 mM. Test groups

consisted of three to five rats per dose level. The vehicle control group (three rats per experiment) was dosed with 5% ethanol in 50 mM NaHCO₃, and positive control animals received 6 mM deoxycholate. Data were presented as an average of the two experiments. The measurement of DNA synthesis in the colon was based on the incorporation of [³H]dThd 12 h after i.r. instillation of Ricinoleic Acid. ODC activity was determined in colonic mucosa that was harvested 3 h after i.r. instillation of Ricinoleic Acid.

Ricinoleic Acid was inactive as a stimulator of DNA synthesis and inducer of ODC activity in the rat colon. Concentrations up to 10 mM resulted in insignificant increases in [³H]dThd incorporation and did not increase the level of ODC activity above control values (Bull et al. 1988).

Anticancer Activity

Extract of Castor Oil

Xie et al. (1992) evaluated the anticancer/antitumor activity of an extract of castor oil using male Kunming mice (weights = 18 to 22 g) and mice bearing S₁₈₀ ARS ascitic fluid tumor cells. Castor oil was saponified and acidified to obtain a coarse, fatty acid mixture that was recrystallized and refined to produce the active anticancer component. Using Tween-80 (Polysorbate 80), an emulsion containing this component was produced. A polyphase liposome from castor oil extract was also produced. The inhibitory action of the anticancer component on S₁₈₀ tumor cells was evaluated. Ascites was obtained from mice that had been inoculated with S₁₈₀ tumor cells (with well-grown ascites) that had been washed with physiological brine in order to collect the cancer cells. The physiological brine was diluted and injected (2 ml) subcutaneously into the right front axilla of each mouse. On the day after injection of the tumor cells, the mice were randomly divided into groups.

The three dilution control groups (8 to 10 mice per group) were injected with 200, 300, or 400 mg/kg of a physiological brine solution containing an equal load of Tween-80. The four polyphase liposome control groups (eight mice per group) were injected with blank liposomes (doses of 300, 300, 400, and 400 mg/kg, respectively). For dilution control and polyphase liposome control groups, injections were made into the abdominal cavity daily for 7 days, after which the mice were killed. Subcutaneous tumors were removed and weighed in order to calculate the tumor suppression rate (%).

Tumor suppression rates for dilution controls were as follows: 30.6% (200 mg/kg dose group), 37% (300 mg/kg dose group), and 53.1% (400 mg/kg dose group). The following tumor suppression rates were reported for the polyphase liposome control groups: 40.2% (300 mg/kg dose group), 36.4% (the other 300 mg/kg dose group), 55.7% (400 mg/kg dose group), and 58% (the other 400 mg/kg dose group).

In another experiment, the inhibitory action of the anticancer component extracted from castor oil on ARS ascites cancer was evaluated according to a similar procedure. Ascites was obtained

from mice inoculated with ARS cancer cells (with well-grown ascites) that had been washed with physiological brine in order to collect the cancer cells. The physiological brine was diluted and injected (0.2 ml) into the abdominal cavity of each mouse. On the day after injection of the cancer cells, each of nine mice was injected with a polyphase liposome that was produced from castor oil extract (dose = 200 mg/kg) daily for 7 days. At the end of the treatment period, the animals were monitored (for survival) for an additional 35 days.

Study results indicate that the castor oil extract had a strong suppressive effect on S₁₈₀ body tumors in mice. Its suppressive effect on ARS ascites cancer was also very strong, with 64% of the ascites tumors in mice being completely cured. Compared to controls, the life extension rate was more than 136% ($p < .0012$) (Xie et al. 1992).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Castor Oil

NTP (1992) (see earlier Subchronic Oral Toxicity section) fed groups of rats and mice diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10% castor oil, respectively, continuously for 13 weeks. A slight decrease in epididymal weight (6% to 7%) was observed in mid- and high-dose groups of male rats; however, this finding was not dose related. No effects on any other male reproductive end point (testes weight and epididymal sperm motility, density, or testicular spermatid head count) or female reproductive endpoint (estrous cycle length, or time spent in each phase of the cycle) were noted. Microscopically, there were no treatment-related lesions in any organ or tissue. These results indicate that there was little or no evidence of any reproductive toxicity in rats that was associated with castor oil in the diet. For male and female mice, castor oil in the diet had no adverse effects on any male or female reproductive parameter.

Litvinova and Fedorchenko (1994) evaluated the influence of single doses of different plant oils on the estrous cycle and fertility using female Wistar rats (number and weights not stated). Castor oil (0.2 ml, single dose) was injected intramuscularly on the first day after estrus. Study of the estrous cycle was based on the following: the cytologic picture that was obtained from vaginal smears, the phase structure (proestrus, estrus, metaestrus, and diestrus) of the cycle, and the frequency of estrus over a 15-day observation period prior to injection of castor oil (control) and a similar length of time after injection (test). Fertility was studied using intact animals (control) and animals that were treated with castor oil. On day 2, after castor oil injection (i.e., during diestrus), the females were mated with male rats. Control females were also mated with male rats on day 2. The first day of pregnancy was defined by the presence of spermatozoa in vaginal smears. Pregnant females were killed on day 20. The estrous cycle phases were recorded 3 to 4 times during the 15-day observation period.

The injection of castor oil resulted in a reduction in the frequency of estrus by a factor of 1.4 and lengthening of the

interestrous phase by 39.6%. The authors concluded that the latter finding may be indicative of prolongation of luteolytic processes and an inhibition of folliculogenesis.

In female fertility experiments, mating occurred over a period of 3.22 ± 0.12 days. The index of fertility was calculated from the ratio of the number of mated females to the total number of females in the test. The fertility index for intact animals (control) was 100%, and pregnancy occurred in 100% of the cases. A decrease in the pregnancy index was reported for female rats injected intramuscularly with castor oil; however, no reliable difference between test and control values was detected.

Compared to controls, castor oil also caused a reduction in the number of corpora lutea in the ovaries, and this observation was said to have been a consequence of the suppression of folliculogenesis and ovulation. Additionally, the number of implantation sites in uteri from female rats injected with castor oil was decreased when compared to control rats. A decrease in the number of live fetuses in uteri and an increase in pre- and postimplantation deaths was also observed in rats injected with castor oil. The authors concluded that castor oil, injected intramuscularly, suppressed ovarian folliculogenesis and also had anti-implantation and abortive effects (Litvinova and Fedorchenko 1994).

Castor oil served as the vehicle control in a study evaluating the effect of long-term treatment with ICI 182,780 (an anti-estrogen) on the rat testis (Oliveira et al. 2001). Two groups of four male, 30-day-old Sprague-Dawley rats served as vehicle controls. In one control group, castor oil (0.2 ml) was injected subcutaneously once per week, and the animals were killed 100 days after the first injection. The second group was dosed according to the same procedure; animals were killed 150 days after the first injection. The experiment was extended to 150 days (group 2 rats), based on results for group 1 ICI-treated and control animals on day 100.

Specifically, Group 1 ICI-treated rat testes were significantly heavier (35% heavier, $p < .05$) than those of the control group, and a significant increase in diameter and luminal areas of the seminiferous tubules was observed. Additionally, in group 1 ICI-treated and control rats, spermatogenesis appeared normal and there was no evidence of degeneration or sloughing of germ cells.

On day 150, a 33% decrease (compared to day 100 results for ICI-treated rats; $p = .065$) in mean testicular weight was noted in ICI-treated rats. Seventy-five percent of the testes weighed less than the mean control value of 1.71 g. Atrophy of the seminiferous tubules was observed in all but one of the testes of ICI-treated rats. Additionally, the rete testis and efferent ductule lumens in all ICI-treated rats were greatly dilated, compared to those of controls.

During the treatment period, mating studies were performed to compare the fertility of ICI-treated and control rats on days 45, 73, 100, 125, and 150. Males were housed individually with two adult females for a 15-day period. Through 100 days of

treatment, there was no difference in male reproductive performance between ICI-treated and control rats. However, after day 100, 100% fertility was maintained in control males, but, by day 150, fertility had decreased to 25% in ICI-treated males (Oliveira et al. 2001).

Extract of Ricinus communis Seeds

The following study is included because castor oil may be extracted from the bean of the tropical plant, *Ricinus communis* by a method that involves the use of a solvent.

Okwuasaba et al. (1991) evaluated anticonceptive and estrogenic effects of a methanol extract of *Ricinus communis* var. *minor* seeds (ether-soluble fraction) using the following animals (groups of 10): adult albino Wistar rats (weights = 160 to 210 g), young albino Wistar rats (weights = 40 to 60 g), immature Swiss albino female mice (21 to 23 days old; weights = 10 to 13 g), and adult female New Zealand white rabbits (2.5 to 3.0 kg).

In the antifertility experiment, adult female rats and rabbits with regular estrus cycles were used. The females were mated overnight (3:1 female/male ratio), and the day of mating was considered day 0. Castor bean extract was injected subcutaneously (s.c. dose of 0.6 or 1.2 g/kg) into female rats once daily for two days, and mating occurred on the third day. Female rabbits were injected intramuscularly with Castor bean extract (dose = 200 mg/kg). Control animals were injected s.c. with corn oil for two consecutive days. A laparotomy was performed to confirm that implantation had occurred.

Castor bean extract (0.6 or 1.2 g/kg dose) prevented nidation in rats, and none of the treated rats delivered pups at term. The results for rabbits (200 mg/kg dose) paralleled those for rats. Nidation was prevented, and the extract protected the rabbits against pregnancy for over three gestation periods (i.e., 110 to 120 days). The normal gestation period for rabbits is 28 to 30 days. Effects induced by Castor bean extract were reversible in rats and rabbits. No fetal abnormalities were observed.

In the study to determine estrogenic activity, the following endpoints were used to estimate the estrogenicity of the Castor bean extract: uterine weight ratio, degree of vaginal cornification, and quantal vaginal opening. In one experiment, groups of 10 Swiss albino female mice (21 to 23 days old; weights = 10 to 13 g) were injected s.c. with 1.0 or 4.0 mg/kg Castor bean extract (in corn oil, 0.2 ml) daily for 4 days. In a similar experiment, bilateral ovariectomy was performed on young, immature rats (groups of five), and the wound was sutured. After a 15-day recovery period, the groups of rats were injected s.c. with 0.6 or 1.2 g/kg Castor bean extract (in corn oil, 0.2 ml) daily for 4 days. In both experiments, suitable controls (injected s.c. with corn oil only) were maintained. Additionally, estradiol-17 β (reference hormone; dose = 10 μ g/kg) was administered to rats (group of 10) and mice (group of 10). Mice and rats were necropsied 24 h after the last injection. Body and uterine wet weights were recorded.

Results for bilaterally ovariectomized rats indicated that doses of 0.6 and 1.2 g/kg induced increases in relative uterine weight of 116.7 ± 6.5 ($p < .01$) and 211.6 ± 8.2 mg/100 g body weight ($p < .001$), respectively, compared to a control value of 83.3 mg/100 g body weight. Compared to rats, Castor bean extract (1.0 and 4.0 mg/kg) induced a qualitatively similar effect in immature mice. In rats and mice, the effect on relative uterine weight appeared to have been dose-dependent. Estradiol- 17β also increased uterine weight in rats and mice. The relative uterine weights (mg/100 g body weight) for rats and mice dosed with estradiol- 17β were reported as follows: 309.2 ± 11.4 (rats) and 517.5 ± 12.3 (mice).

Cornification of the vaginal epithelium and quantal opening of the vagina were noted in immature mice and bilaterally ovariectomized rats (both dose groups for each). A dose-related decrease in the number of leukocytes and increases in cornified and epithelial cell counts were also reported for both species. No significant changes in body weight were observed.

The authors concluded that the ether-soluble portion of the methanol extract of *Ricinus communis* var. *minor* seeds possesses anti-implantation, anticonceptive, and estrogenic activity in rats and mice when administered subcutaneously (Okwuasaba et al. 1991).

CLINICAL ASSESSMENT OF SAFETY

Metabolism and Excretion

Castor Oil

Watson et al. (1963) studied the absorption and excretion of castor oil in five subjects (ages and weights not stated). The composition of the castor oil was as follows: palmitic acid (1%), palmitoleic acid (0.1%), stearic acid (1%), oleic acid (3.2%), linoleic acid (4.7%), and Ricinoleic Acid (90%). The castor oil (of medicinal purity) contained a trace amount of oil labelled with ^{131}I , and the doses administered ranged from 4 to 60 g (approximately 6 μCi of radioactivity per dose). Castor oil was administered to the five hypertensive patients on the day before a scheduled intravenous pyelogram; thereafter, only a light meal of coffee and toast was allowed. Stool collections were made during the first 24 h after dosing and during the subsequent 72 h. Urine was collected in 24-h samples. Small doses of oil were administered to the three normal volunteers, and free diet was allowed. Stools were collected at 2 and 3 days after dosing.

Fecal recovery of ^{131}I (%) ranged from 11.4% (for 10 g dose of castor oil) to 86.0% (for 44.4 g dose of castor oil). The authors concluded that castor oil can be absorbed by human subjects, that absorption is inversely related to the administered dose, and, at small doses (4 g), that absorption is virtually complete (Watson et al. 1963).

Hagenfeldt et al. (1986) administered castor oil (10 to 15 ml) orally to three healthy subjects. Urine was collected between 2 and 8 h post dosing. The following three epoxydicarboxylic acids were excreted in the urine: 3,6-epoxyoctanedioic acid;

3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid. These three Ricinoleic Acid metabolites were also detected in the urine of rats as described earlier.

Induction of Labor

Castor Oil

Davis (1984) investigated the use of castor oil to stimulate labor using 196 patients with premature rupture of membranes (PROM), at least 4 h in duration, who were between 37 and 42 weeks of gestation. Patients were identified by reviewing charts of all patients who were admitted at an out-of-hospital birthing center from 1976 through 1981. Of the 196 patients, 107 (mean age = 28.6 years) were dosed orally with castor oil (2 oz) and 89 (mean age = 27.6 years) were not. Castor oil was administered only to PROM patients who had a latency period of at least 4 h. All patients were observed for labor onset for 24 h after the onset of PROM. If labor did not occur at this time, the patients were transferred to a hospital for oxytocin stimulation. The longest interval between rupture of the membranes and delivery was 48 h.

Of the 107 patients dosed with castor oil, 80 (75%) had labor onset. Spontaneous labor occurred in 52 (58%) of the 89 control patients. This difference between patients dosed with castor oil and controls was statistically significant ($p < .05$). The interval between castor oil administration and the onset of labor ranged from 1 to 13 h (mean = 4 h).

Labor outcomes were also evaluated for type of delivery, incidence of oxytocin stimulation, and infant well-being. The need for cesarean sections was nearly three times greater in the control group (15.7% incidence) than in patients dosed with castor oil (5.6% incidence). This difference was found to be statistically significant ($p < .01$). Additionally, the group dosed with castor oil did not require oxytocin stimulation as frequently (36% incidence) when compared to the control group (43% incidence), and the difference was not statistically significant.

Infant outcomes in the two groups were studied by observing Apgar scores at 1 and 5 min, and looking for any evidence of meconium staining. Two infants with Apgar scores of <7 were reported for both groups. At the time of membrane rupture, the presence of meconium was very low in both groups. Meconium staining was not observed after dosing with castor oil. It is also important to note that there were no maternal deaths and no significant maternal morbidity. The authors concluded that castor oil can be used safely and effectively to stimulate labor (Davis 1984).

In a study by Mitri et al. (1987), the amniotic fluid was examined at the time of rupture of membranes in 478 of the 498 women in labor. The amniotic fluid was meconium-stained in 174 subjects (mean age = 28.5 ± 0.65 years) and clear in the remaining 304 subjects (mean age = 25.9 ± 0.37 years). Cesarean section, low Apgar score, and the recent ingestion of castor oil were significantly more common in subjects with meconium-stained amniotic fluid. The authors concluded that

the passage of fetal meconium was predictive of poor labor outcome in terms of Apgar scores and the need for cesarean section. It was recommended that women who take castor oil in late pregnancy should be identified as a high-risk group for the passage of fetal meconium.

In a case report by Steingrub et al. (1988), a 33-year-old pregnant female (at week 40 of gestation) ingested castor oil to induce labor. Within 60 min of ingestion, cardiopulmonary arrest occurred and was reportedly due to amniotic fluid embolism.

Garry et al. (2000) evaluated the use of castor oil to induce labor in 52 pregnant women (mean age = 24.8 ± 6.7 years) at Saint Mary's Hospital in Brooklyn, New York. The untreated control group consisted of 48 pregnant women (mean age = 24.4 ± 4.9 years). The two groups of women did not differ in maternal age, parity, or gestational age. Castor oil was administered as a 60-ml dose in orange or apple juice, and its use was deemed successful only if active labor began within 24 h. Labor was defined as one or more contractions every 5 min, with cervical dilatation of 4 cm or more. Active labor was induced in 30 (57.7%) of the 52 women dosed with castor oil, compared to 2 of the 48 women in the control group ($p < .001$). The cesarean section rate for women dosed with castor oil was 19.2% (10 of 52 women), compared to 8.3% (4 of 48 controls) in the untreated control group. No relationship between dosing with castor oil, birth weight, and mode of delivery ($p = .66$) was found. Additionally, no adverse outcomes for the mother or fetus were identified. The authors concluded that women dosed with castor oil had an increased likelihood of initiation of labor within 24 h, compared to women who were not dosed with castor oil.

Ocular Irritation

Castor Oil

In a study by Secchi et al. (1990), a double-masked clinical trial was performed using a group of nine patients (ages not stated) with vernal keratoconjunctivitis. One eye was treated with 2% cyclosporine in castor oil four times daily for 15 days. The other eye was treated with castor oil solution only according to the same procedure. Mild and transient discomfort and minor epithelial changes were observed in both eyes.

In another clinical study (Gluud et al. 1981), vital staining was used to investigate the eyes of 100 patients (ages not stated) following the instillation of castor oil and the eyes of 50 patients following the instillation of 0.9% saline. One drop (0.01 ml) of sterile fluorescein-rose bengal (RB) dye mixture was instilled into the lower conjunctival sac and the ocular mucosa was examined using a slit lamp. White light was used to examine RB-stained spots and cobalt blue light was used to examine fluorescein-stained spots. The ocular mucosa was divided into five regions, and the number of stained spots in each region was counted/estimated and graded. The authors concluded that castor oil affected the cornea and conjunctiva, i.e., degeneration and death of epithelial cells (stained with RB) and continuity breaks in the epithelium (stained with fluorescein).

Skin Irritation/Dermal Toxicity

Castor Oil

Motoyoshi et al. (1979) evaluated the skin irritation potential of undiluted castor oil using 50 adult male volunteers (ages not stated). Individuals with known allergic reactions were excluded. Patches containing 0.05 g of the test material were applied to skin of the back and remained for 48 h. At the end of the application period, test sites were swabbed with dry gauze to remove any residual test material and reactions were scored 30 minutes later according to the following scale: – (negative reading) to + + + + (bullous reaction). Castor oil was mildly irritating to the skin of human subjects.

In a study by Meyer et al. (1976), undiluted castor oil was applied to test fields delineated on the right thigh of each of three male subjects (22 to 31 years old). The control field was located on the opposite side. According to the test procedure, castor oil was rubbed onto the skin gently (<30 s) on 10 successive days. The control field was massaged only. A tissue section (1×1 cm) was excised from the center of each test field and five to eight sections ($7 \mu\text{m}$ in thickness) per test area were subjected to microscopic examination. Macroscopic skin changes were not observed in either of the three subjects.

At microscopic examination, clear hyperchromasia and an increase in the number of cells were observed in the basal cell layer. Slight widening of the granular cell layer was also noted (Meyer et al. 1976).

Hydrogenated Castor Oil

In a study by de Groot (1994), members of the Dutch Contact Dermatitis Group and nonmember dermatologists patch tested 1 to 20 patients (ages not stated) either suffering from or suspected of suffering from contact allergy to cosmetic products. Details regarding the patch test procedure were not included. Patch test results indicated no reactions to 30% Hydrogenated Castor Oil in petrolatum.

Ethyl Ricinoleate

The skin irritation potential of 20% Ethyl Ricinoleate in petrolatum was evaluated using 32 healthy male volunteers (ages not stated) in a 48-h closed patch test. Skin irritation was not observed (RIFM 2000).

Allergenicity

Predictive Tests

Ethyl Ricinoleate

The skin sensitization potential of 20% Ethyl Ricinoleate in petrolatum was evaluated using 32 healthy male volunteers in the maximization test. The test substance was applied (under occlusion) to the same site on the forearms of each subject for five alternate-day 48-h periods. Each test site was pretreated with 5% aqueous sodium lauryl sulfate (under occlusion) for 24 h. At the end of a 10- to 14-day nontreatment period, challenge

patches were applied (under occlusion) to new test sites for 48 h. Challenge applications were preceded by 30-min applications of 2% aqueous sodium lauryl sulfate (under occlusion) on the left side. On the right side, the challenge application was not preceded by treatment with sodium lauryl sulfate. A fifth site (challenge with petrolatum) served as the control. Reactions classified as either significantly irritating or allergic were not observed (RIFM 2000).

Provocative Tests

Castor Oil

Fujimoto et al. (1997) conducted a study involving 332 patients (25 males, 307 females; ages $\approx$ 20 to 70) suspected of having cosmetic contact dermatitis. The subjects were patch-tested with numerous cosmetic products and cosmetic ingredients. Patch tests (Finn chambers) were applied to the back for 48 h, and the test sites were examined at 30 minutes after patch removal, 1 day later, and 4 to 5 days after patch removal. None of the 49 patients patch-tested with castor oil had a positive reaction.

In a study by Hino et al. (2000), 346 patients (31 males, 315 females; ages $\approx$ 20 to 70 years) suspected of having cosmetic dermatitis were patch tested with various cosmetic products and cosmetic ingredients. Patch tests (Finn chambers) were applied to the back for 48 h. Test sites were examined according to the schedule in the preceding study. Of the 76 patients patch-tested with castor oil, one had a positive reaction. This reaction was observed only during the second reading (i.e., the day after the 30-min reading).

Hydrogenated Castor Oil

Lehrer et al. (1980) evaluated the sensitivity of three human subjects (with occupational hypersensitivity to castor allergens) to castor bean extract and four Castor Wax extracts (solvent = SLS, PBS, urea-NaCl, or Triton X-100). Seven normal laboratory personnel served as controls. The test substances were applied to the skin using both patch and prick tests. Only the castor bean extract and the SLS extract of Castor Wax were evaluated in the prick test, and the four Castor Wax extracts were evaluated in the patch test. In the prick test (to detect IgE-mediated hypersensitivity), a drop of allergen extract was applied to the skin. Following application to the skin, the underlying superficial layer of the skin was pricked with a 25-gauge needle. Reactions were scored 15 min after application of the allergen. A positive prick test reaction was defined as a wheal and flare reaction with edema >5 mm. Castor bean extract was tested at concentrations up to 1000 $\mu\text{g/ml}$ and, SLS Castor Wax extract, at concentrations up to 22,000 $\mu\text{g/ml}$. Results from the prick test indicated no immediate skin reactivity to castor bean extract or the SLS Castor Wax extract.

In patch tests (to detect cell-mediated hypersensitivity), a semioclusive patch containing either of the four Castor Wax extracts (concentration not stated) or paraffin (control) was ap-

plied to the skin for 24 and 48 h. Reactions were scored at 24 and 48 h post removal.

The three patients were highly sensitive to castor allergen in the prick test (positive skin reaction to 1.0 or 0.1 $\mu\text{g/ml}$ castor bean extract). The patients also had a positive skin reaction to the SLS Castor Wax extract, where the level of sensitivity was 100- to 100,000-fold less than that induced by castor bean extract. None of the seven normal subjects had a delayed reaction to any of the four Castor Wax extracts that were tested. Prick test results (normal subjects) indicated no immediate skin reactivity to castor bean extract or the SLS Castor Wax extract.

Because immediate hypersensitivity to Castor Wax was observed in the three patients who were sensitive to castor bean, additional tests (prick tests) were performed to determine whether Castor Wax solubilized in different organic solvents or an underarm deodorant stick containing Castor Wax would induce irritation and elicit a positive immediate hypersensitivity reaction in these three patients. Positive skin reactions to Castor Wax (in different solvents or in a deodorant stick) were not detected.

The four Castor Wax extracts and paraffin (control) were evaluated in patch tests for cell-mediated hypersensitivity. None of the three patients had a delayed reaction to any of the four Castor Wax extracts (test concentration not stated).

The positive skin reactions (immediate skin reactivity) in sensitized individuals, together with the positive PCA reactions in mice and positive direct RAST for reaginic castor allergens (summarized earlier in this report) that were induced by SLS Castor Wax extract, indicate that allergens are present in Castor Wax at low concentrations.

A direct RAS study was conducted to determine whether the SLS extract of Castor Wax contains specific antigens or non-specifically inhibits the RAS assay. Discs were coated with castor bean extract or the SLS Castor Wax extract and a direct RAS assay was performed using serum from one patient who was sensitive to castor allergens, a patient who was sensitive to peanuts, or pooled human serum (control). The patient sensitive to castor allergens had a significant RAS test ratio of 18.87 to castor bean allergen and a significant RAS test ratio of 8.04 to SLS Castor Wax extract. The patient sensitive to peanuts did not have a significant RAS test to either castor bean extract or the Castor Wax extract. The results from this direct RAS study indicate that SLS Castor Wax extract does contain Castor bean allergens, although the SLS Castor Wax extract can nonspecifically inhibit the RAS assay (Lehrer et al. 1980).

Ricinoleic Acid

In a retrospective study by Lim and Goh (2000), 202 consecutive patients (182 females, 20 males) with eczematous cheilitis who attended a contact and occupational dermatoses clinic in Singapore between January of 1996 and December of 1999 were patch-tested. Mean ages for female and male patients were 31.1 and 28.8 years, respectively. Patch tests were conducted according to International Contact Dermatitis Research Group (ICDRG) recommendations. Twenty-nine patients (2 males,

27 females) had positive reactions to Ricinoleic Acid. Of the 29 reactions, 22 were considered relevant positives.

Allergenicity/Photoallergenicity

Castor Oil

In a study by Hashimoto et al. (1990), 103 patients (ages not stated) suspected of having cosmetic-related contact dermatitis were patch tested with castor oil (as is). Both patch tests and photopatch tests were conducted according to ICDRG basic standards. The patch test units consisted of a combined use of both Finn chambers and Scanpor tape. One patient had a positive patch test reaction to castor oil. No positive photopatch test reactions were reported.

Case Reports

Case reports involving Castor Oil and Ricinoleic Acid esters are summarized in Table 6.

Occupational Exposure

Göhte et al. (1983) conducted a study involving 28 persons (14 men, 14 women; age range = 17 to 65 years) who were employed by a company involved with importing, preparing, and distributing plant products that are used in spices and as ingredients of health foods. The period of employment varied from two months to 20 years, and 25 of the 28 were smokers. Thirteen of the 28 developed the following work-related symptoms: rhinitis, conjunctivitis, asthma, itch, or urticaria. Blood samples from 25 subjects were subjected to IgE analysis using Phadebas IgE PRIST (paper radioimmunosorbent test). Phadebas RAST (radioallergosorbent test) was performed on 25 persons against antigens from an extract of castor oil bean. Fifteen subjects were prick-tested and 14 were patch-tested with an extract of castor oil bean. Of the three tests, only the RAST test yielded positive results; 1 of 25 subjects had an allergic reaction to an extract of castor oil bean. None of the subjects without work-related symptoms had positive reactions.

SUMMARY

Ricinus Communis (Castor) Seed Oil, Ricinoleic Acid, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate function, in cosmetics, as skin-conditioning agents, emulsion stabilizers, and surfactants. Ricinus Communis (Castor) Seed Oil also functions as a fragrance and Hydrogenated Castor Oil also functions as a viscosity-increasing agent—nonaqueous. In the case of Zinc Ricinoleate, functions include deodorant agent, opacifying agent, and anticaking agent.

Ricinoleic Acid accounts for 87% to 90% of the fatty acyl groups of Ricinus Communis (Castor) Seed Oil and the following other fatty acids comprise the remaining fatty acyl groups:

oleic acid (2% to 7%), linoleic acid (3% to 5%), palmitic acid (1% to 2%), stearic acid (1%), dihydrostearic acid (1%), and trace amounts of other fatty acyl groups.

Hydrogenated Castor Oil consists primarily of glyceryl-trihydroxystearate. The National Formulary has the following requirements for Hydrogenated Castor Oil: free fatty acids (free fatty acids in 20 g require for neutralization not more than 11.0 ml of 0.1 N sodium hydroxide), heavy metals (0.001%), hydroxyl value (between 154 and 162), iodine value (not more than 5), and saponification value (between 176 and 182).

Ricinus Communis (Castor) Seed Oil is produced by cold pressing of the seeds of *Ricinus communis* and subsequent clarification of the oil by heat. Castor Oil does not contain ricin because ricin does not partition into the oil, due to its water-solubility. Hydrogenated Castor Oil is the end product of controlled hydrogenation of Ricinus Communis (Castor) Seed Oil. One of the simplest methods for obtaining Ricinoleic Acid is the hydrolysis of castor oil.

Ricinus Communis (Castor) Seed Oil and Glyceryl Ricinoleate absorb UV light, with a maximum absorbance at 270 nm.

Reportedly, Ricinus Communis (Castor) Seed Oil and Hydrogenated Castor Oil were used in 769 and 202 cosmetic products, respectively, in 2002. The following use frequencies were reported for Ricinoleic Acid and its salts and esters: Glyceryl Ricinoleate (16), Ricinoleic Acid (6), Sodium Ricinoleate (12), Zinc Ricinoleate (3), and Cetyl Ricinoleate (55).

The highest reported use concentration for Ricinus Communis (Castor) Seed Oil is associated with lipsticks (81%). Other maximum ingredient use concentrations are: Hydrogenated Castor Oil (up to 39%), Glyceryl Ricinoleate (up to 12%), Zinc Ricinoleate (up to 2%), Cetyl Ricinoleate (up to 10%), and Octyldodecyl Ricinoleate (up to 5%).

Potassium Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, and Methyl Ricinoleate are not currently reported to FDA as in use, nor are there industry survey data indicating a current use concentration.

Castor oil is classified by FDA as generally recognized as safe and effective for use as a stimulant laxative. An acceptable daily intake (for man) of 0 to 0.7 mg/kg body weight has been established by FAO/WHO for castor oil.

Castor oil is a triglyceride that is hydrolyzed in the small intestine by pancreatic enzymes, leading to the release of glycerol and Ricinoleic Acid. Ricinoleic Acid was rapidly metabolized in a study of adult rats fed a diet containing 48.4% castor oil for 4 to 6 weeks. These animals did not have significant amounts of Ricinoleic Acid in phospholipids of the small intestine, liver, and skeletal muscle, nor in glycerides of the liver. A close correlation between the dose administered in the diet and the percentage of Ricinoleic Acid in the feces (greater absorption of the smaller dose) was noted in rats. Castor oil was readily absorbed and metabolized in two groups of male rats that were fed 10% castor oil in the diet (cholesterol-enriched and cholesterol-free, respectively) for 20 days. Fecal recovery of Ricinoleic Acid was

TABLE 6
Case reports with patch test results for Castor Oil and Ricinoleic Acid esters and salts

Subjects	Findings/patch test results	References
22-year-old female (with cheilitis)	Cheilitis worsened after application of various lipsticks and lip creams. Product concentrations of Castor Oil ranged from 10% to 67%. ++ patch test reactions to Castor Oil and each lipstick or lip cream that contained Castor Oil. Also, ++ patch test reactions to Ricinoleic Acid (as is), 30% Ricinoleic Acid in petrolatum, and purified Castor Oil (as is). No reactions to products that did not contain Castor Oil.	Sai 1983
23-year-old female (history of facial eczema) with acute dermatitis of the face	++ reactions to Castor Oil and make-up remover containing Castor Oil.	Brandle et al. 1983
29-year-old female (history of deodorant dermatitis)	Acute edematous dermatitis on the lips and perioral area, which spread to entire face and neck, after using a lipstick product containing Castor Oil. ++ patch test (Finn chambers, International Contact Dermatitis Research Group [ICDRG] recommendations) results for Castor Oil.	Andersen and Nielsen 1984
24-year-old female	Swelling of lips over 10-month period. Negative patch test results for Castor Oil and five brands of lipstick containing Castor Oil.	Yoshikawa et al. 1986
31-year-old female (no history of dermatitis)	Developed itchy rashes in the axillae, which spread over the entire body. Positive patch test reaction (++, at 38 and 96 h) to a deodorant that was used. Repeated open application test results for Castor Oil and a Zinc Ricinoleate mixture (Zinc Ricinoleate (88%), triethanolamine, zinc resinate, isostearic acid, dipropylene glycol, sodium lactate, and abietic acid) were positive.	Dooms-Goosens et al. 1987
45-year-old female (history of intolerance to cosmetics and adhesives)	Presented with an itchy dermatitis on both axillae, and red papules scattered over face and trunk. Patch test results indicated a red erythematous response to a deodorant that was used. Patch test results for Castor Oil were negative at 72 h and +/- at 96 h. Repeated open application test results for Castor Oil were negative after 7 days; ++ patch test results for 20% Glyceryl Ricinoleate (in petrolatum) at 72 and 96 h. Also, ++ reaction to Zinc Ricinoleate mixture (defined in preceding case report) at 96 h. This mixture also produced an erythematous test response in 1 of 10 control subjects.	Dooms-Goosens et al. 1987
40-year-old chemist (history of eczema due to chemical exposure on the job)	Developed eczema on the knee 10 days after joint surgery. Positive patch test results for surgical adhesive containing Castor Oil. Negative patch test results for Castor Oil.	Jost et al. 1989
20-year-old female	Allergic cheilitis (itching, swelling, and redness of the lips) after using a total of 16 lipstick products. Positive patch test results for Castor Oil and each product.	Fisher 1991
17-year-old female (with lip dermatitis)	Positive patch test reactions to Castor Oil and 3 lipsticks.	Fisher 1991

TABLE 6Case reports with patch test results for Castor Oil and Ricinoleic Acid esters and salts (*Continued*)

Subjects	Findings/patch test results	References
17-year-old female (allergic to metals)	Developed itchy erythematovesicular reaction on right hand after using a liquid wart remover containing flexible collodion (contains 1.67% Castor Oil). + + + patch test reaction to wart remover. ++ patch test reactions to Castor Oil and 20% Castor Oil in petrolatum. Negative patch test reactions to Castor Oil and 20% Castor Oil in petrolatum in 15 control subjects.	Lodi et al. 1992
51-year-old female	Developed two roundish, erythematous vesicular plaques in left gluteal and right anterolateral neck regions (application sites) after 20 days of treatment with an anti-wart solution (flexible collodion, common component of wart removers, contains Castor Oil). ++ patch test reactions to Castor Oil 20% Castor Oil in petrolatum, and the wart remover.	Tabar et al. 1993
65-year-old male (history of rash following wood cutting in orchard)	Rash on face, neck, and hands. Same rash appeared 3 years earlier, following wood cutting. Patch test results for Castor Oil (100%) were negative.	Manzur et al. 1995
30-year-old female (history of mild atopic eczema)	Hand dermatitis after exposure to cream containing Castor Oil and zinc. + + + patch test reaction to Castor Oil. Negative results for 10 control subjects.	Wakelin et al. 1996
29-year-old female (nonatopic)	Sore, cracked lips, followed by vesicular facial edema, after use of the same lipstick product for several years. ++ patch test (Finn chambers, ICDRG criteria) results for Castor Oil.	Tan et al. 1997
24-year-old female (history of hay fever and dry lips)	Pruritic papules, swelling, and pigmentation on and around lips after applying lipstick. Negative patch test results for Castor Oil (as is).	Inoue et al. 1998
20-year-old army recruit	Rashes developed after applying a camouflage stick containing 47.1% Castor Oil. A mildly pruritic vesicular eruption appeared on the neck, chin, face, and hands; swelling of eyelid also observed. Symptoms lasted for 3 or 4 days.	Goon et al. 1999
43-year-old female (history of sinus aspergillosis and facial edema after oral dosing with tixocortol pivalate)	Recurrent facial dermatitis and cheilitis after use of a facial moisturizer containing 8% Castor Oil. +/+ patch test (Finn chambers) reactions to the moisturizer, Castor Oil, 15% Castor Oil in petrolatum, and 10% Castor Oil in petrolatum. + to ++ reactions to several lipstick and lip balm products containing Castor Oil.	Le Coz and Ball 2000
51-year-old female	Pruritic erythema in both axillae after use of a deodorant containing 76% Zinc Ricinoleate. One week later, developed acute contact dermatitis of the lips after using perfumed lipstick containing Glyceryl Ricinoleate. Lipstick was previously tolerated. + patch test reaction to deodorant and lipstick. + patch test reaction to 30% Glyceryl Ricinoleate in petrolatum. Re-patch testing yielded the following results: 76% Zinc Ricinoleate in petrolatum (?+ reaction on day 3) and no reactions to 30%, 15%, or 1% Zinc Ricinoleate in petrolatum 20% Glyceryl Ricinoleate in petrolatum (+ reaction on day 3), 30% Glyceryl Ricinoleate in petrolatum (+ reaction on day 3), and Castor Oil, as is (no reaction).	Magerl et al. 2001

(Continued on next page)

TABLE 6

Case reports with patch test results for Castor Oil and Ricinoleic Acid esters and salts (*Continued*)

Subjects	Findings/patch test results	References
58-year-old female (history of allergy to adhesive tapes)	After knee surgery, acute contact dermatitis around surgical incision rapidly became blistered and spread to right lower limb. Patch test results for Castor Oil (1% and 10% in petrolatum) were negative.	Reichert-Pénétrat et al. 2001
50-year-old female (history of allergy to adhesive tapes)	After hip surgery, acute dermatitis around surgical incision spread to lower right limb. Patch test results for Castor Oil (1% and 10% in petrolatum) were negative.	Reichert-Pénétrat et al. 2001
30-year-old female (with pigmented contact cheilitis)	Presented with scaly erythema with associated diffuse hyperpigmentation and itchy swelling for past one year after using various lipsticks. ++ patch test reactions to Ricinoleic Acid at day 3.	Leow et al. 2003

approximately 0.5% of the total ingested. 3,6-epoxyoctanedioic acid, 3,6-epoxydecanedioic acid, and 3,6-epoxydodecanedioic acid were excreted by rats given castor oil intragastrically. These acids were not detected in the urine prior to dosing with castor oil.

Following the oral administration of Hydrogenated Castor Oil to rats at dietary concentrations of 0.865% and 8.65%, the deposition of hydroxystearic acid in the abdominal fat and other body lipids was reported. In all cases, hydroxystearic acid was accompanied by hydroxypalmitic acid, hydroxymyristic acid, and hydroxylauric acid (hydroxystearic acid metabolites). Ricinoleic Acid or Methyl Ricinoleate administered by gastric intubation to male rats resulted in peak absorption of Ricinoleic Acid within 30 min post dosing in the following fractions: triglyceride, diglyceride, monoglyceride, and free fatty acid.

Castor oil (labeled with ^{131}I) was administered to five hypertensive patients on the day before a scheduled intravenous pyelogram, with results demonstrating that castor oil can be absorbed by human subjects, that absorption is inversely related to the administered dose, and, at small doses (4 g), that absorption is virtually complete.

Following oral administration of castor oil (10 to 15 ml) to three healthy subjects, the following three epoxydicarboxylic acids were excreted in the urine: 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid.

Castor oil caused a marked decrease in the transepidermal water loss rate from full-thickness, cartilage-stripped skin from the ventral ear of the male Syrian golden hamster. In another study, Ricinoleic Acid enhanced the in vitro transdermal permeation of 5-fluorouracil in hairless mouse skin.

Oral dosing with Sodium Ricinoleate, Ricinoleic Acid, or castor oil had both stimulatory and inhibitory effects on smooth muscle (canine small bowel) contraction in vivo. Sodium Ricinoleate, but not Methyl Ricinoleate, depressed the smooth muscle twitch response in a guinea pig ileum preparation at concentrations ranging from 1.25×10^{-5} to 4×10^{-4} M.

Unlike prostaglandin E_1 (chemically similar to Ricinoleic Acid), Ricinoleic Acid did not induce dose-dependent stimulation of adenylate cyclase in villus cell (from hamster small intestine) homogenates. Compared to saline-treated controls, castor oil significantly reduced the infiltration of leukocytes and the prostaglandin E_2 (inflammatory mediator) content of the rat aqueous humor and iris-ciliary body.

Sodium Ricinoleate significantly inhibited (considered modest; $p < .05$) cytokine-induced endothelial adhesion molecule expression when incubated with human saphenous vein endothelial cells. In a similar experiment, Ricinoleic Acid significantly decreased IL-4-induced VACM-1 expression (50% inhibitory concentration between 10 and 100 μM). Neither cell number nor viability was increased in this concentration range. Ricinoleic Acid did not inhibit $\text{TNF}\alpha$ -induced vascular cell adhesion molecule-1 expression to any significant extent. Castor oil in the diet induced a significant increase in prostaglandin E_2 concentrations in tissues of the intestinal mucosa, placenta, amnion, and amniotic cells in groups of pregnant Wistar rats.

Castor oil did not have antimicrobial activity in the *Staphylococcus aureus*, *Escherichia coli*, or *Candida albicans* bacterial strains. There was no correlation between Sodium Ricinoleate antibacterial activity against cells in suspension and antiplaque activity.

Following the oral administration of castor oil (2 ml), macroscopic damage, characterized mainly by vasocongestion, was observed throughout the duodenum and jejunum in rats. After male albino rats were dosed intraperitoneally with 100 mg Ricinoleic Acid, all animals were dead within 24 h. The acute oral LD_{50} for Ethyl Ricinoleate exceeded 5.0 g/kg in rats. A single oral dose (2.5 ml/kg) of castor oil caused generalized hyperemia of the intestinal mucosa up to 72 h post dosing in most of 12 ponies. An acute oral LD_{50} of >10 g/kg was reported for Hydrogenated Castor Oil in a study involving rats. The acute dermal LD_{50} for Ethyl Ricinoleate exceeded 5.0 g/kg in rabbits. One of the rabbits died. The skin reactions observed included

moderate erythema in six rabbits, moderate edema in five rabbits, and slight edema in one rabbit.

In an acute intravenous toxicity study in which eight mongrel dogs were dosed with castor oil (single bolus dose = 0.1 ml/kg), none of the animals died. Erythema was the only clinical sign that was reported. An increase in blood histamine occurred in one animal.

The short-term subcutaneous administration of a vehicle consisting of castor oil and benzyl benzoate to groups of five C₅₇Bl/6J mice caused morphological alterations suggestive of stress-induced changes. Using electron microscopy, the changes observed in the adrenal cortex included disruption of parenchymal mitochondria in the zona fasciculata, increase in the size of some of the mitochondria, loss of the vesicular orientation of the inner mitochondrial membrane, and diminution of the mitochondrial matrix. Mitochondrial changes were also observed in the zona reticularis and zona fasciculata.

Intragastric administration of Ricinoleic Acid (single 0.1 ml dose) to CD-1 specific pathogen-free mice resulted in the erosion of duodenal villi. In another study, perfusion of the rabbit colon with Sodium Ricinoleate solution (5.0, 7.5, and 10 mM) led to mucosal damage (i.e., the loss of epithelial cells). A dose-response relationship for mucosal damage was noted.

In an NTP subchronic oral toxicity study, the administration of diets containing up to 10% castor oil to groups of male and female F344/N rats continuously for 13 weeks was not associated with any toxicities.

The subchronic oral toxicity of Hydrogenated Castor Oil (dietary concentrations up to 17.3%) was evaluated in female rats in a preliminary feeding trial. A reduced growth rate in rats fed 8.65% and 17.3% Hydrogenated Castor Oil, respectively, was the only abnormality that was observed. Based on organ weight determinations and the results of hematological and microscopic examinations, no adverse effects were observed.

In a 16-week study, groups of 15 male albino rats were fed diets containing 0.865% or 8.65% Hydrogenated Castor Oil. Except for the reduced growth rate in rats fed 8.65% Hydrogenated Castor Oil, no adverse effects were observed.

The instillation of undiluted castor oil (0.5 ml) into the rabbit eye resulted in an ocular injury score of 1 (maximum score possible = 20). In contrast, undiluted castor oil induced slight congestion of the iris and conjunctiva in the rabbit eye in another study, but the instillation of castor oil (10 drops daily for 3 weeks) into the eyes of ten rabbits in a third study produced no damage to the corneal epithelium or endothelium.

Castor oil swabbed onto the dorsum of each of 216 albino or Long-Evans rats daily for five days to 2 weeks produced a mild effect on the epidermis. Undiluted castor oil was applied for 24 h to two areas on the dorsal surface of six albino angora rabbits. Severe skin irritation was observed. Undiluted castor oil applied to the dorsal skin of six male Hartley guinea pigs, six male Wistar rats, and six miniature swine produced mild skin irritation in guinea pigs and rats, but not in miniature swine. Repeated applications of undiluted castor oil to the flanks of five

female albino rabbits daily for 30 days induced slight erythema and edema. Both open skin irritation and repeated application (8 weeks) tests for undiluted castor oil and 10% aqueous castor oil were well tolerated by rabbits in another study. Slight reddening of the application site (flank) was observed in a study in which six albino guinea pigs and six young pigs received applications of undiluted castor oil on 10 successive days.

In a predictive prick test in which seven normal subjects were tested with an SLS extract of Castor Wax (concentrations up to 22,000 µg/ml), no immediate skin reactivity was observed. None of the seven subjects patch tested with the SLS Castor Wax extract or the remaining three extracts of Castor Wax (concentrations not stated) had a delayed skin reaction. In a provocative prick test in the same study, three patients with occupational hypersensitivity to castor allergens were tested with the SLS extract of Castor Wax at concentrations up to 22,000 µg/ml. All three patients had a positive reaction to the SLS Castor Wax extract. None of the three patients patch-tested had a delayed reaction to the SLS Castor Wax extract or the remaining three extracts of Castor Wax (concentrations not stated).

The positive skin reactions (immediate skin reactivity) in sensitized individuals, together with the positive PCA reactions in mice and positive direct RAST for reaginic castor allergens that were induced by SLS Castor Wax extract, indicate that allergens are present in Castor Wax at low concentrations.

Neither erythema nor edema was observed following a single topical application of Ricinoleic Acid (in peanut oil) to the paws of 8 to 10 male Swiss mice. The application of Ricinoleic Acid (in peanut oil) to the entire eyelid surface of each of six male albino Dunkin-Hartley guinea pigs induced eyelid reddening and edema at doses of 10, 30, or 100 mg. Cetyl Ricinoleate was classified as a non-irritant following application to the skin of three male New Zealand albino rabbits. Diluted TEGODEO HY 77 (trade name mixture that generally contains >50% Zinc Ricinoleate) was applied, under occlusive patches and after patch removal. Well-defined erythema was observed at 48 and 72 h at the abraded sites of all six rabbits and at the intact sites of four rabbits. This mixture did not produce skin sensitization in a study involving 30 white guinea pigs.

Castor oil was not comedogenic when applied to the ears of rabbits for 2 weeks, but there was a slight increase in keratin content within the follicle, with essentially no change in the follicular epithelium.

Sodium Ricinoleate caused dose-related increases in cytotoxicity in cultures of epithelial cells that were isolated from the small intestines of male Syrian hamsters. In another study, Sodium Ricinoleate did not induce significant toxicity in human saphenous vein endothelial cell cultures at concentrations ≤25 µM. At concentrations of 0.1% and 1.0% Sodium Ricinoleate, applied to serosal surface or rat jejunum, a significant reduction in the number of ganglion cells in the myenteric or submucosal plexus was noted. This was not true for the lowest test concentration (0.01%). Castor oil did not have a toxic effect

on the tubular epithelium following intraluminal injection into the kidneys of five male white albino rats. In a study evaluating the nephrotoxicity of cyclosporine, castor oil served as the vehicle control.

Neither castor oil nor Sodium Ricinoleate was mutagenic to the following *Salmonella typhimurium* strains either with or without metabolic activation: TA98, TA100, TA102, TA1535, and TA1537. Results were also negative for castor oil in *Escherichia coli* strain WP2/pKM102. Groups of male and female mice that received diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10.0% castor oil (in DMSO) for 13 weeks had no evidence of induction of micronuclei in peripheral erythrocytes. Castor oil did not induce sister chromatid exchanges either with or without metabolic activation. Sodium Ricinoleate interfered with cell division in an *Escherichia coli* strain, causing the organisms to develop as filaments. Ricinoleic Acid was inactive as a stimulator of DNA synthesis and inducer of ornithine decarboxylase activity in the rat colon. Concentrations up to 10 mM resulted in insignificant increases in [³H]dThd incorporation and did not increase the level of ornithine decarboxylase activity above control values.

None of the 20 mice injected intravaginally with 2% Ricinoleic Acid (in gum tragacanth) had neoplasms or hyperplastic lesions of the corpus uteri, cervix uteri, vagina, or perineal skin. However, benign lung adenomas were observed in 10 of the 13 mice dosed with Ricinoleic Acid and in 6 of the 24 vehicle control mice that were killed after the 14th month of dosing.

Neither undiluted castor oil, Ricinoleic Acid, nor Glyceryl Ricinoleate was a tumor promoter in a study involving groups of ten mice. However, the three test substances induced slight epidermal hyperplasia in groups of three mice following the application of each to a small area of skin in the interscapular region.

Castor oil extract had a strong suppressive effect on S₁₈₀ body tumors in male Kunming mice. Its suppressive effect on ARS ascites cancer was also very strong, with 64% of the ascites tumors in mice being completely cured. Compared to controls, the life extension rate was more than 136% ($p < .0012$).

Groups of mice and rats fed diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10% Castor Oil continuously for 13 weeks had a slight decrease in epididymal weight (6% to 7%) in mid- and high-dose groups of male rats; however, this finding was not dose-related. No effects on any other male reproductive end point (testes weight and epididymal sperm motility, density, or testicular spermatid head count) or female reproductive endpoint (estrous cycle length, or time spent in each phase of the cycle) were noted.

Female Wistar rats injected intramuscularly with castor oil (0.2 ml, single dose) on the first day after estrus had suppressed ovarian folliculogenesis and anti-implantation and abortive effects. Anticonceptive and estrogenic effects of a methanol extract of *Ricinus communis* var. *minor* seeds (ether-soluble fraction) were studied in adult albino Wistar rats, young albino Wistar rats, immature Swiss albino female mice, and adult fe-

male New Zealand white rabbits. Subcutaneous administration of the extract produced anti-implantation, anticonceptive, and estrogenic activity in rats and mice.

Castor oil served as the vehicle control in a study evaluating the effect of long-term treatment with ICI 182,780 (an antiestrogen) on the rat testis. In the control group, four male Sprague-Dawley rats were injected subcutaneously with castor oil (0.2 ml) once per week and then killed 100 days after the first injection. Spermatogenesis appeared normal in each of the four control rats.

Castor oil (2 oz) was used to stimulate labor in 196 patients (between 37 and 42 weeks of gestation) with premature rupture of membranes. The need for cesarean sections was nearly three times greater in the control group (15.7% incidence) than in patients dosed with castor oil (5.6% incidence). No relationship between dosing with Castor Oil (administered as a 60-ml dose in orange or apple juice), birth weight, and mode of delivery was found in a study in which castor oil was used to induce labor in 52 pregnant women. The cesarean section rate for women dosed with castor oil was 19.2% (10 of 52 women), compared to 8.3% (4 of 48 controls) in the untreated control group. No adverse outcomes for the mother or fetus were identified.

Mild and transient discomfort and minor epithelial changes were observed in the eyes of nine patients after treatment (instillation) with a castor oil solution four times daily for 15 days. In another study involving 100 patients, the instillation of castor oil affected the cornea and conjunctiva. Specifically, the degeneration and death of epithelial cells and continuity breaks in the epithelium were observed.

Mild skin irritation was reported in 50 adult males patch tested with undiluted castor oil (0.05 g applied to back). None of the 1 to 20 patients, either suffering from or suspected of suffering from contact allergy to cosmetic products, patch tested with 30% Hydrogenated Castor Oil had irritant reactions. Undiluted castor oil rubbed gently onto the right thigh of each of three male subjects on 10 successive days produced, at microscopic examination of excised skin, clear hyperchromasia and an increase in the number of cells was observed in the basal cell layer. Slight widening of the granular cell layer was also noted. No skin irritation was seen with 20% Ethyl Ricinoleate in petrolatum using 32 healthy male volunteers in a 48-h closed patch test.

No skin sensitization or irritation was seen with 20% Ethyl Ricinoleate in a maximization test using 32 healthy male volunteers. In 49 patients with contact dermatitis patch-tested (48-h Finn chambers) with castor oil, none had a positive reaction. One of the 76 dermatitis patients patch-tested with Castor Oil had a positive reaction, observed only during the second reading (i.e., the day after the 30-min reading). Of 202 consecutive patients with eczematous cheilitis who attended a contact and occupational dermatoses clinic in Singapore, 29 patients had positive reactions to Ricinoleic Acid. Of the 29 positive reactions, 22 were considered relevant positives. In an allergenicity-photoallergenicity study, 103 patients suspected of having cosmetic-related dermatitis were patch tested

with castor oil. One patient had a positive patch test reaction. None of the patients had a positive photopatch test reaction.

In case reports that included patch test results for castor oil, Ricinoleic Acid, or esters of Ricinoleic Acid, both positive and negative reactions were reported. Of a group of 25 employees at a company involved with the preparation of plant products, 1 employee had an allergic reaction to an extract of the castor oil bean.

DISCUSSION

The CIR Expert Panel considered that the available data on *Ricinus Communis* (Castor) Seed Oil, Hydrogenated Castor Oil, Ricinoleic Acid, and salts and esters of Ricinoleic Acid in the current safety assessment are sufficient for evaluating the safety of Glyceryl Ricinoleate and Glyceryl Ricinoleate SE, as well. Because *Ricinus Communis* (Castor) Seed Oil contains Ricinoleic Acid as the primary fatty acid group, safety test data on the oil is considered broadly applicable to this entire group of cosmetic ingredients. Overall, the available data demonstrate few toxic effects in acute, subchronic, or chronic toxicity tests. Additionally, there were no genotoxic effects of castor oil in in vitro or in vivo tests. It was noted that the available data include a 50-week chronic study in which none of the 20 mice injected with Ricinoleic Acid twice per week had neoplasms or hyperplastic lesions of the corpus uteri, cervix uteri, vagina, or perineal skin. UV absorption spectra on *Ricinus Communis* (Castor) Seed Oil and Glyceryl Ricinoleate indicate maximum absorbance at 270 nm, suggesting that there would be no photosensitization potential of Glyceryl Ricinoleate or *Ricinus Communis* (Castor) Seed Oil in human subjects at relevant solar UV exposures.

Reactions classified as either significantly irritating or allergic were not observed in a maximization test on Ethyl Ricinoleate involving 32 healthy male subjects. Although there is a paucity of predictive patch test data on Ricinoleic Acid esters/salts, the Panel agreed that the negative guinea pig sensitization data on a trade name mixture containing more than 50% Zinc Ricinoleate, in conjunction with the human predictive patch test data, may be extended to support the safety of all of the cosmetic ingredients that are included in this safety assessment.

The Panel did consider the 22 positive reactions to Ricinoleic Acid in a retrospective study involving 202 consecutive patients with eczematous cheilitis. Recognizing that this study represents a case series on cheilitis that involves a select patient population, the Panel agreed that the incidence of sensitization reactions reported in the study may be expected in that select patient group, but not in the general population. Based on the Panel's experience and expertise in the area of patient patch testing, the incidence of positive reactions to Ricinoleic Acid is generally very low.

In the absence of inhalation toxicity data on *Ricinus Communis* (Castor) Seed Oil, Hydrogenated Castor Oil, Ricinoleic Acid, and salts and esters of Ricinoleic Acid in this safety assessment, the Panel determined that these ingredients can be used

safely in aerosolized products because packaging and use ensure that particulates are not respirable (are greater than 10 μm). The Panel reasoned that the particle size of anhydrous hair sprays (60 to 80 μm) and pump hair sprays (>80 μm) is large compared to the median aerodynamic diameter of $4.25 \pm 1.5 \mu\text{m}$ for a respirable particulate mass.

The CIR Expert panel recognizes that certain ingredients in this group are reportedly used in a given product category, but the concentration of use is not available. For other ingredients in this group, information regarding use concentration for specific product categories is provided, but the number of such products is not known. In still other cases, an ingredient is not in current use, but may be used in the future.

Although there are gaps in knowledge about product use, the overall information available on the types of products in which these ingredients are used and at what concentration indicate a pattern of use. Within this overall pattern of use, the Expert Panel considers all ingredients in this group to be safe.

CONCLUSION

The CIR Expert Panel concluded that *Ricinus Communis* (Castor) Seed Oil, Hydrogenated Castor Oil, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

REFERENCES

- Achaya, K. T. 1971. Chemical derivatives of castor oil. *J. Am. Oil Chem. Soc.* 48:758–763.
- Allegri, R., G. C. Deschel, V. Filippi, M. Gibellini, E. Portioli, and D. Veneri. 1981. Proposal for the pharmacopoeia: hydrogenated castor oil [translation]. *Boll. Chim. Farm.* 120:557–558.
- Ames, B. N., J. McCann, and E. Yamasaki. 1975. Methods for detecting carcinogens and mutagens with the *Salmonella*/mammalian-microsome mutagenicity test. *Mutat. Res.* 31:347–364.
- Andersen, K. E., and R. Nielsen. 1984. Lipstick dermatitis related to castor oil. *Contact Dermatitis* 11:253–254.
- Aplin P.J., and Eiseo T. 1997. Ingestion of castor oil plant seeds. *Med. J. Aust.* 167:260–261.
- Ayorinde, F. O., K. Garvin, and K. Saeed. 2000. Determination of the fatty acid composition of saponified vegetable oils using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Rapid. Commun. Mass Spectrom.* 14:608–615.
- Baynes, R. E., and J. E. Riviere. 2004. Mixture additives inhibit the dermal permeation of the fatty acid, ricinoleic acid. *Toxicol. Lett.* 147:15–26.
- Behrens-Baumann, W., S. Theuring, and H. Brewitt. 1986. The effect of topical cyclosporin A on the rabbit cornea. A clinical and electron microscopic study. *Graefes Arch. Clin. Exp. Ophthalmol.* 224:520–552.
- Binder, R. G., A. N. Booth, D. J. Robbins, and G. Fuller. 1970. Hydroxystearic acid deposition and metabolism in rats fed hydrogenated castor oil. *Lipids* 5:832–837.
- Blair, R. M., H. Fang, W. S. Branham et al. 2000. The estrogen receptor relative binding affinities of 188 natural and xenochemicals: Structural diversity of ligands. *Toxicol. Sci.* 54:138–153.

- Bower, D. 1999. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting.²
- Boyland, D., F. J. C. Roe, and B. C. V. Mitchley. 1966. Test of certain constituents of spermicide for carcinogenicity in genital tract of female mice. *Br. J. Cancer* 20:184–189.
- Brandle, I., A. Boujnah-Khouadja, and J. Fousereau. 1983. Allergy to castor oil. *Contact Dermatitis* 9:424–425.
- Bronaugh, R. L., and R. F. Stewart. 1985. Methods for in vitro percutaneous absorption studies. IV: The flow-through diffusion cell. *J. Pharm. Sci.* 74:64–66.
- Beubler, E., and A. Schirgi-Degen. 1992. Stimulation of enterocyte protein kinase C by laxatives in vitro. *J. Pharm. Pharmacol.* 45:59–62.
- Budavari, S., ed. 1989. *The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals*, 11th ed., 290, 1307. Rahway, NJ: Merck & Co.
- Bull, A. W., N. D. Nigro, W. A. Golembieski, J. D. Crissman, and L. J. Marnett. 1984. *In vivo* stimulation of DNA synthesis and induction of ornithine decarboxylase activity in rat colon by hydroperoxides, autoxidation products of unsaturated fatty acids. *Cancer Res* 44:4924–4928.
- Bull, A. W., N. D. Nigro, and L. J. Marnett. 1988. Structural requirements for stimulation of colonic cell proliferation by oxidized fatty acids. *Cancer Res* 48:1771–1776.
- Butcher, E. O. 1951. The effects of applications of various substances on the epidermis of the rat. *J. Invest. Dermatol.* 16:85–90.
- Butcher, E. O. 1952. The penetration of fat and fatty acid into the skin of the rat. *J. Invest. Dermatol.* 21:43–48.
- Campbell & Co. 2002. Castor oil & castor oil derivatives. Product data—castor waxes. <http://www.campbelluv.com/castor.html> [accessed September 2004].
- Capasso, F., N. Mascolo, G. Autore, and V. Romano. 1986. Laxatives and the production of autacoids by rat colon. *J. Pharm. Pharmacol.* 38:627–629.
- Capasso, F., N. Mascolo, A. A. Izzo, and T. S. Gaginella. 1994. Dissociation of castor oil-induced diarrhea and intestinal mucosal injury in rat: Effect of *N*^G-nitro-L-arginine methyl ester. *Br. J. Pharmacol.* 113:1127–1130.
- Carpenter, C. P., and H. F. Smyth, Jr. 1946. Chemical burns of the rabbit cornea. *Am. J. Ophthalmol.* 29:1363–1372.
- Chakravarty, D., and A. Bose. 1963. A note on the preparation of ricinoleic acid by urea complexing. *J. Pharm. Pharmacol.* 15:337–338.
- Committee of Revision of the United States Pharmacopeial Convention. 2004a. *The United States Pharmacopoeia*, 27th ed., 348. Rockville, MD: United States Pharmacopeial Convention.
- Committee of Revision of the United States Pharmacopeial Convention. 2004b. *The National Formulary*, 22nd ed., 2844. Rockville, MD: United States Pharmacopeial Convention.
- Cornell University. 2001. Castor Oil. <http://www.ansci.cornell.edu/plants/castorbean.html> [accessed October 2003].
- Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Use concentration data from industry survey. Unpublished data submitted by CTFA, May 2004. 3 pages.²
- Croci T., M. Landi, X. Emonds-Alt, G. Le Fur, J. P. Maffrand, and L. Manara. 1997. Role of tachykinins in castor oil diarrhea in rats. *Br. J. Pharmacol.* 121:375–380.
- Davis, L. 1984. The use of castor oil to stimulate labor in patients with premature rupture of membranes. *J. Nurse-Midwifery* 29:366–370.
- De Caterina, R., and W. Bernini. 1998. Structural requirements for inhibition of cytokine-induced endothelial activation by unsaturated fatty acids. *J. Lipid Res.* 39:1062–1070.
- De Caterina, R., H. Tanaka, T. Nakagawa, P. J. Hauptman, and P. Libby. 1995. The direct effect of injectable cyclosporine and its vehicle, cremophor, on endothelial vascular cell adhesion molecule-1 expression. *Transplantation* 60:270–275.
- De Groot, A. C., ed. 1994. *Patch testing. Test concentrations and vehicles for 3700 Chemicals*, 2nd ed., 11, 145. Amsterdam: Elsevier.
- Degussa. 2001. Product data record. TEGODEO HY 77. Unpublished data submitted by CTFA, May 5, 2004. 2 pages.²
- Dooms-Gossens, A. K. Dupré, A. Borghijs, C. Swinnen, M. Dooms, and H. Degreef. 1987. Zinc ricinoleate: Sensitizer in deodorants. *Contact Dermatitis* 16:292–294.
- Drugstore.com, Inc. 2004. Rite Aid Castor oil, stimulant laxative U.S.P. Package details: Directions. <http://www.drugstore.com> [accessed December 2004].
- Elder, R. L., ed. 1988. Final report on the safety assessment of glyceryl ricinoleate. *J. Am. Coll. Toxicol.* 7:721–739.
- Fisher, A. A. 1991. Allergic cheilitis due to castor oil in lipsticks. *Cutis* 47:389–390.
- Food and Drug Administration (FDA). 1985. Laxative drug products for over-the-counter human use; Tentative final monograph. *Federal Register* 50:2124–2158.
- FDA. 1990. Wart remover drug products for over-the-counter human use. Final monograph. *Federal Register* 55:33246–33256.
- FDA. 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.
- FDA. 2003a. OTC Drug Review Ingredient Report. *FDA database*. Washington, DC: FDA.
- FDA. 2003b. Inactive Ingredients Guide (Redacted), January 1996. <http://www.fda.gov/cder/drug/iig/default.htm> [accessed August 2003].
- Fox, D. A., M. L. Epstein, and P. Bass. 1983. Surfactants selectively ablate enteric neurons of the rat jejunum. *J. Pharmacol. Exp. Ther.* 227:538–544.
- Frankel, E. N., W. E. Neff, D. D. Brooks, and K. Fujimoto. 1987. Fluorescence formation from the interaction of DNA with lipid oxidation degradation products. *Biochim. Biophys. Acta* 919:239–244.
- Fredholt, K., D. H. Larsen, and C. Larsen. 2000. Modification of in vitro drug release rate from oily parenteral depots using a formulation approach [translation]. *Eur. J. Pharm. Sci.* 11:231–237.
- Fujimoto, M., N. Higashi, A. Kume, K. Ueda, and N. Hino. 1997. Patch test results in 332 patients suspected of cosmetic dermatitis. *Environ. Dermatol.* 4:268–276.
- Fulton, J. E. Jr. 1989. Comedogenicity and irritancy of commonly used ingredients in skin care products. *J. Soc. Cosmet. Chem.* 40:321–333.
- Fulton, J. E. Jr., S. Bradley, A. Aquidez, and T. Black. 1976. Non-comedogenic cosmetics. *Cutis* 17:344–351.
- Gaginella, T. S., and P. Bass. 1978. Laxatives: An update on mechanism of action. *Life Sci.* 23:1001–1010.
- Gaginella, T. S., V. S. Chadwick, J. C. Debongnie, J. C. Lewis, and S. F. Phillips. 1977a. Perfusion of rabbit colon with ricinoleic acid: Dose-related mucosal injury, fluid secretion, and increased permeability. *Gastroenterology* 73:95–101.
- Gaginella, T. S., A. C. Haddad, V. L. W. Go, and S. F. Phillips. 1977b. Cytotoxicity of ricinoleic acid (castor oil) and other intestinal secretagogues on isolated intestinal epithelial cells. *J. Pharmacol. Exp. Ther.* 201:259–266.
- Gaginella, T. S., S. F. Phillips, R. R. Dozois, and V. L. Go. 1978. Stimulation of adenylate cyclase in homogenates of isolated intestinal epithelial cells from hamsters. Effects of gastrointestinal hormones, prostaglandins, and deoxycholic and ricinoleic acids. *Gastroenterology* 74:11–15.
- Gao, J., N.-H. Sun, F.-Y. Wang, and N. Hao. 1999. Effects of castor oil-diet on the synthesis of prostaglandin E2 in pregnant rats [translation]. *Zhonghua Fu Chan Ke Za Zhi* 34:147–149.
- Garry, D., R. Figueroa, J. Guillaume, and V. Cucco. 2000. Use of castor oil in pregnancies at term. *Altern. Ther. Health Med.* 6:77–79.
- Gennaro, A. R., ed. 1990. *Remington's Pharmaceutical Sciences*, 18th ed., 785. Easton, PA: Mack Publishing.
- Gluud, B. S., T. Boesen, and M. Norn. 1981. The effect of a fatty vehicle on the cornea and conjunctiva. In vivo staining following instilling of oil [translation]. *Ugeskr. Laeger* 143:2345–2347.
- Göhte, C. J., G. Wieslander, K. Ancker, and M. Forsbeck. 1983. Buckwheat allergy: Health food, an inhalation health risk. *Allergy* 38:155–159.

²Available from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

- Goon, A. T.-J., P. P.-L. Ng, and S.-K. Ng. 1999. Allergic contact dermatitis from military camouflage. *Contact Dermatitis* 40:290–291.
- Gottschalk, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed. Washington, DC: CTFA.
- Grainger, D. N., R. Cross, and J. A. Barrowman. 1982. Effects of various secretagogues and human carcinoid serum on lymph flow in the cat ileum. *Gastroenterology* 83:896–901.
- Grant J, ed. 1972. *Hackh's Chemical Dictionary*, 4th ed., 584. New York: McGraw-Hill Book Co.
- Guillot, J. P., J. Y. Giauffret, and M. C. Martini. 1979. Etude de tolerances oculaire et cutanee chez la lapin, de differentes matieres premieres utilisees en cosmetologie, et provenant de fabrications diverses (2eme partie). *Int. J. Cosmet. Sci.* 1:27–57.
- Gunstone, F. D. 1989. Chemical reactions of fats and oils. *Biochem Soc Trans* 17:1141–1142.
- Hachiya, N. 1987. Evaluation of chemical genotoxicity by a series of short-term tests. *Akita J Med* 14:269–292.
- Hagenfeldt, L., L. Blomquist, and T. Midtvedt. 1986. Epoxycarboxylic aciduria resulting from the ingestion of castor oil. *Clin Chim Acta* 161:157–163.
- Hashimoto, Y., T. Sugai, A. Shoji, S. Asoh, K. Watanabe, and A. Inoue. 1990. Incidence of positive reactions in patch tests with ingredients of cosmetic products in 1989 and representative cases of cosmetic dermatitis (Translation). *Skin Res.* 32:115–124.
- Haworth, S., T. Lawlor, K. Mortelmans, W. Speck, and E. Zeiger. 1983. *Salmonella* mutagenicity test results for 250 chemicals. *Environ Mutagen* 5:3–142.
- Hino, N., M. Ikushima-Fujimoto, K. Ueda, A. Kume, and N. Higashi. 2000. Patch test results in 346 patients of suspected cosmetic dermatitis (1993–1996) [translation]. *Environ Dermatol* 7:144–153.
- Hui, Y. H., ed. 1996. *Bailey's Industrial Oil & Fat Products. Industrial and Consumer Nonedible Products from Oils and Fats*, 5th ed., vol. 5., 368. New York: John Wiley & Sons.
- Ihara-Watanabe, M., T. Shiroyama, G. Konda, H. Umekawa, T. Takahashi, T. Yamada and Y. Furuichi. 1999. Effects of castor oil on lipid metabolism in rats. *Biosci Biotechnol Biochem* 63:595–597.
- Inoue, A., A. Shoji, and S. Aso. 1998. Allergic lipstick cheilitis due to ester gum and ricinoleic acid. *Contact Dermatitis* 39:39.
- International Bio-Research, Inc. 1977a. Delayed contact sensitization (guinea pigs). Compound: "Grilloclin HY 77" (undiluted) (Translation). Unpublished data submitted by CTFA. 18 pages.²
- International Bio-Research, Inc. 1977b. Patch test for primary skin irritation and corrosivity of the compound: "Grilloclin HY 77" (10% soy bean oil). Unpublished data submitted by CTFA. 7 pages.²
- Jensen, P. A., and D. O'Brien. 1993. Industrial hygiene. In: *Aerosol Measurement. Principles, Techniques and Applications*, ed. K. Willeke and P.A. Baron, 538–540. New York: John Wiley and Sons.
- Johnsen, M. A. 2004. The influence of particle size. *Spray Technology and Marketing*. November:24–27.
- Johnson, C. M., J. M. Cullen, and M. C. Roberts. 1993. Morphologic characterization of castor oil-induced colitis in ponies. *Vet Pathol* 30:248–255.
- Jost, T., Y. Sell, and J. Foussereau. 1989. Contact allergy to Manilla resin. Nomenclature and physico-chemistry of Manilla, kauri, damar and copal resins. *Contact Dermatitis* 21:228–238.
- Kathren, R. L., H. Price, J. C. Rogers. 1959. Air-borne castor-bean pomace allergy; a new solution to an old problem. *AMA Arch Ind Health* 19:487–489.
- Kato, A., and Y. Yamaura. 1970. A rapid gas chromatographic method for the determination of fatty acid compositions of soybean oil and castor oil. *Chem Ind* 39:1260.
- KIC Chemicals, Inc. 2004. Hydrogenated castor oil, standard grade. Specifications. <http://www.kicchem.com/hcostandard.htm> [accessed September 2004].
- Laboratoire De Recherche Et D'Experimentation. 1994. Acute oral toxicity and skin irritation and/or corrosion tests on cetyl ricinoleate. Unpublished data submitted by CTFA, April 13, 2004. 2 pages.²
- Langer, K. H., W. Thoenes, and M. Wiederholt. 1968. Light and electron microscopic investigations of proximal convoluted tubules of the rat kidney after intraluminal injection of oil [translation]. *Pflugers Arch* 302:149–165.
- Larsen, S. W., E. Rinvar, O. Svendsen, J. Lykkesfeldt, G. J. Friis, and C. Larsen. 2001. Determination of the disappearance rate of iodine-125 labelled oils from the injection site after intramuscular and subcutaneous administration to pigs. *Int J Pharm* 230:67–75.
- le Coz, C. J., and C. Ball. 2000. Recurrent allergic contact dermatitis and cheilitis due to castor oil. *Contact Dermatitis* 42:114–115.
- Lehrer, S. B., R. M. Karr, D. J. G. Müller, and J.E. Salvaggio. 1980. Detection of castor allergens in castor wax. *Clin. Allergy* 10:33–41.
- Leow, Y. H., S. H. Tan, and S. K. Ng. 2003. Pigmented contact cheilitis from ricinoleic acid in lipsticks. *Contact Dermatitis* 49:48–49.
- Lewis, R. J. Sr. 1997. *Hawley's Condensed Chemical Dictionary*, 13th ed., 221, 749, 922, 972, 1027, 1200. New York: John Wiley & Sons.
- Lewis, R. J., Sr., ed. 2000. *Sax's Dangerous Properties of Industrial Materials*, 10th ed., 738. New York: John Wiley & Sons.
- Lide, D. R., and H. P. R. Frederiske, eds. 1993. *CRC Handbook of Chemistry and Physics*, 74th ed., 3-453. Boca Raton, FL: CRC Press.
- Lieb, L. M., R. A. Nash, J. R. Matias, and N. Orentreich. 1988. A new in vitro method for transepidermal water loss: A possible method for moisturizer evaluation. *J Soc Cosmet Chem* 39:107–119.
- Lim, S. W., and C. L. Goh. 2000. Epidemiology of eczematous cheilitis at a tertiary dermatological referral centre in Singapore. *Contact Dermatitis* 43:322–326.
- Litvinova, L. B., and T. V. Fedorchenko. 1994. The effect of plant oils on the female reproductive system [translation]. *Eksp Klin Farmakol* 57:49–51.
- Lodge, N. J. 1994. Direct vasoconstrictor effects of sandimmune (cyclosporine A) are mediated by its vehicle Cremophor EL: Inhibition by the thromboxane A₂/prostaglandin endoperoxide receptor antagonist ifetroban. *J Pharmacol Exp Ther* 271:730–734.
- Lodi, A., S. Leuchi, L. Mancini, G. Chiarelli, and C. Crosti. 1992. Allergy to castor oil and colophony in a wart remover. *Contact Dermatitis* 26:266–267.
- Lorenz, W., A. Schmal, H. Schult et al. 1982. Histamine release and hypotensive reactions in dogs by solubilizing agents and fatty acids: Analysis of various components in cremophor EL and development of a compound with reduced toxicity. *Agents Actions* 12:64–80.
- Magerl, A., R. Heiss, and P. J. Frosch. 2001. Allergic contact dermatitis from zinc ricinoleate in a deodorant and glyceryl ricinoleate in a lipstick. *Contact Dermatitis* 44:119–121.
- Maier, M., D. Staupendahl, H. R. Duerr, and H. J. Refior. 1999. Castor oil decreases pain during extracorporeal shock wave application. *Arch Orthop Trauma Surg* 119:423–427.
- Manzur, F., F. El Sayed, and J. Bazex. 1995. Contact allergy to cinnamic aldehyde and cinnamic alcohol in Oléophytal. *Contact Dermatitis* 32:55.
- Masri, M. S., L. A. Goldblatt, F. DeEds, and G. O. Kohler. 1962. Relation of cathartic activity to structural modifications of ricinoleic acid of castor oil. *J Pharm Sci* 51:999–1002.
- Mathias, J. R., J. L. Martin, T. W. Burns, G. M. Carlson, and R. P. Shields. 1978. Ricinoleic acid effect on the electrical activity of the small intestine in rabbits. *J Clin Invest* 61:640–644.
- McKeon, T. A., G. Q. Chen, and J. T. Lin. 2000. Biochemical aspects of castor oil biosynthesis. *Biochem Soc Trans* 28:972–974.
- Meyer, F. U., C. Wollmann, N. Exner, and G. Exner. 1976. Comparative studies on the skin of guinea pigs, swine and man following the effect of various external agents [translation]. *Dermatol Monatsschr* 162:986–991.
- Migally, N. 1979. Effect of castor oil and benzyl benzoate used as a vehicle for antiandrogens on the adrenal cortex. *Arch Androl* 2:365–369.
- Mitri, F., G. J. Hofmeyr, and C. J. Van Geldren. 1987. Meconium during labor-self-medication and other associations. *SAMJ* 431–433.
- Mordenti, J. J., R. E. Lindstrom, and J. M. Tanzer. 1982. Activity of sodium ricinoleate against in vitro plaque. *Pharm Sci* 71:1419–1421.

- Morehouse, J. L., R. D. Specian, J. J. Stewart, and R. D. Berg. 1986. Translocation of indigenous bacteria from the gastrointestinal tract of mice after oral ricinoleic acid treatment. *Gastroenterology* 91:673–682.
- Morris, J. A., A. Khettry, and E. W. Seitz. 1979. Antimicrobial activity of aroma chemicals and essential oils. *J. Am. Oil Chem. Soc.* 56:595–603.
- Morris, W. E., and S. C. Kwan. 1983. Use of the rabbit ear model in evaluating the comedogenic potential of cosmetic ingredients. *J Soc Cosmet Chem* 34:215–225.
- Motoyoshi, K., Y. Toyoshima, M. Sato, and M. Yoshimura. 1979. Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man. *Cosmet Toilet* 94: 41.
- Muldoon, D. F., E. A. Hassoun, and S. J. Stohs. 1992. Ricin-induced hepatic lipid peroxidation, glutathione depletion, and DNA single-strand breaks in mice. *Toxicol* 30:977–984.
- National Academy of Sciences (NAS). 1996. *Food Chemicals Codex*, 4th ed., 94 Washington, DC: National Academy Press.
- National Toxicology Program (NTP). 1992. NTP technical report on the toxicity studies of castor oil (CAS No. 8001-79-4) in F344/N rats and B6C3F1 mice (dosed feed studies). NTIS Report No. PB93151439.
- NTP. 2003. *NTP Chemical Repository*. Castor Oil. Research Triangle Park, NC: NTP.
- Nikitakis, J. M., and G. N. McEwen Jr., eds. 1990. *CTFA Compendium of Cosmetic Ingredient Composition—Descriptions I and II*. Washington, DC: CTFA.
- Ohia, E. O., M. Mancino, and P. S. Kulkarni. 1992. Effects of steroids and immunosuppressive drugs on endotoxin-uveitis in rabbits. *J Ocul Pharmacol* 8:295–307.
- Okui, S., M. Uchiyama, R. Sato, and M. Mizugaki. 1964. Metabolism of hydroxy fatty acids. III. Characterization of hydroxy acids in depot fat after feeding of ricinoleic acid. *J Biochem* 55:81–86.
- Okwuasaba, F. K., U. A. Osunkwo, M. M. Ekwenchi, et al. 1991. Anticonceptive and estrogenic effects of a seed extract of *Ricinus communis* var. minor. *J Ethnopharmacol* 34:141–145.
- Oliveira, C. A., K. Carnes, L. R. Franca, and R. A. Hess. 2001. Infertility and testicular atrophy in the antiestrogen-treated adult male rat. *Biol Reprod* 65:913–920.
- Ordman, D. 1955. An outbreak of bronchial asthma in South Africa, affecting more than 200 persons, caused by castor bean dust from an oil-processing factory. *Int Arch Allergy* 7:10.
- Paul, H., and C. M. McCay. 1942. The utilization of rats by herbivora. *Arch Biochem* 1:247–253.
- Paulus, G. L., and M. H. Champion. 1972. Gas-liquid chromatographic determination of castor oil as methyl ricinoleate in lipstick. *J Soc Cosmet Chem* 23:313–319.
- Physical & Theoretical Chemistry Lab. 2004. Safety (MSDS) data for hydrogenated castor oil. http://ptcl.chem.ox.ac.uk/MSDS/HY/hydrogenated_castor_oil.html [accessed September 2004].
- Pinto, A., A. Calignano, N. Mascolo, G. Autore, and F. Capasso. 1989. Castor oil increases intestinal formation of platelet-activating factor and acid phosphatase release in the rat. *Br J Pharmacol* 96:872–874.
- Pösch, G. 1971. Assay of phosphodiesterase with radioactively labeled cyclic 3'5'-AMP as substrate. *Naunyn-Schmiedeberg's Arch Pharmacol* 268:272–299.
- Polgar, P., and L. Taylor. 1977. Effects of prostaglandin on substrate uptake and cell division in human diploid fibroblasts. *Biochem J.* 162:1–8.
- Racusen, L. C., B. C. Kone, A. Whelton, and K. Solez. 1986. Renal blood flow, glomerular filtration rate, and renal morphology in cyclosporine-induced acute renal failure in Munich-Wistar rats. *Am J Kidney Dis* 8:319–322.
- Ramsey, J. D., T. D. Lee, M. D. Osselton, and A. C. Moffat. 1980. Gas liquid chromatographic retention indices of 296 nondrug substances on SE-30 or OV-1 likely to be encountered in toxicological analyses. *J Chromatogr* 184:185–206.
- Rantuccio, F., D. Sinisi, A. Scardigno, and C. Coviello. 1981. Histological changes in rabbits after application of medicaments and cosmetic bases. II. *Contact Dermatitis* 7:94–97.
- Rao, M. K., N. Risser, and E. G. Perkins. 1969. The incorporation of ricinoleic acid into rat lymph lipids. *Proc Soc Exp Biol Med* 131:1369–1372.
- Ratner, B., and H. L. Gruehl. 1929. Respiratory anaphylaxis (asthma) and ricin poisoning induced with castor bean dust. *Am J Hyg* 10:236.
- Reichert-Pénétrat, S., A. Barbaud, E. Reichert-Pénétrat, F. Granel, and J.-L. Schmutz. 2001. Allergic contact dermatitis from surgical paints. *Contact Dermatitis* 45:116–117.
- Research Institute for Fragrance Materials (RIFM). 2000. Fragrance raw materials monographs. Ethyl ricinoleate. *FCT* 38:S91–S92.
- Sai, S. 1983. Lipstick dermatitis caused by castor oil. *Contact Dermatitis* 9:75, 524.
- Salomon, Y., C. Londos, and M. Rodbell. 1974. A highly sensitive adenylate cyclase assay. *Anal Biochem* 58:541–548.
- Sasol North America, Inc. No date. UV spectrum for castor oil and glyceryl ricinoleate. Unpublished data submitted by CTFA, April 14, 2004. 1 page.²
- Scarpa, A., and A. Guerri. 1982. Various uses of the castor oil plant (*Ricinus communis* L.). A review. *J Ethnopharmacol* 5:117–137.
- Secchi, A. G., M. S. Tognon, and A. Leonardi. 1990. Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. *Am J Ophthalmol* 110:641–645.
- Shubik, P. 1950. Studies on the promoting phase in the stages of carcinogenesis in mice, rats, rabbits, and guinea pigs. *Cancer Res* 10:13–17.
- Simon, B., and H. Kather. 1980. Interaction of laxatives with enzymes of cyclic AMP metabolism from human colonic mucosa. *Eur J Clin Invest* 10:231–234.
- Smolinske, S. C. 1992. *Handbook of Food, Drug, and Cosmetic Excipients*, 70. Boca Raton, FL: CRC Press.
- Song, J. F., C. A. Lau-Cm, and K. H. Kim. 2001. Monohydroxylation and esterification as determinants of the effects of cis- and trans-9-octadecenoic acids on the permeation of hydrocortisone and 5-fluorouracil across hairless mouse skin in vitro. *Int J Pharmaceut* 212:153–160.
- Srinivasulu, C., and S. N. Mahapatra. 1973. A rapid method for detecting groundnut oil in castor oil. *J Chromatogr* 86:261–262.
- Steingrub, J. S., T. Lopez, D. Teres, and R. Steingart. 1988. Amniotic fluid embolism associated with castor oil ingestion. *Crit Care Med* 16:642–643.
- Stewart, J. J., and P. Bass. 1976. Effects of ricinoleic acid and oleic acids on the digestive contractile activity of the canine small and large bowel. *Gastroenterology* 70:371–376.
- Stewart, J. J., T. S. Gaginella, and P. Bass. 1975. Actions of ricinoleic acid and structurally related fatty acids on the gastrointestinal tract. I. Effects on smooth muscle contractility in vitro. *J Pharmacol Exp Ther* 195:347–354.
- Stewart, W. C., and R. G. Sinclair. 1945. The absence of ricinoleic acid from phospholipids of rats fed castor oil. *Arch Biochem* 8:7.
- Stübiger, G., E. Pittenauer, and G. Allmaier. 2003. Characterization of castor oil by on-line and of-line non-aqueous reverse-phase high-performance liquid chromatography-mass spectrometry (APCI and UV/MALDI). *Phytochem Anal* 14:337–346.
- Tabar, A. I., M. D. Muro, S. Quirce, and J. M. Olaguibel. 1993. Contact dermatitis due to sensitization to lactic acid and castor oil in a wart remover solution. *Contact Dermatitis* 29:49–50.
- Tan, B. B., A. L. Noble, M. E. Roberts, J. T. Lear, and J. S. English. 1997. Allergic contact dermatitis from oleyl alcohol in lipstick cross-reacting with ricinoleic acid in castor oil and lanolin. *Contact Dermatitis* 37:41–42.
- Thompson, W. G. 1980. Laxatives: Clinical pharmacology and rational use. *Drugs* 19:49–58.
- TNO BIBRA International Ltd. 1999. Toxicity profile. Castor oil. Surrey, United Kingdom: TNO BIBRA International Ltd. 9 pages.
- Uchiyama, M., R. Sato, and M. Mizugaki. 1963. Characterization of hydroxyacids in depot fat after feeding of ricinoleic acid. *Biochem Biophys Acta* 70:344–346.
- Vanderhoek, J. Y., R. W. Bryant, and J. M. Bailey. 1980. Communication. 15-hydroxy-5,8,11,13-eicosatetraenoic acid. A potent and selective inhibitor of platelet lipoxigenase. *J Biol Chem* 255:5996–5998.

- Vieira, C., S. Evangelista, R. Cirillo, R. Terracciano, A. Lippi, C.A. Maggi, and S. Manzini. 2000. Antinociceptive activity of ricinoleic acid, a capsaicin-like compound devoid of pungent properties. *Eur J Pharmacol* 407:109–116.
- Vieira, C., S. Tetzner, S. K. Sauer, et al. 2001. Pro- and anti-inflammatory actions of ricinoleic acid: Similarities and differences with capsaicin. *Naunyn-Schmiedeberg's Arch Pharmacol* 364:87–95.
- Wakelin, S. H., A. J. Harris, and S. Shaw. 1996. Contact dermatitis from castor oil in zinc and castor oil cream. *Contact Dermatitis* 35:259.
- Watson, W. C., and R. S. Gordon Jr. 1962. Studies on the digestion, absorption and metabolism of castor oil. *Biochem Pharmacol* 11:229–236.
- Watson, W. C., R. S. Gordon Jr, A. Karmen, and A. Jover. 1963. The absorption and excretion of castor oil in man. *J Pharm Pharmacol* 15:183–188.
- Whiteside-Carlson, V., B. F. Feaster, and W. W. Carlson. 1955. Filament induction in *Escherichia coli* by ricinoleic acid. *Proc Soc Exp Biol Med* 89:382–385.
- Wineburg, J. P., and D. Swern. 1973. NMR chemical shift reagents in structural determination of lipid derivatives: III. Methyl ricinoleate and methyl 12-hydroxystearate. *J Am Oil Chem Soc* 50:142–146.
- World Health Organization (WHO). 1980. Evaluation of certain food additives. Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives, 1–45. World Health Organization Technical Report Series 648. Geneva: WHO.
- Xie, S. A., D. S. Liu, B. L. Li, Z. H. Wang, and J.Y. Tao. 1992. Antitumor effect of castor oil extract [translation]. *Zhongguo Zhong Yao Za Zhi* 17:560–561.
- Yagaloff, K. A., L. Franco, F. Simko, and B. Burghardt. 1995. Essential fatty acids are antagonists of the leukotriene B4 receptor. *Prostaglandins Leukotriene Essent. Fatty Acids* 52:293–297.
- Yahagi, T., M. Degawa, Y. Seino, T. Matsushima, M. Nagao, T. Sugimura, and Y. Hashimoto. 1975. Mutagenicity of carcinogenic azo dyes and their derivatives. *Cancer Lett* 1:91–96.
- Yoshikawa, K., T. Kozuka, T. Doi, Y. Kataoka, K. Fujimoto, and S. Hashimoto. 1986. A case of allergic contact dermatitis to castor oil. 10th Anniversary Meeting of Japan Patch Test Research Group on Contact Dermatitis and Patch Test VII, Kobe, Japan, December 7–8, 1985. *Skin Res* 28(Suppl. 2):263–265.
- Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, and K. Mortelmans. 1988. Mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ Mol Mutagen* 11(Suppl. 12):1–158.

Copyright of International Journal of Toxicology is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

GLYCERYL BEHENATE	03A - Eyebrow Pencil	2
GLYCERYL BEHENATE	03B - Eyeliner	1
GLYCERYL BEHENATE	03C - Eye Shadow	2
GLYCERYL BEHENATE	03D - Eye Lotion	1
GLYCERYL BEHENATE	03F - Mascara	12
GLYCERYL BEHENATE	03G - Other Eye Makeup Preparati	2
GLYCERYL BEHENATE	05C - Hair Straighteners	1
GLYCERYL BEHENATE	05G - Tonics, Dressings, and Othe	2
GLYCERYL BEHENATE	07C - Foundations	4
GLYCERYL BEHENATE	07E - Lipstick	7
GLYCERYL BEHENATE	07I - Other Makeup Preparations	3
GLYCERYL BEHENATE	08B - Cuticle Softeners	1
GLYCERYL BEHENATE	08G - Other Manicuring Preparation	1
GLYCERYL BEHENATE	10E - Other Personal Cleanliness F	1
GLYCERYL BEHENATE	12A - Cleansing	6
GLYCERYL BEHENATE	12C - Face and Neck (exc shave)	7
GLYCERYL BEHENATE	12D - Body and Hand (exc shave)	6
GLYCERYL BEHENATE	12F - Moisturizing	17
GLYCERYL BEHENATE	12G - Night	2
GLYCERYL BEHENATE	12H - Paste Masks (mud packs)	1
GLYCERYL BEHENATE	12J - Other Skin Care Preps	10
GLYCERYL BEHENATE	13B - Indoor Tanning Preparations	1
GLYCERYL CAPRATE	01B - Baby Lotions, Oils, Powders,	1
GLYCERYL CAPRATE	03B - Eyeliner	1
GLYCERYL CAPRATE	03C - Eye Shadow	1
GLYCERYL CAPRATE	03D - Eye Lotion	2
GLYCERYL CAPRATE	07A - Blushers (all types)	2
GLYCERYL CAPRATE	07B - Face Powders	1
GLYCERYL CAPRATE	07C - Foundations	1
GLYCERYL CAPRATE	07E - Lipstick	7
GLYCERYL CAPRATE	07I - Other Makeup Preparations	1
GLYCERYL CAPRATE	10B - Deodorants (underarm)	5
GLYCERYL CAPRATE	11A - Aftershave Lotion	3
GLYCERYL CAPRATE	11E - Shaving Cream	3
GLYCERYL CAPRATE	11G - Other Shaving Preparation P	1
GLYCERYL CAPRATE	12A - Cleansing	5
GLYCERYL CAPRATE	12C - Face and Neck (exc shave)	6
GLYCERYL CAPRATE	12D - Body and Hand (exc shave)	2
GLYCERYL CAPRATE	12F - Moisturizing	2
GLYCERYL CAPRATE	12G - Night	1
GLYCERYL CAPRATE	12H - Paste Masks (mud packs)	2
GLYCERYL CAPRATE	12I - Skin Fresheners	4
GLYCERYL CAPRATE	12J - Other Skin Care Preps	6
GLYCERYL CAPRYLATE	03B - Eyeliner	9
GLYCERYL CAPRYLATE	03C - Eye Shadow	7
GLYCERYL CAPRYLATE	03D - Eye Lotion	6
GLYCERYL CAPRYLATE	03F - Mascara	3
GLYCERYL CAPRYLATE	03G - Other Eye Makeup Preparati	4
GLYCERYL CAPRYLATE	05A - Hair Conditioner	3
GLYCERYL CAPRYLATE	05F - Shampoos (non-coloring)	1
GLYCERYL CAPRYLATE	05G - Tonics, Dressings, and Othe	2
GLYCERYL CAPRYLATE	07A - Blushers (all types)	11
GLYCERYL CAPRYLATE	07B - Face Powders	16
GLYCERYL CAPRYLATE	07C - Foundations	7
GLYCERYL CAPRYLATE	07E - Lipstick	20

GLYCERYL CAPRYLATE	07F - Makeup Bases	2
GLYCERYL CAPRYLATE	07H - Makeup Fixatives	1
GLYCERYL CAPRYLATE	07I - Other Makeup Preparations	10
GLYCERYL CAPRYLATE	10B - Deodorants (underarm)	2
GLYCERYL CAPRYLATE	11D - Preshave Lotions (all types)	1
GLYCERYL CAPRYLATE	12A - Cleansing	5
GLYCERYL CAPRYLATE	12C - Face and Neck (exc shave)	25
GLYCERYL CAPRYLATE	12D - Body and Hand (exc shave)	12
GLYCERYL CAPRYLATE	12F - Moisturizing	19
GLYCERYL CAPRYLATE	12G - Night	6
GLYCERYL CAPRYLATE	12H - Paste Masks (mud packs)	4
GLYCERYL CAPRYLATE	12I - Skin Fresheners	6
GLYCERYL CAPRYLATE	12J - Other Skin Care Preps	8
GLYCERYL CAPRYLATE/CAPRATE	05B - Hair Spray (aerosol fixatives)	1
GLYCERYL CAPRYLATE/CAPRATE	05F - Shampoos (non-coloring)	1
GLYCERYL COCOATE	05F - Shampoos (non-coloring)	2
GLYCERYL COCOATE	05I - Other Hair Preparations	1
GLYCERYL COCOATE	12C - Face and Neck (exc shave)	5
GLYCERYL COCOATE	12D - Body and Hand (exc shave)	5
GLYCERYL COCOATE	12H - Paste Masks (mud packs)	1
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	03B - Eyeliner	1
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	03C - Eye Shadow	20
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	05G - Tonics, Dressings, and Othe	1
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	07A - Blushers (all types)	6
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	07B - Face Powders	4
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	07C - Foundations	4
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	07E - Lipstick	1
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	07F - Makeup Bases	1
GLYCERYL ETHYLHEXANOATE/STEARATE/ADIPATE	12A - Cleansing	1
GLYCERYL HYDROGENATED ROSINATE	03C - Eye Shadow	1
GLYCERYL HYDROGENATED ROSINATE	03F - Mascara	13
GLYCERYL HYDROGENATED ROSINATE	05G - Tonics, Dressings, and Othe	1
GLYCERYL HYDROGENATED ROSINATE	07E - Lipstick	6
GLYCERYL HYDROGENATED ROSINATE	12B - Depilatories	7
GLYCERYL HYDROGENATED ROSINATE	12J - Other Skin Care Preps	1
GLYCERYL HYDROXYSTEARATE	03A - Eyebrow Pencil	1
GLYCERYL HYDROXYSTEARATE	03D - Eye Lotion	1
GLYCERYL HYDROXYSTEARATE	03F - Mascara	1
GLYCERYL HYDROXYSTEARATE	03G - Other Eye Makeup Preparati	7
GLYCERYL HYDROXYSTEARATE	12F - Moisturizing	2
GLYCERYL HYDROXYSTEARATE	12G - Night	1
GLYCERYL HYDROXYSTEARATE	13A - Suntan Gels, Creams, and Li	1
GLYCERYL ISOSTEARATE	03C - Eye Shadow	4
GLYCERYL ISOSTEARATE	05I - Other Hair Preparations	1
GLYCERYL ISOSTEARATE	06A - Hair Dyes and Colors (all typ	65
GLYCERYL ISOSTEARATE	06B - Hair Tints	23
GLYCERYL ISOSTEARATE	07C - Foundations	2

GLYCERYL ISOSTEARATE	07E - Lipstick	1
GLYCERYL ISOSTEARATE	11E - Shaving Cream	1
GLYCERYL ISOSTEARATE	12A - Cleansing	1
GLYCERYL ISOSTEARATE	12F - Moisturizing	5
GLYCERYL ISOSTEARATE	12J - Other Skin Care Preps	1
GLYCERYL ISOTRIDECANOATE/STEARATE/ADIPATE	12F - Moisturizing	1
GLYCERYL LANOLATE	12F - Moisturizing	1
GLYCERYL LAURATE	01B - Baby Lotions, Oils, Powders,	3
GLYCERYL LAURATE	01C - Other Baby Products	3
GLYCERYL LAURATE	02D - Other Bath Preparations	3
GLYCERYL LAURATE	03B - Eyeliner	1
GLYCERYL LAURATE	03C - Eye Shadow	2
GLYCERYL LAURATE	03D - Eye Lotion	1
GLYCERYL LAURATE	03E - Eye Makeup Remover	1
GLYCERYL LAURATE	03G - Other Eye Makeup Preparati	4
GLYCERYL LAURATE	04E - Other Fragrance Preparation	1
GLYCERYL LAURATE	05A - Hair Conditioner	2
GLYCERYL LAURATE	05F - Shampoos (non-coloring)	17
GLYCERYL LAURATE	05G - Tonics, Dressings, and Othe	2
GLYCERYL LAURATE	05I - Other Hair Preparations	5
GLYCERYL LAURATE	07A - Blushers (all types)	2
GLYCERYL LAURATE	07B - Face Powders	1
GLYCERYL LAURATE	07C - Foundations	4
GLYCERYL LAURATE	07E - Lipstick	6
GLYCERYL LAURATE	07I - Other Makeup Preparations	3
GLYCERYL LAURATE	09C - Other Oral Hygiene Products	2
GLYCERYL LAURATE	10A - Bath Soaps and Detergents	38
GLYCERYL LAURATE	10B - Deodorants (underarm)	15
GLYCERYL LAURATE	10E - Other Personal Cleanliness F	23
GLYCERYL LAURATE	11A - Aftershave Lotion	3
GLYCERYL LAURATE	11E - Shaving Cream	4
GLYCERYL LAURATE	11G - Other Shaving Preparation P	2
GLYCERYL LAURATE	12A - Cleansing	16
GLYCERYL LAURATE	12C - Face and Neck (exc shave)	3
GLYCERYL LAURATE	12D - Body and Hand (exc shave)	7
GLYCERYL LAURATE	12F - Moisturizing	18
GLYCERYL LAURATE	12G - Night	2
GLYCERYL LAURATE	12H - Paste Masks (mud packs)	1
GLYCERYL LAURATE	12J - Other Skin Care Preps	13
GLYCERYL LAURATE	13B - Indoor Tanning Preparations	2
GLYCERYL LINOLEATE	01B - Baby Lotions, Oils, Powders,	2
GLYCERYL LINOLEATE	03D - Eye Lotion	2
GLYCERYL LINOLEATE	03E - Eye Makeup Remover	1
GLYCERYL LINOLEATE	03G - Other Eye Makeup Preparati	5
GLYCERYL LINOLEATE	05A - Hair Conditioner	5
GLYCERYL LINOLEATE	05B - Hair Spray (aerosol fixatives)	1
GLYCERYL LINOLEATE	05F - Shampoos (non-coloring)	5
GLYCERYL LINOLEATE	05G - Tonics, Dressings, and Othe	1
GLYCERYL LINOLEATE	05I - Other Hair Preparations	5
GLYCERYL LINOLEATE	06D - Hair Shampoos (coloring)	1
GLYCERYL LINOLEATE	07E - Lipstick	1

GLYCERYL LINOLEATE	08B - Cuticle Softeners	1
GLYCERYL LINOLEATE	08E - Nail Polish and Enamel	1
GLYCERYL LINOLEATE	08G - Other Manicuring Preparation	2
GLYCERYL LINOLEATE	10A - Bath Soaps and Detergents	1
GLYCERYL LINOLEATE	12A - Cleansing	1
GLYCERYL LINOLEATE	12C - Face and Neck (exc shave)	25
GLYCERYL LINOLEATE	12D - Body and Hand (exc shave)	5
GLYCERYL LINOLEATE	12F - Moisturizing	8
GLYCERYL LINOLEATE	12G - Night	7
GLYCERYL LINOLEATE	12H - Paste Masks (mud packs)	3
GLYCERYL LINOLEATE	12J - Other Skin Care Preps	4
GLYCERYL LINOLENATE	01B - Baby Lotions, Oils, Powders,	2
GLYCERYL LINOLENATE	03D - Eye Lotion	2
GLYCERYL LINOLENATE	03E - Eye Makeup Remover	1
GLYCERYL LINOLENATE	03G - Other Eye Makeup Preparati	4
GLYCERYL LINOLENATE	05A - Hair Conditioner	5
GLYCERYL LINOLENATE	05B - Hair Spray (aerosol fixatives)	1
GLYCERYL LINOLENATE	05F - Shampoos (non-coloring)	5
GLYCERYL LINOLENATE	05G - Tonics, Dressings, and Othe	1
GLYCERYL LINOLENATE	05I - Other Hair Preparations	5
GLYCERYL LINOLENATE	06D - Hair Shampoos (coloring)	1
GLYCERYL LINOLENATE	07E - Lipstick	1
GLYCERYL LINOLENATE	08B - Cuticle Softeners	1
GLYCERYL LINOLENATE	08E - Nail Polish and Enamel	1
GLYCERYL LINOLENATE	08G - Other Manicuring Preparation	2
GLYCERYL LINOLENATE	10A - Bath Soaps and Detergents	1
GLYCERYL LINOLENATE	12A - Cleansing	2
GLYCERYL LINOLENATE	12C - Face and Neck (exc shave)	14
GLYCERYL LINOLENATE	12D - Body and Hand (exc shave)	6
GLYCERYL LINOLENATE	12F - Moisturizing	7
GLYCERYL LINOLENATE	12G - Night	4
GLYCERYL LINOLENATE	12J - Other Skin Care Preps	4
GLYCERYL OLEATE	01A - Baby Shampoos	5
GLYCERYL OLEATE	01B - Baby Lotions, Oils, Powders,	2
GLYCERYL OLEATE	01C - Other Baby Products	6
GLYCERYL OLEATE	02A - Bath Oils, Tablets, and Salts	2
GLYCERYL OLEATE	02B - Bubble Baths	17
GLYCERYL OLEATE	02D - Other Bath Preparations	2
GLYCERYL OLEATE	03A - Eyebrow Pencil	9
GLYCERYL OLEATE	03B - Eyeliner	16
GLYCERYL OLEATE	03C - Eye Shadow	36
GLYCERYL OLEATE	03D - Eye Lotion	3
GLYCERYL OLEATE	03E - Eye Makeup Remover	1
GLYCERYL OLEATE	03F - Mascara	10
GLYCERYL OLEATE	03G - Other Eye Makeup Preparati	12
GLYCERYL OLEATE	04E - Other Fragrance Preparation	1
GLYCERYL OLEATE	05A - Hair Conditioner	17
GLYCERYL OLEATE	05B - Hair Spray (aerosol fixatives)	1
GLYCERYL OLEATE	05F - Shampoos (non-coloring)	83
GLYCERYL OLEATE	05G - Tonics, Dressings, and Othe	2
GLYCERYL OLEATE	05I - Other Hair Preparations	10
GLYCERYL OLEATE	06A - Hair Dyes and Colors (all typ	1
GLYCERYL OLEATE	06D - Hair Shampoos (coloring)	2
GLYCERYL OLEATE	06G - Hair Bleaches	2
GLYCERYL OLEATE	07A - Blushers (all types)	1

GLYCERYL OLEATE	07B - Face Powders	7
GLYCERYL OLEATE	07C - Foundations	4
GLYCERYL OLEATE	07E - Lipstick	29
GLYCERYL OLEATE	07F - Makeup Bases	2
GLYCERYL OLEATE	07H - Makeup Fixatives	1
GLYCERYL OLEATE	07I - Other Makeup Preparations	10
GLYCERYL OLEATE	09B - Mouthwashes and Breath Fr	5
GLYCERYL OLEATE	10A - Bath Soaps and Detergents	154
GLYCERYL OLEATE	10C - Douches	3
GLYCERYL OLEATE	10E - Other Personal Cleanliness F	50
GLYCERYL OLEATE	11D - Preshave Lotions (all types)	1
GLYCERYL OLEATE	11E - Shaving Cream	10
GLYCERYL OLEATE	11G - Other Shaving Preparation P	25
GLYCERYL OLEATE	12A - Cleansing	52
GLYCERYL OLEATE	12C - Face and Neck (exc shave)	14
GLYCERYL OLEATE	12D - Body and Hand (exc shave)	7
GLYCERYL OLEATE	12E - Foot Powders and Sprays	1
GLYCERYL OLEATE	12F - Moisturizing	29
GLYCERYL OLEATE	12G - Night	6
GLYCERYL OLEATE	12I - Skin Fresheners	1
GLYCERYL OLEATE	12J - Other Skin Care Preps	6
GLYCERYL OLEATE	13A - Suntan Gels, Creams, and Li	1
GLYCERYL OLEATE	13B - Indoor Tanning Preparations	2
GLYCERYL OLEATE	13C - Other Suntan Preparations	2
GLYCERYL OLEATE/ELAIDATE	05F - Shampoos (non-coloring)	2
GLYCERYL OLEATE/ELAIDATE	12F - Moisturizing	2
GLYCERYL MONOPALMITATE	12A - Cleansing	1
GLYCERYL MONOPALMITATE	12D - Body and Hand (exc shave)	3
GLYCERYL RICINOLEATE	03B - Eyeliner	10
GLYCERYL RICINOLEATE	07C - Foundations	3
GLYCERYL RICINOLEATE	07E - Lipstick	16
GLYCERYL RICINOLEATE	07I - Other Makeup Preparations	3
GLYCERYL RICINOLEATE	10A - Bath Soaps and Detergents	2
GLYCERYL RICINOLEATE	11A - Aftershave Lotion	1
GLYCERYL RICINOLEATE	12F - Moisturizing	6
RICINOLEIN	03A - Eyebrow Pencil	1
GLYCERYL ROSINATE	03C - Eye Shadow	2
GLYCERYL ROSINATE	03F - Mascara	4
GLYCERYL ROSINATE	05I - Other Hair Preparations	1
GLYCERYL ROSINATE	06H - Other Hair Coloring Preparat	2
GLYCERYL ROSINATE	07B - Face Powders	1
GLYCERYL ROSINATE	07C - Foundations	5
GLYCERYL ROSINATE	07E - Lipstick	20
GLYCERYL ROSINATE	07I - Other Makeup Preparations	1
GLYCERYL ROSINATE	12B - Depilatories	12
GLYCERYL ROSINATE	12F - Moisturizing	2
GLYCERYL STEARATE	01A - Baby Shampoos	1
GLYCERYL STEARATE	01B - Baby Lotions, Oils, Powders,	28
GLYCERYL STEARATE	01C - Other Baby Products	4

GLYCERYL STEARATE	02A - Bath Oils, Tablets, and Salts	1
GLYCERYL STEARATE	02B - Bubble Baths	6
GLYCERYL STEARATE	02D - Other Bath Preparations	3
GLYCERYL STEARATE	03A - Eyebrow Pencil	14
GLYCERYL STEARATE	03B - Eyeliner	49
GLYCERYL STEARATE	03C - Eye Shadow	53
GLYCERYL STEARATE	03D - Eye Lotion	115
GLYCERYL STEARATE	03E - Eye Makeup Remover	9
GLYCERYL STEARATE	03F - Mascara	247
GLYCERYL STEARATE	03G - Other Eye Makeup Preparati	79
GLYCERYL STEARATE	04B - Perfumes	8
GLYCERYL STEARATE	04E - Other Fragrance Preparation	9
GLYCERYL STEARATE	05A - Hair Conditioner	156
GLYCERYL STEARATE	05C - Hair Straighteners	2
GLYCERYL STEARATE	05D - Permanent Waves	5
GLYCERYL STEARATE	05E - Rinses (non-coloring)	9
GLYCERYL STEARATE	05F - Shampoos (non-coloring)	25
GLYCERYL STEARATE	05G - Tonics, Dressings, and Othe	79
GLYCERYL STEARATE	05I - Other Hair Preparations	41
GLYCERYL STEARATE	06A - Hair Dyes and Colors (all typ	151
GLYCERYL STEARATE	06B - Hair Tints	21
GLYCERYL STEARATE	06C - Hair Rinses (coloring)	6
GLYCERYL STEARATE	06D - Hair Shampoos (coloring)	1
GLYCERYL STEARATE	06F - Hair Lighteners with Color	1
GLYCERYL STEARATE	06H - Other Hair Coloring Preparat	20
GLYCERYL STEARATE	07A - Blushers (all types)	3
GLYCERYL STEARATE	07B - Face Powders	20
GLYCERYL STEARATE	07C - Foundations	41
GLYCERYL STEARATE	07D - Leg and Body Paints	14
GLYCERYL STEARATE	07E - Lipstick	30
GLYCERYL STEARATE	07F - Makeup Bases	23
GLYCERYL STEARATE	07I - Other Makeup Preparations	38
GLYCERYL STEARATE	08B - Cuticle Softeners	4
GLYCERYL STEARATE	08C - Nail Creams and Lotions	4
GLYCERYL STEARATE	08F - Nail Polish and Enamel Rem	1
GLYCERYL STEARATE	08G - Other Manicuring Preparation	2
GLYCERYL STEARATE	10A - Bath Soaps and Detergents	54
GLYCERYL STEARATE	10B - Deodorants (underarm)	42
GLYCERYL STEARATE	10C - Douches	1
GLYCERYL STEARATE	10E - Other Personal Cleanliness F	87
GLYCERYL STEARATE	11A - Aftershave Lotion	51
GLYCERYL STEARATE	11E - Shaving Cream	23
GLYCERYL STEARATE	11G - Other Shaving Preparation P	5
GLYCERYL STEARATE	12A - Cleansing	229
GLYCERYL STEARATE	12B - Depilatories	1
GLYCERYL STEARATE	12C - Face and Neck (exc shave)	495
GLYCERYL STEARATE	12D - Body and Hand (exc shave)	877
GLYCERYL STEARATE	12E - Foot Powders and Sprays	8
GLYCERYL STEARATE	12F - Moisturizing	1297
GLYCERYL STEARATE	12G - Night	205
GLYCERYL STEARATE	12H - Paste Masks (mud packs)	106
GLYCERYL STEARATE	12I - Skin Fresheners	5
GLYCERYL STEARATE	12J - Other Skin Care Preps	225
GLYCERYL STEARATE	13A - Suntan Gels, Creams, and Li	25
GLYCERYL STEARATE	13B - Indoor Tanning Preparations	80
GLYCERYL STEARATE	13C - Other Suntan Preparations	14
GLYCERYL STEARATE SE	01B - Baby Lotions, Oils, Powders,	3

GLYCERYL STEARATE SE	03B - Eyeliner	1
GLYCERYL STEARATE SE	03C - Eye Shadow	15
GLYCERYL STEARATE SE	03D - Eye Lotion	10
GLYCERYL STEARATE SE	03E - Eye Makeup Remover	1
GLYCERYL STEARATE SE	03F - Mascara	20
GLYCERYL STEARATE SE	03G - Other Eye Makeup Preparati	12
GLYCERYL STEARATE SE	04E - Other Fragrance Preparation	1
GLYCERYL STEARATE SE	05A - Hair Conditioner	22
GLYCERYL STEARATE SE	05F - Shampoos (non-coloring)	4
GLYCERYL STEARATE SE	05G - Tonics, Dressings, and Othe	14
GLYCERYL STEARATE SE	05I - Other Hair Preparations	5
GLYCERYL STEARATE SE	06A - Hair Dyes and Colors (all typ	317
GLYCERYL STEARATE SE	06B - Hair Tints	22
GLYCERYL STEARATE SE	06H - Other Hair Coloring Preparat	1
GLYCERYL STEARATE SE	07A - Blushers (all types)	2
GLYCERYL STEARATE SE	07C - Foundations	9
GLYCERYL STEARATE SE	07E - Lipstick	1
GLYCERYL STEARATE SE	07F - Makeup Bases	2
GLYCERYL STEARATE SE	07I - Other Makeup Preparations	3
GLYCERYL STEARATE SE	08C - Nail Creams and Lotions	1
GLYCERYL STEARATE SE	10A - Bath Soaps and Detergents	8
GLYCERYL STEARATE SE	10B - Deodorants (underarm)	1
GLYCERYL STEARATE SE	10E - Other Personal Cleanliness F	13
GLYCERYL STEARATE SE	11A - Aftershave Lotion	5
GLYCERYL STEARATE SE	11E - Shaving Cream	5
GLYCERYL STEARATE SE	12A - Cleansing	61
GLYCERYL STEARATE SE	12B - Depilatories	7
GLYCERYL STEARATE SE	12C - Face and Neck (exc shave)	67
GLYCERYL STEARATE SE	12D - Body and Hand (exc shave)	185
GLYCERYL STEARATE SE	12E - Foot Powders and Sprays	1
GLYCERYL STEARATE SE	12F - Moisturizing	500
GLYCERYL STEARATE SE	12G - Night	29
GLYCERYL STEARATE SE	12H - Paste Masks (mud packs)	15
GLYCERYL STEARATE SE	12I - Skin Fresheners	3
GLYCERYL STEARATE SE	12J - Other Skin Care Preps	35
GLYCERYL STEARATE SE	13A - Suntan Gels, Creams, and Li	7
GLYCERYL STEARATE SE	13B - Indoor Tanning Preparations	12
GLYCERYL UNDECYLENATE	03D - Eye Lotion	1
GLYCERYL UNDECYLENATE	03F - Mascara	1
GLYCERYL UNDECYLENATE	05A - Hair Conditioner	1
GLYCERYL UNDECYLENATE	05G - Tonics, Dressings, and Othe	1
GLYCERYL UNDECYLENATE	12C - Face and Neck (exc shave)	3
GLYCERYL UNDECYLENATE	12D - Body and Hand (exc shave)	2
GLYCERYL UNDECYLENATE	12E - Foot Powders and Sprays	1
GLYCERYL UNDECYLENATE	12F - Moisturizing	5
GLYCERYL UNDECYLENATE	12G - Night	1
GLYCERYL UNDECYLENATE	12H - Paste Masks (mud packs)	1

Concentration of Use by FDA Product Category – Glyceryl Monoesters*

Glyceryl Abietate	Glyceryl Laurate
Glyceryl Abietate/Maleate	Glyceryl Laurate/Oleate
Glyceryl Acetate	Glyceryl Laurate SE
Glyceryl Adipate	Glyceryl Linoleate
Glyceryl Alginate	Glyceryl Linolenate
Glyceryl Arachidate	Glyceryl Montanate
Glyceryl Arachidonate	Glyceryl Myristate
Glyceryl Behenate	Glyceryl Oleate
Glyceryl Behenate/Eicosadioate	Glyceryl Oleate/Elaidate
Glyceryl Caprate	Glyceryl Oleate SE
Glyceryl Caprylate	Glyceryl Olivatate
Glyceryl Caprylate/Caprate	Glyceryl Palmitate
Glyceryl Citrate/Lactate/Linoleate/Oleate	Glyceryl Palmitate/Stearate
Glyceryl Cocoate	Glyceryl Palmitoleate
Glyceryl Cocoate/Citrate/Lactate	Glyceryl Pentadecanoate
Glyceryl Collagenate	Glyceryl Polyacrylate
Glyceryl Erucate	Glyceryl/Polyglyceryl-6 Isostearate/Behenate
Glyceryl Ethylhexanoate	Esters
Glyceryl Ethylhexanoate/Stearate/Adipate	Glyceryl Polyisobutenylsuccinate
Glyceryl Glycyrrhetinate	Glyceryl Polymethacrylate
Glyceryl Heptanoate	Glyceryl Ricinoleate
Glyceryl Hydrogenated Rapeseedate	Glyceryl Ricinoleate SE
Glyceryl Hydrogenated Rosinate	Glyceryl Rosinate
Glyceryl Hydrogenated Soyate	Glyceryl/Sorbitol Oleate/Hydroxystearate
Glyceryl Hydroxystearate	Glyceryl Stearate/Malate
Glyceryl Hydroxystearate/Oleate Esters	Glyceryl Tallowate
Glyceryl Isopalmitate	Glyceryl Thioglycolate
Glyceryl Isostearate	Glyceryl Thiopropionate
Glyceryl Isostearate/Myristate	Glyceryl Undecylenate
Glyceryl Isotridecanoate/Stearate/Adipate	Glyceryl Stearate
Glyceryl Lanolate	Glyceryl Stearate SE

Ingredient	Product Category	Maximum Concentration of Use
Glyceryl Behenate	Eyeliners	0.3%
Glyceryl Behenate	Eye shadow	0.38%
Glyceryl Behenate	Mascara	1.5%
Glyceryl Behenate	Tonics, dressings and other hair grooming aids	0.48%
Glyceryl Behenate	Foundations	0.31-2.5%
Glyceryl Behenate	Makeup bases	0.43%
Glyceryl Behenate	Other manicuring preparations	0.27% (rinse-off)
Glyceryl Behenate	Face and neck products not spray	0.45%
Glyceryl Behenate	Body and hand products not spray	2%

Glyceryl Behenate/Eicosadioate	Eyebrow pencil	3.4%
Glyceryl Behenate/Eicosadioate	Eyeliners	0.11%
Glyceryl Behenate/Eicosadioate	Rinses (noncoloring)	0.4%
Glyceryl Behenate/Eicosadioate	Tonics, dressings and other hair grooming aids	0.03%
Glyceryl Behenate/Eicosadioate	Lipstick	0.75-3%
Glyceryl Behenate/Eicosadioate	Other personal cleanliness products	4.1%
Glyceryl Behenate/Eicosadioate	Skin cleansing products	4%
Glyceryl Behenate/Eicosadioate	Face and neck products not spray	1.5%
Glyceryl Behenate/Eicosadioate	Body and hand products not spray	0.8%
Glyceryl Caprate	Deodorants pump spray	1%
Glyceryl Caprylate	Eyebrow pencil	1%
Glyceryl Caprylate	Eye liner	1%
Glyceryl Caprylate	Eye shadow	0.28-1%
Glyceryl Caprylate	Mascara	0.03-0.06%
Glyceryl Caprylate	Other eye makeup preparations	1%
Glyceryl Caprylate	Hair conditioners	1%
Glyceryl Caprylate	Shampoos (noncoloring)	0.01-1%
Glyceryl Caprylate	Tonics, dressings and other hair grooming aids	1%
Glyceryl Caprylate	Blushers (all types)	1.5%
Glyceryl Caprylate	Face powders	0.98%
Glyceryl Caprylate	Foundations	1%
Glyceryl Caprylate	Lipstick	0.3-1%
Glyceryl Caprylate	Rouges	0.5%
Glyceryl Caprylate	Deodorants not spray	1.5%
Glyceryl Caprylate	Beard softeners	1%
Glyceryl Caprylate	Skin cleansing products	0.05-1.5%
Glyceryl Caprylate	Face and neck products not spray	0.001-1%
Glyceryl Caprylate	Body and hand products not spray	1%
Glyceryl Caprylate	Other skin care preparations	0.05% (leave-on)
Glyceryl Caprylate	Suntan products not spray	0.15%
Glyceryl Citrate/Lactate/Linoleate/Oleate	Hair conditioners	0.004%
Glyceryl Citrate/Lactate/Linoleate/Oleate	Hair sprays pump spray	0.0004%
Glyceryl Citrate/Lactate/Linoleate/Oleate	Rinses (noncoloring)	0.004%

Glyceryl Cocoate	Shampoos (noncoloring)	1%
Glyceryl Cocoate	Bath soaps and detergents	2%
Glyceryl Cocoate	Deodorant pump spray	2%
Glyceryl Cocoate	Aftershave lotions	2%
Glyceryl Ethylhexanoate/Stearate/Adipate	Eyeliners	3%
Glyceryl Ethylhexanoate/Stearate/Adipate	Eye shadow	0.8-1.2%
Glyceryl Ethylhexanoate/Stearate/Adipate	Blushers	0.8%
Glyceryl Ethylhexanoate/Stearate/Adipate	Face powders	1-1.4%
Glyceryl Ethylhexanoate/Stearate/Adipate	Foundations	0.6-2%
Glyceryl Hydrogenated Rosinate	Mascara	3-4.8%
Glyceryl Hydrogenated Rosinate	Tonics, dressings and other hair grooming aids	6.5%
Glyceryl Hydrogenated Rosinate	Lipstick	4-10%
Glyceryl Hydrogenated Rosinate	Depilatories	65-76-8%
Glyceryl Hydroxystearate	Eyebrow pencil	1%
Glyceryl Hydroxystearate	Mascara	2%
Glyceryl Hydroxystearate	Deodorants not spray	0.9%
Glyceryl Hydroxystearate	Body and hand products not spray	0.5%
Glyceryl Hydroxystearate	Moisturizing products not spray	0.74%
Glyceryl Isostearate	Hair conditioners	0.3%
Glyceryl Isostearate	Blushers	1%
Glyceryl Isostearate	Foundations	2%
Glyceryl Isostearate	Skin cleansing products	1.5%
Glyceryl Isostearate	Face and neck products not spray	0.8-1%
Glyceryl Isostearate	Suntan products not spray	1%
Glyceryl Isostearate/Myristate	Face and neck products not spray	1%
Glyceryl Laurate	Bubble baths	1%
Glyceryl Laurate	Eye lotion	0.48%
Glyceryl Laurate	Eye makeup removers	0.000065-0.24%
Glyceryl Laurate	Shampoos (noncoloring)	0.088-1.5%
Glyceryl Laurate	Tonics, dressings and other hair grooming aids	0.2%
Glyceryl Laurate	Bath soaps and detergents	0.3-4.5%
Glyceryl Laurate	Other personal cleanliness	0.000065%

	products	
Glyceryl Laurate	Skin cleansing products	0.1-0.24%
Glyceryl Laurate	Face and neck products not spray	0.1%
Glyceryl Laurate	Body and hand products not spray	0.5%
Glyceryl Laurate	Moisturizing products not spray	0.000065%
Glyceryl Linoleate	Eyeliners	2.5%
Glyceryl Linoleate	Tonics, dressings and other hair grooming aids	0.000055%
Glyceryl Linoleate	Foundations	0.003%
Glyceryl Linoleate	Lipstick	0.056-2.5%
Glyceryl Linoleate	Basecoats and undercoats	0.019%
Glyceryl Linoleate	Cuticle softeners	4.6%
Glyceryl Linoleate	Nail creams and lotions	4.6%
Glyceryl Linoleate	Face and neck products not sprays	0.003-0.75%
Glyceryl Linoleate	Skin fresheners	0.0002%
Glyceryl Linoleate	Other skin care preparations	0.11%
Glyceryl Linolenate	Eyeliners	0.2%
Glyceryl Linolenate	Tonics, dressings and other hair grooming aids	0.00045%
Glyceryl Linolenate	Lipstick	0.046-0.2%
Glyceryl Linolenate	Basecoats and undercoats	0.001%
Glyceryl Linolenate	Cuticle softeners	0.4%
Glyceryl Linolenate	Nail creams and lotions	0.4%
Glyceryl Linolenate	Other skin care preparations	0.09%
Glyceryl Myristate	Face and neck products not spray	1%
Glyceryl Oleate	Eye brow pencil	0.01-0.06%
Glyceryl Oleate	Eyeliners	0.0075-0.062%
Glyceryl Oleate	Eye shadow	0.0075-0.75%
Glyceryl Oleate	Eye lotion	1%
Glyceryl Oleate	Mascara	0.0075-2.3%
Glyceryl Oleate	Colognes and toilet waters	1.4%
Glyceryl Oleate	Hair conditioners	0.5-2.7%
Glyceryl Oleate	Rinses (noncoloring)	0.3%
Glyceryl Oleate	Shampoo (noncoloring)	0.1-1.5%
Glyceryl Oleate	Tonics, dressings and other hair grooming aids	0.0092%
Glyceryl Oleate	Other hair preparations (noncoloring)	0.15%
Glyceryl Oleate	Hair dyes and colors	2%
Glyceryl Oleate	Foundations	0.0075%
Glyceryl Oleate	Lipstick	0.0001-0.075%

Glyceryl Oleate	Makeup bases	2%
Glyceryl Oleate	Cuticle softeners	0.015%
Glyceryl Oleate	Bath soaps and detergents	0.25-2.4%
Glyceryl Oleate	Other personal cleanliness products	0.3-2%
Glyceryl Oleate	Aftershave lotions	0.3%
Glyceryl Oleate	Shaving cream	2%
Glyceryl Oleate	Skin cleansing	0.11-1%
Glyceryl Oleate	Face and neck products not spray	0.3-1.8%
Glyceryl Oleate	Body and hand products not spray	0.0028-3%
Glyceryl Oleate	Moisturizing products not spray	0.0083%
Glyceryl Oleate	Night products not spray	0.0083-0.45%
Glyceryl Oleate	Skin fresheners	0.13%
Glyceryl Oleate	Other skin care preparations	0.26% (rinse-off)
Glyceryl Oleate	Suntan products not spray	0.075%
Glyceryl Polyacrylate	Eye lotion	0.03-0.3%
Glyceryl Polyacrylate	Mascara	5.3%
Glyceryl Polyacrylate	Hair sprays pump spray	0.35%
Glyceryl Polyacrylate	Tonics, dressings and other hair grooming aids	0.2%
Glyceryl Polyacrylate	Aftershave lotions	0.17%
Glyceryl Polyacrylate	Skin cleansing products	0.68%
Glyceryl Polyacrylate	Face and neck products not spray	0.1-1.2%
Glyceryl Polyacrylate	Body and hand products not spray	0.029-0.87%
Glyceryl Polyacrylate	Foot products	0.025%
Glyceryl Polyacrylate	Moisturizing products not spray	0.34%
Glyceryl Polyacrylate	Suntan products not spray	0.15%
Glyceryl Polyacrylate	Other suntan preparations	0.011%
Glyceryl/Polyglyceryl-6 Isostearate/Behenate Esters	Body and hand products not spray	2%
Glyceryl Polymethacrylate	Eyebrow pencil	32.8%
Glyceryl Polymethacrylate	Eye shadow	0.08%
Glyceryl Polymethacrylate	Eye lotion	0.8%
Glyceryl Polymethacrylate	Mascara	11.3%
Glyceryl Polymethacrylate	Other eye makeup preparations	0.024%
Glyceryl Polymethacrylate	Hair sprays	

	aerosol	0.091%
Glyceryl Polymethacrylate	Foundations	0.055-0.8%
Glyceryl Polymethacrylate	Makeup bases	0.047%
Glyceryl Polymethacrylate	Aftershave lotions	0.16%
Glyceryl Polymethacrylate	Shaving soap	0.26%
Glyceryl Polymethacrylate	Skin cleansing	7.7%
Glyceryl Polymethacrylate	Face and neck products not spray	0.46-7.9%
Glyceryl Polymethacrylate	Body and hand products not spray	3.4-3.6%
Glyceryl Polymethacrylate	Foot products	0.18%
Glyceryl Polymethacrylate	Other skin care preparations	0.23% (leave-on)
Glyceryl Polymethacrylate	Suntan products not spray	0.9%
Glyceryl Ricinoleate	Eyeliners	1.5-11.6%
Glyceryl Ricinoleate	Eye shadow	5-11.1%
Glyceryl Ricinoleate	Foundations	10.5%
Glyceryl Ricinoleate	Lipstick	11.9-15.2%
Glyceryl Ricinoleate	Makeup bases	12.6%
Glyceryl Ricinoleate SE	Eyebrow pencil	6.8%
Glyceryl Rosinate	Eyeliners	6%
Glyceryl Rosinate	Eye shadow	0.3-4%
Glyceryl Rosinate	Mascara	8%
Glyceryl Rosinate	Other hair coloring preparations	2.6% (rinse-off)
Glyceryl Rosinate	Blushers	0.018%
Glyceryl Rosinate	Foundations	4.1%
Glyceryl Rosinate	Lipstick	0.48-0.5%
Glyceryl Rosinate	Other makeup preparations	0.14%
Glyceryl Rosinate	Depilatories	72-96%
Glyceryl Stearate/Malate	Eyebrow pencil	0.25%
Glyceryl Stearate/Malate	Mascara	0.25%
Glyceryl Thioglycolate	Permanent waves	17.2-80%
Glyceryl Undecylanate	Moisturizing products not spray	1%
Glyceryl Undecylanate	Paste masks and mud packs	1%
Glyceryl Stearate	Baby lotions, oils and creams not powders	1.8%
Glyceryl Stearate	Other baby products	1.8%
Glyceryl Stearate	Bubble baths	1%
Glyceryl Stearate	Other bath preparations	10%
Glyceryl Stearate	Eyebrow pencil	0.014-2.5%
Glyceryl Stearate	Eye liner	0.069-2.2%
Glyceryl Stearate	Eye shadow	0.018-3%
Glyceryl Stearate	Eye lotion	1.5-4.8%
Glyceryl Stearate	Eye makeup remover	0.5-1.3%
Glyceryl Stearate	Mascara	2.6-9%

Glyceryl Stearate	Other eye makeup preparations	2.7-2.8%
Glyceryl Stearate	Perfumes	2-14%
Glyceryl Stearate	Sachets	14%
Glyceryl Stearate	Other fragrance preparations	2-12.6%
Glyceryl Stearate	Hair conditioners	0.15-4.8%
Glyceryl Stearate	Hair straighteners	0.88-1.8%
Glyceryl Stearate	Rinses (noncoloring)	0.75-0.85%
Glyceryl Stearate	Shampoos (noncoloring)	0.5-2%
Glyceryl Stearate	Tonics, dressings and other hair grooming aids	0.5-4.1%
Glyceryl Stearate	Other hair preparations (noncoloring)	4%
Glyceryl Stearate	Hair dyes and colors	0.9-7%
Glyceryl Stearate	Hair bleaches	2.2%
Glyceryl Stearate	Other hair coloring preparations	2%
Glyceryl Stearate	Blushers	2.5%
Glyceryl Stearate	Face powders	0.05-3%
Glyceryl Stearate	Foundations	2-7.1%
Glyceryl Stearate	Lipstick	0.0002-3%
Glyceryl Stearate	Makeup bases	0.075-2%
Glyceryl Stearate	Makeup fixatives	1.2%
Glyceryl Stearate	Other makeup preparations	0.88-2%
Glyceryl Stearate	Cuticle softeners	1.4-3%
Glyceryl Stearate	Nail creams and lotions	2-6%
Glyceryl Stearate	Nail polish and enamel removers	0.006%
Glyceryl Stearate	Other manicuring preparations	2-5%
Glyceryl Stearate	Bath soaps and detergents	1.1-1.3%
Glyceryl Stearate	Deodorants not spray	0.25-17%
Glyceryl Stearate	Other personal cleanliness products	0.78-18% (rinse-off)
Glyceryl Stearate	Aftershave lotions	0.5-2.1%
Glyceryl Stearate	Shaving cream	0.05%
Glyceryl Stearate	Other shaving preparations	2% (leave-on)
Glyceryl Stearate	Skin cleansing	0.25-18.9%
Glyceryl Stearate	Face and neck products not spray	0.75-5%
Glyceryl Stearate	Body and hand products not spray	0.0083-10%
Glyceryl Stearate	Foot products	2.3-6%
Glyceryl Stearate	Moisturizing products not spray	0.0083-5%
Glyceryl Stearate	Night products not spray	0.0083-3.6%
Glyceryl Stearate	Paste masks and mud packs	0.5-11%
Glyceryl Stearate	Other skin preparations	1.1-6%

Glyceryl Stearate	Suntan products not spray	1.3-3%
Glyceryl Stearate	Indoor tanning preparations	1-4.8%
Glyceryl Stearate	Other suntan preparations	1.2-2%
Glyceryl Stearate SE	Other bath preparations	6%
Glyceryl Stearate SE	Eye liner	1.7%
Glyceryl Stearate SE	Eye lotion	0.2-3%
Glyceryl Stearate SE	Mascara	0.47-5%
Glyceryl Stearate SE	Other eye makeup preparations	5%
Glyceryl Stearate SE	Other fragrance preparations	3%
Glyceryl Stearate SE	Hair conditioners	0.5-4%
Glyceryl Stearate SE	Rinses (noncoloring)	1-1.2%
Glyceryl Stearate SE	Shampoos (noncoloring)	3.6%
Glyceryl Stearate SE	Tonics, dressings and other hair grooming aids	0.001-3%
Glyceryl Stearate SE	Hair dyes and colors	3-6%
Glyceryl Stearate SE	Hair bleaches	6%
Glyceryl Stearate SE	Foundations	0.5-5.7%
Glyceryl Stearate SE	Makeup bases	2-2.2%
Glyceryl Stearate SE	Other makeup preparations	2.2-3.3%
Glyceryl Stearate SE	Bath soaps and detergents	5%
Glyceryl Stearate SE	Other personal cleanliness products	3-5% (5% in a foot scrub)
Glyceryl Stearate SE	Aftershave lotions	0.5-3%
Glyceryl Stearate SE	Skin cleansing products	1-6%
Glyceryl Stearate SE	Depilatories	3%
Glyceryl Stearate SE	Face and neck products not spray	0.2-10%
Glyceryl Stearate SE	Body and hand products not spray	0.4-10%
Glyceryl Stearate SE	Foot products	2-3.9%
Glyceryl Stearate SE	Moisturizing products not spray	0.3-4.8%
Glyceryl Stearate SE	Night products not spray	0.75-5%
Glyceryl Stearate SE	Paste masks and mud packs	4%
Glyceryl Stearate SE	Other skin care preparations	3-10%
Glyceryl Stearate SE	Suntan products not spray	0.3-0.95%
Glyceryl Stearate SE	Indoor tanning preparations	1.5-2.9%

*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 April 28, 2014

Updated August 7, 2015: Glyceryl Rosinate, mascara corrected from 99.9% to 8%

