Amended Safety Assessment of Triglycerides as Used in Cosmetics

Status:	Re-Review for Panel Review
Release Date:	March 17, 2017
Panel Meeting Date:	April 10-11, 2017

The 2017 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, Chemist.

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

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Assistant Director/Senior Scientific Analyst
Date: March 17, 2017
Subject: Amended Safety Assessment of Triglycerides as Used in Cosmetics

Enclosed is the Safety Assessment of Triglycerides as Used in Cosmetics. (It is identified as *trygly042017rep* in the pdf document.) This is a re-review that is being initiated in accord with CIR's Procedures to reassess previously-reviewed conclusions after a period of 15 years.

In 2000, the Panel published a safety assessment of Trihydroxystearin with the conclusion, "Based on the available animal and clinical data, which included summary data from the CIR safety assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, the Panel concluded that Trihydroxystearin is safe as used in cosmetics." In 2015, the Panel re-evaluated the safety of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, reaffirming that Hydroxystearic Acid is safe as a cosmetic ingredient in the present practices of use and concluding that Glyceryl Stearate and Glyceryl Stearate SE are safe in the present practices of use and concentration.

A report strategy presented to the Panel at the September 2014 meeting suggested including Trilaurin and 22 additional glyceryl triesters as part of the re-review; a CIR report on these ingredients was published in 2001, so this group was due for re-review. Additionally, two add-on ingredients were proposed. The Panel agreed that the strategy on these 25 ingredients was appropriate.

Also at that meeting, discussion ensued about including additional ingredients, but a decision was never finalized. In 2003, the Panel reaffirmed the original conclusion in the 1980 Final Report of the Safety Assessment for Caprylic/Capric Triglyceride, that Caprylic/Capric Triglyceride is safe as used. Also, there are another 24 triglycerides named in the *International Cosmetic Ingredient Dictionary and Handbook* and 3 named in the VCRP database (but not found in the *Dictionary*) that have not been reviewed. Because the possibility was raised to include the additional ingredients, those ingredients have been included in the safety assessment. (Table 1 in of the report provides a complete list of all 54 ingredients.)

Concentration of use data were received from the Council for the ingredients that were named in the report strategy memo (*trygly042017data*). However, because a decision to include the additional ingredients was never finalized, use concentrations for those ingredients have not yet been surveyed. Also included are 2017 VCRP data (*trygly042017FDA)*; the frequency of use of all ingredients included in this report is provided.

Based on the available information, it appears that both the frequency and concentrations of use for most of the ingredients have increased since they were originally reviewed. Of particular note, Caprylic/Capric Triglyceride is now reported to be used in 6000 ingredients, as compared to 763 uses reported in 2003. (A concentration of use survey has not been conducted yet for this ingredient, but it was used at relatively high concentrations, including maximum concentrations of up to 84% in perfumes and up to 54% in lipsticks, in 2003).

Summary information from the original reports on Trihydroxystearin, Trilaurin and other glyceryl triesters, and Caprylic/Capric Triglyceride has been included in italicized text in the safety assessment, as appropriate. The original reports are included for your review so that the detailed information is easily accessible.

The Panel is now being asked to consider several issues:

1. Is the grouping of ingredients appropriate as presented in the current document?
2. Are the data sufficient to make a determination of safety? If not, what should be requested in the Insufficient Data Announcement?
3. If the data are sufficient, can a tentative conclusion be issued even though use concentration data are not currently complete? Are the current use concentrations given in the report sufficiently high to alleviate concerns about the unknown concentrations?

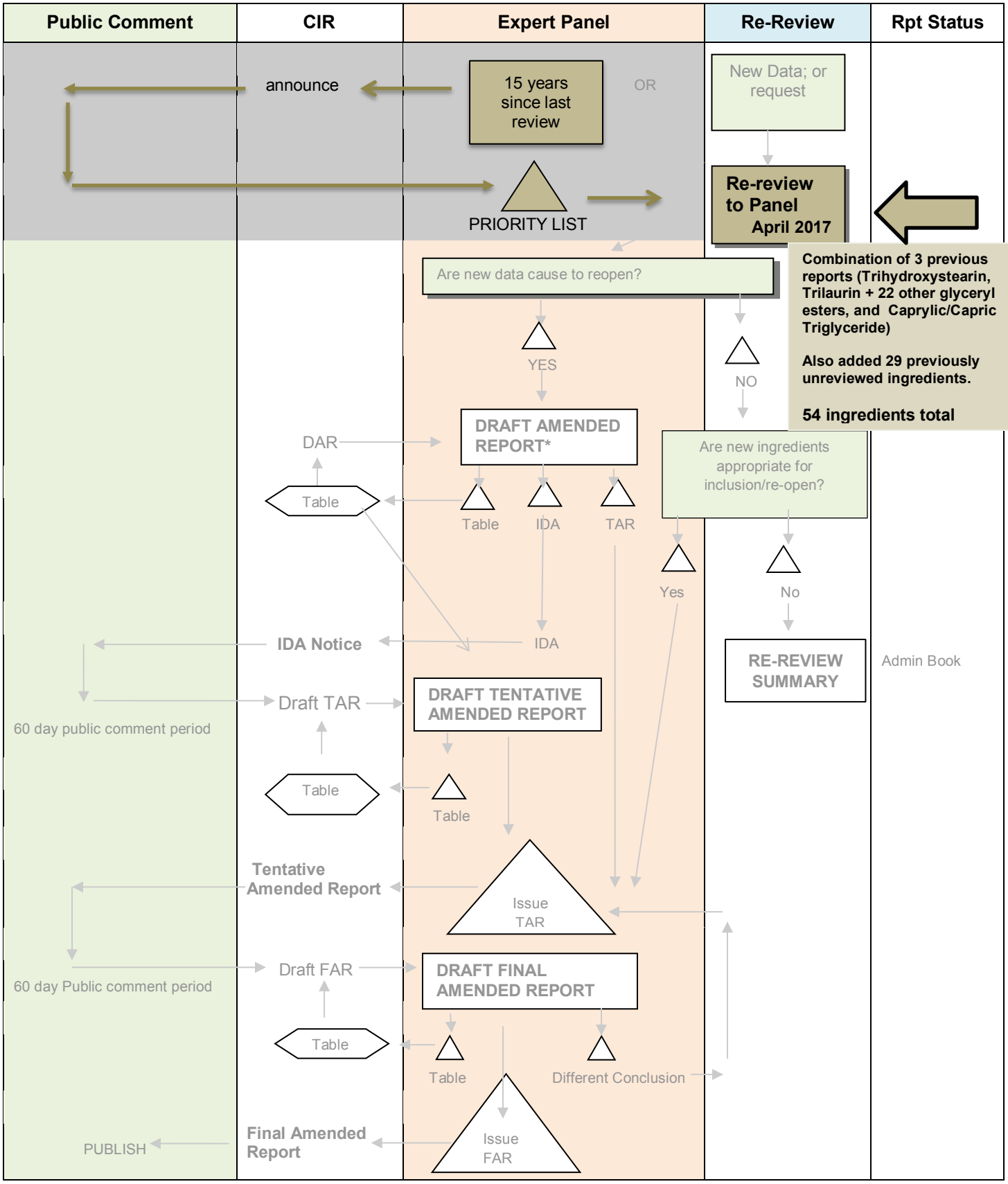
The following are included in this package for your review:

trygly042017rep: re-review document
trygly042017prev_1: Final Report on the Safety Assessment of Trihydroxystearin (2000)
glyest042017prev_2: Final Report on the Safety Assessment of Trilaurin and other glyceryl triesters (2001)
glyest042017prev_3: Final Report on the Safety Assessment of Caprylic/Capric Triglyceride (1980)
glyest042017prev_4: Caprylic/Capric Triglyceride re-review summary (2003)
trygly042017strat_memo: report strategy memo that was presented at the September 2014 meeting
trygly042017flow: report flowchart
trygly042017data: concentration of use data available to date
trygly042017FDA: 2017 VCRP data
trygly042017prof: data profile
trygly042017hist: history
trygly042017min: minutes from the deliberations of Trihydroxystearin and Trilaurin and glyceryl triesters

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Triglycerides

MEETING April 2017



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

History - Triglycerides

Trihydroxystearin
2000: The Panel published a safety assessment with a conclusion that stated based on the available animal and clinical data, which included summary data from the CIR safety assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, the Panel concluded that Trihydroxystearin is safe as used in cosmetics

Trilaurin + 22 additional Glyceryl Esters
2001: the Panel published a final report with a conclusion of safe as used

Caprylic/Capric Triglyceride
1980: the Panel published a final report with a conclusion of safe as used; this conclusion was reaffirmed in 2003

April 2017: Re-Review
The re-review document was presented to Panel.

Triglycerides - (new data only) – Apr 2017 – Monice Fiume																			
	Reported Use - current	**Method of Mfg**	**Impurities**	**ADME**	**Dermal Penetration**	**Animal Tox – Acute, Dermal**	**Animal Tox – Acute, Oral**	**Animal Tox, Acute, Inhalation**	**Animal Tox – Rptd Dose, Dermal**	**Animal Tox, Rptd Dose, Oral**	**Animal Tox – Rptd Dose, Inhalation**	**DART**	**Genotoxicity**	**Carcinogenicity**	**Dermal Irritation**	**Dermal Sensitization**	**Case Reports**	**Ocular Irritation**	**Mucous Membrane Irr**
Triglycerides (general)		X		X															
MCT OR MLCT (generic)		X					X			X			X						
Linear Chain, Saturated																			
Triheptanoin	X					X	X			X					X	X		X	
Tricaprylin	X											X							
Tricaprin	X																		
Triundecanoin	X																		
Trilaurin	X																		
Trimyristin	X																		
Tripalmitin	X																		
Tristearin	X					X							X		X	X		X	
Triarachidin																			
Tribehenin	X																		
Linear, Mixed Chain length, saturated																			
Glyceryl Stearate Diacetate																			
Caprylic/Capric Triglyceride	X									X			X		X	X		X	
Caprylic/Capric/Lauric Triglyceride	X																		
C8-12 Acid Triglyceride																		X	
Caprylic/Capric/Myristic/Stearic Triglyceride	X																		
Caprylic/Capric/Palmitic/Stearic Triglyceride																			
Caprylic/Capric/Stearic Triglyceride	X																		
C10-18 Triglycerides	X																		
C12-18 Acid Triglyceride	X																		
Palmitic/Stearic Triglyceride	X																		
C18-36 Triglyceride	X																		
C18-38 Acid Triglyceride	X																		

Triglycerides - (new data only) – Apr 2017 – Monice Fiume																			
	Reported Use - current	Method of Mfg	Impurities	ADME	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Dermal	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhalation	DART	Genotoxicity	Carcinogenicity	Dermal Irritation	Dermal Sensitization	Case Reports	Ocular Irritation	Mucous Membrane Irr
Coconut Triglycerides	X																		
Branched Chain																			
Triethylhexanoin (previously Trioctanoin)	X			X			X						X						
Triisononanoin	X												X		X	X		X	
Triisopalmitin																			
Triisostearin	X						X											X	
Triheptylundecanoin																			
Branched, Mixed Chain Length																			
C10-40 Isoalkyl Acid Triglyceride	X																		
Tripalmitolein																			
Triolein	X						X									X			
Oleic/Linoleic Triglyceride																			
Docosahexenoic/ Docosapentenoic/Oleic/ Palmitic Triglyceride																			
Isomerized Safflower Glycerides																			
Trilinolein	X																		
Trilinolenin	X																		
Trierucin																			
Triricinolein																			
Trihydroxystearin	X																		
Acetylated Hydroxyacid Triglycerides																			
Glyceryl Triacetyl Hydroxystearate	X																		
Glyceryl Triacetyl Ricinoleate	X																		
Mixed chain – others																			
Acetic/Linoleic/Palmitic Triglyceride																			
Capric/Lauric/Myristic/ Oleic Triglyceride																			
Caprylic/Capric/Linoleic Triglyceride																			
Cod Liver/Mink/Tallow Triglyceride																			

Triglycerides - (new data only) – Apr 2017 – Monice Fiume																			
	Reported Use - current	**Method of Mfg**	**Impurities**	**ADME**	**Dermal Penetration**	**Animal Tox – Acute, Dermal**	**Animal Tox – Acute, Oral**	**Animal Tox, Acute, Inhalation**	**Animal Tox – Rptd Dose, Dermal**	**Animal Tox, Rptd Dose, Oral**	**Animal Tox – Rptd Dose, Inhalation**	**DART**	**Genotoxicity**	**Carcinogenicity**	**Dermal Irritation**	**Dermal Sensitization**	**Case Reports**	**Ocular Irritation**	**Mucous Membrane Irr**
Glyceryl Tribehenate/Isostearate/Eicosandioate	X																		
Glyceryl Tri-Hydrogenated Rosinate																			
Glyceryl Tripalmate/Palm Kernelate/ Olivate/ Macadamiate/Rapeseedate																			
Hydrogenated C12-18 Triglycerides	X																		
Jojoba Oil/Caprylic/Capric Triglyceride Esters																			
Lauric/Palmitic/Oleic Triglyceride																			
Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride																			
Ricinoleic/Caproic/Caprylic/Capric Triglyceride																			
Tallow Triglyceride	X																		

Note: ingredients that were previously reviewed are indicated in blue;' ingredients that were found in the VCRP but not the *Dictionary* are indicated in green

ORIGINAL REPORTS																	
	Method of Manufacture	Impurities/Composition	ADME	Dermal Absorption	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhal.	Animal Tox – Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhal	Repro/Dev Toxicity	Genotoxicity	Carcinogenicity	Dermal Irr/Sens	Ocular Irritation	Mucous Membrane Irr	Phototoxicity
Final Report on the Safety Assessment of Trihydroxystearin (2000)																	
Trihydroxystearin	X					X						X		X	X		
Hydroxystearic Acid	X		X						X		X	X	X	X			
Glyceryl Sterarate/SE	X					X		X	X				X	X	X		
Final Report on the Safety Assessment of Trilaurin and other glyceryl triesters (2001)																	
Trilaurin	X		X						X			X		X	X		
Triarachidin																	
Tribehenin						X								X	X		
Tricaprin			X														
Tricaprylin			X			X			X		X	X	X				
Trierucin									X								
Triheptanoin																	
Triheptylundecanoin																	
Triisononanoin																	
Triisopalmitin																	
Triisostearin		X				X						X		X	X		X
Trilinolein			X														
Trimyristin																	
Trioctanoin (now Triethylhexanoin)			X			X					X	X	X	X	X		
Triolein	X		X	X					X			X	X				
Tripalmitin			X														
Tripalmitolein																	
Triricinolein																	
Tristearin	X		X			X			X			X		X	X		

ORIGINAL REPORTS																	
	Method of Manufacture	**Impurities/Composition**	**ADME**	**Dermal Absorption**	**Animal Tox – Acute, Dermal**	**Animal Tox – Acute, Oral**	**Animal Tox, Acute, Inhal.**	**Animal Tox – Rptd Dose, Derm**	**Animal Tox, Rptd Dose, Oral**	**Animal Tox – Rptd Dose, Inhal**	**Repro/Dev Toxicity**	**Genotoxicity**	**Carcinogenicity**	**Dermal Irr/Sens**	**Ocular Irritation**	**Mucous Membrane Irr**	**Phototoxicity**
Triundecanoin	X	X															
Glyceryl Triacetyl Hydroxystearate																	
Glyceryl Triacetyl Ricinoleate																	
Glyceryl Stearate Diacetate																	
Amended Final Report of the Safety Assessment of Caprylic/Capric Triglyceride (1980)																	
Caprylic/Capric Triglyceride		X	X			X	X	X	X		X			X	X		

Triglycerides RR

Ingredient	CAS #	InfoB	SciFin	PubMed		FDA	EU	ECHA		SIDS	ECETOC		NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
PREVIOUSLY REVIEWED																				
Caprylic/Capric Triglyceride – reviewed in 1980	65381-09-1 73398-61-5	√	√	√		---	√	X		X			---							
Glyceryl Stearate Diacetate	84931-78-2	√	√	√		---	√	preR		---			---							
Glyceryl Triacetyl Hydroxystearate	27233-00-7	√	√	√		---	√	preR		---			---							
Glyceryl Triacetyl Ricinoleate	101-34-8	√	√	√		---	√	preR		---			---							
Triarachidin	620-64-4	√	√	√		---	√	preR		---			---							
Tribehenin	18641-57-1	√	√	√		---	√	preR		---			---							
Tricaprin	621-71-6	√	√	√		---	√	preR		---			---							
Tricaprylin	538-23-8	√	√	√		---	√	preR		X			---		in orig					
Trierucin	2752-99-0	√	√	√		---	√	preR		---			---							
Triethylhexanoin	7360-38-5	√	√	√		---	√	X		---			EX/138							
Triheptanoin	620-67-7	√	√	√		---	√	X		---			---							
Triheptylundecanoin	105214-66-2	√	√	√		---	√	---		---			---							
Trihydroxystearin	139-44-6	√	√	√		---	√	preR		---			---							
Triisononanoin	206354-95-2 56554-53-1	√	√	√		---	√	X		---			---							
Triisopalmitin	68957-79-9	√	√	√		---	√	preR		---			---							
Triisostearin	26942-95-0	√	√	√		---	√	X		---			---							
Trilaurin	538-24-9	√	√	√		---	√	preR		---			---							
Trilinolein	537-40-6	√	√	√		---	√	preR		---			---							
Trimyristin	555-45-3	√	√	√		---	√	preR		---			---							
Triolein	122-32-7 6915-08-8	√	√	√		---	√	X		X			---							
Tripalmitin	555-44-2	√	√	√		---	√	preR		---			---							
Tripalmitolein	129784-33-4 20246-55-3	√	√	√		---	√	---		---			---							
Triricinolein	15505-14-3 2540-54-7	√	√	√		---	√	preR		---			---							
Tristearin	555-43-1	√	√	√		21 CFR 172.811	√	X		---			---							
Triundecanoin	13552-80-2	√	√	√		---	√	preR		---			---							
ADD-ONS																				

Ingredient	CAS #	InfoB	SciFin	PubMed		FDA	EU	ECHA		SIDS	ECETOC		NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Isomerized Safflower Glycerides	303101-61-3	√	√	√		---	√	---		---			---							
Trilinolenin	14465-68-0	√	√	√		---	√	preR		---			---							
POTENTIAL ADD-ONS																				
C8-12 Acid Triglyceride	---	√	√			---	√	---		---			---							
C10-18 Triglycerides	85665-33-4	√		√		21CFR 172.861	√	preR		---			---							
C12-18 Acid Triglyceride		√	√			---	√	---		---			---							
C18-36 Acid Triglyceride	91052-08-3	√	√	√		---	√	preR		---			---							
C12-18 Acid Triglyceride	---	√	√			---	√	---		---			---							
C10-40 Isoalkyl Acid Triglyceride	---	√	√			---	√	---		---			---							
Acetic/Linoleic/Palmitic Triglyceride	221139-79-3	√	√	√		---	√	---		---			---							
Capric/Lauric/Myristic/ Oleic Triglyceride	---	√		√		---	√	---		---			---							
Caprylic/Capric/Lauric Triglyceride	123465-33-8	√	√	√		---	√	---		---			---							
Caprylic/Capric/Linoleic Triglyceride	---	√	√	√		---	√	---		---			---							
Caprylic/Capric/Myristic/ Stearic Triglyceride	---	√	√	√		---	√	---		---			---							
Caprylic/Capric/Palmitic/ Stearic Triglyceride	---	√	√	√		---	√	---		---			---							
Caprylic/Capric/Stearic Triglyceride	---	√	√	√		---	√	---		---			---							
Cod Liver/Mink/Tallow Triglyceride	---	√	√			---	√	---		---			---							
Docosahexenoic/Docosa-pentenoic/Oleic/Palmitic Triglyceride	---	√	√	√		---	√	---		---			---							
Glyceryl Tribehenate/ Isostearate/Eicosandioate	945031-36-7	√		√		---	√	---		---			---							
Glyceryl Tri-Hydrogenated Rosinate	---	√		√		---	√	---		---			---							
Glyceryl Tripalmate/Palm Kernelate/Olivate/ Macadamiate/Rapeseedate	---	√		√		---	√	---		---			---							
Hydrogenated C12-18 Triglycerides	---	√	√			---	√	---		---			---							
Jojoba Oil/Caprylic/ Capric Triglyceride Esters	---	√	√	√		---	√	---		---			---							

Ingredient	CAS #	InfoB	SciFin	PubMed		FDA	EU	ECHA		SIDS	ECETOC		NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Lauric/Palmitic/Oleic Triglyceride	---	√	√			---	√	preR		---			---							
Oleic/Linoleic Triglyceride	---	√	√	√		---	√	preR		---			---							
Oleic/Palmitic/Lauric/ Myristic/Linoleic Triglyceride	---	√	√	√		---	√	---		---			---							
Palmitic/Stearic Triglyceride	---	√	√	√		---	√	---		---			---							
Ricinoleic/Caproic/Caprylic/Capric Triglyceride	---	√	√	√		---	√	---		---			---							
In VCRP, but not in Dictionary																				
C18-38 Acid Triglyceride			√	√		---		---					---							
Coconut Triglycerides			√	√		21CFR172.861; 21CFR176.210		---					---							
Tallow Triglyceride			√	√		---		---					---							
Generic Terms																				
short chain triglycerides				√																
medium-chain triglycerides				√		X														
long-chain triglycerides				√																
triglycerides, general																				

Search Strategy

2/17/17 - all previously-reviewed ingredients, EXCEPT Caprylic/Capric Triglyceride, were searched 1995+

PubMed

(((glyceryl AND stearate AND diacetate) OR (glyceryl) AND triacetyl AND Hydroxystearate) OR (Glyceryl) AND Triacetyl AND Ricinoleate) OR Triarachidin OR Tribehenin OR Tricaprin OR Tricaprylin OR Trierucin OR Triethylhexanoin OR Triheptanoin OR Triheptylundecanoin OR Trihydroxystearin OR Triisononanoin OR Triisopalmitin OR Triisostearin OR Trilaurin OR Trilinolein OR Trimyristin OR Triolein OR Tripalmitin OR Tripalmitolein OR Triricinolein OR Tristearin OR Triundecanoin OR 84931-78-2[EC/RN Number] OR 27233-00-7[EC/RN Number] OR 101-34-8[EC/RN Number] OR 620-64-4[EC/RN Number] OR 18641-57-1[EC/RN Number] OR 621-71-6[EC/RN Number] OR 538-23-8[EC/RN Number] OR 2752-99-0[EC/RN Number] OR 7360-38-5[EC/RN Number] OR 620-67-7[EC/RN Number] OR 105214-66-2[EC/RN Number] OR 139-44-6[EC/RN Number] OR 206354-95-2[EC/RN Number] OR 56554-53-1[EC/RN Number] OR 68957-79-9[EC/RN Number] OR 26942-95-0[EC/RN Number] OR 538-24-9[EC/RN Number] OR 537-40-6[EC/RN Number] OR 555-45-3[EC/RN Number] OR 122-32-7[EC/RN Number] OR 6915-08-8[EC/RN Number] OR 555-44-2[EC/RN Number] OR 129784-33-4[EC/RN Number] OR 20246-55-3[EC/RN Number] OR 15505-14-3[EC/RN Number] OR 2540-54-7[EC/RN Number] OR 555-43-1[EC/RN Number] OR 13552-80-2[EC/RN Number]) AND ("1995"[Date - Publication] : "3000"[Date - Publication])) – 1890 hits/5 papers ordered

((trilinolenin) OR 14465-68-0[EC/RN Number]) OR (isomerized AND safflower AND glycerides) OR 303101-61-3[EC/RN Number] – 23 hits/0 useful

medium chain triglycerides toxicity – 79 hits/5 useful
dermal effects of triglycerides – 32 hits/0 useful
carcinogenicity of triglycerides – 34 hits/

For Potential Add-Ons
((“long chain triglyceride”) OR (“long chain triglycerides”) OR (“medium chain triglyceride”) OR (“medium chain triglycerides”) OR (“short chain triglyceride”) OR (“short chain triglycerides”) OR (65381-09-1[EC/RN Number] OR 73398-61- 5[EC/RN Number] OR 85665-33-4[EC/RN Number] OR 91052-08-3[EC/RN Number] OR 221139-79-3[EC/RN Number] OR 123465-33-8[EC/RN Number]) OR ((Caprylic OR Capric OR Lauric OR Myristic OR Oleic OR Linoleic OR Stearic OR Palmitic) AND Triglyceride) OR (Docosahexenoic AND Docosapentenoic AND Oleic AND Palmitic AND Triglyceride) OR (Jojoba AND Oil AND Caprylic AND Capric AND Triglyceride) OR (Coconut AND Triglyceride) OR (Linolenic AND Acid AND Triglyceride) or (Tallow AND Triglyceride)) (NOT (84931-78-2[EC/RN Number] OR 27233-00-7[EC/RN Number] OR 101-34-8[EC/RN Number] OR 620-64-4[EC/RN Number] OR 18641-57-1[EC/RN Number] OR 621-71-6[EC/RN Number] OR 538-23-8[EC/RN Number] OR 2752-99-0[EC/RN Number] OR 7360-38-5[EC/RN Number] OR 620-67-7[EC/RN Number] OR 105214-66-2[EC/RN Number] OR 139-44-6[EC/RN Number] OR 206354-95-2[EC/RN Number] OR 56554-53-1[EC/RN Number] OR 68957-79-9[EC/RN Number] OR 26942-95-0[EC/RN Number] OR 538-24-9[EC/RN Number] OR 537-40-6[EC/RN Number] OR 555-45-3[EC/RN Number] OR 122-32-7[EC/RN Number] OR 6915-08-8[EC/RN Number] OR 555-44-2[EC/RN Number] OR 129784-33-4[EC/RN Number] OR 20246-55-3[EC/RN Number] OR 15505-14-3[EC/RN Number] OR 2540-54-7[EC/RN Number] OR 555-43-1[EC/RN Number] OR 13552-80-2[EC/RN Number])) – 558 hits/no additional useful finds

(945031-36-7[EC/RN Number]) OR (glyceryl AND ((Tribehenate AND Isostearate AND Eicosandioate) OR (hydrogenated AND rosinate) OR (Tripalmate AND Palm AND Kernelate AND Olivate AND Macadamiate AND Rapeseedate)) – 6 hits/1 useful

SciFinder
searched 1995+: 84931-78-2; 27233-00-7; 101-34-8; 620-64-4; 18641-57-1; 621-71-6; 538-23-8; 2752-99-0; 7360-38-5; 620-67-7; 105214-66-2; 139-44-6; 206354-95-2; 56554-53-1; 68957-79-9; 26942-95-0; 538-24-9; 537-40-6; 555-45-3; 122-32-7; 6915-08-8; 555-44-2; 129784-33-4; 20246-55-3; 15505-14-3; 2540-54-7; 555-43-1; 13552-80-2;
searched all years: 14465-68-0; 303101-61-3 (all refined by document type) – 6725 hits

results further refined by research topic
dermal effects - 69 hits/0 useful
toxicity – 240 hits/4 useful
irritation - 59 hits
sensitization - 6 hits/0 useful
carcinogenicity - 226 hits/0 useful
genotoxicity –6 hits/0 useful
toxicokinetics - 240 hits/1 useful
teratogenicity - 3 hits/0 useful
develomental toxicity - 11 hits/0 useful

Potential Add-Ons: 5381-09-1; 73398-61-5; 85665-33-4; 91052-08-3; 221139-79-3; 123465-33-8; C8-12 Acid Triglyceride; C10-40 Isoalkyl Acid Triglyceride; C12-18 Acid Triglyceride ; Capric/Lauric/Myristic/Oleic Triglyceride; Caprylic/Capric/Linoleic Triglyceride; Caprylic/Capric/Myristic/Stearic Triglyceride; Caprylic/Capric/Palmitic/Stearic Triglyceride; Caprylic/Capric/Stearic Triglyceride; Caprylic/Capric Triglyceride PEG-4 Esters; Cod Liver/Mink/Tallow Triglyceride; Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride; Hydrogenated C12-18 Triglycerides; Jojoba Oil/Caprylic/Capric Triglyceride Esters; Lauric/Palmitic/Oleic Triglyceride; Oleic/Linoleic Triglyceride; Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride; Palmitic/Stearic Triglyceride; Ricinoleic/Caproic/Caprylic/Capric Triglyceride – 65 hits/2 useful

long chain triglycerides, short chain triglycerides, and medium chain triglycerides – 5625 refs
by research topic
dermal effects - 29 hits/0 useful
toxicity – 204 hits/7 useful
irritation - 27 hits/1 useful
dermal sensitization - 0 hits
carcinogenicity - 250 hits/0 useful
genotoxicity – 3 hits/0 useful
teratogenicity - 4 hits/0 useful
develomental toxicity - 10 hits/1 useful

CFR Citations

Tristearin: 21CFR172.811 (updated 9/21/16)
PART 172 -- Food Additives Permitted For Direct Addition To Food For Human Consumption; Subpart I --Multipurpose Additives
The food additive glyceryl tristearate may be safely used in food in accordance with the following prescribed conditions:
(a) The food additive (CAS Reg. No. 555-43-1) is prepared by reacting stearic acid with glycerol in the presence of a suitable catalyst.
(b) The food additive meets the following specifications:
Acid number: Not to exceed 1.0.
Iodine number: Not to exceed 1.0.
Saponification number: 186-192.
Hydroxyl number: Not to exceed 5.0.
Free glycerol content: Not to exceed 0.5 percent.
Unsaponifiable matter: Not to exceed 0.5 percent.
Melting point (Class II): 69 deg. C-73 deg. C.
(c) The additive is used or intended for use as follows when standards of identity established under section 401 of the Act do not preclude such use:

Uses	Limitations
1. As a crystallization accelerator in cocoa products, in imitation chocolate, and in compound coatings	Not to exceed 1 percent of the combined weight of the formulation.
2. As a formulation aid as defined in 170.3(o)(14) of this chapter, lubricant and release agent as defined in 170.3(o)(18) of this chapter, and surface-finishing agent as defined in 170.3(o)(30) of this chapter in food	Not to exceed 0.5 percent.
3. As a formulation aid as defined in 170.3(o)(14) of this chapter in confections	Not to exceed 3.0 percent of the combined weight of the formulation.
4. As a formulation aid as defined in 170.3(o)(14) of this chapter in fats and oils as defined in 170.3 (n)(12) of this chapter	Not to exceed 1.0 percent of the combined weight of the formulation.
5. As a winterization and fractionation aid in fat and oil processing	Not to exceed 0.5 percent by weight of the processed fat or oil.

(d) To assure safe use of the additive:
(1) In addition to the other information required by the act, the label or labeling of the additive shall bear the name of the additive.
(2) The label of the additive shall bear adequate directions to provide a final product that complies with the limitations prescribed in paragraph (c) of this section

C10-18 Triglycerides; Coconut Triglycerides: 21CFR172.861 (updated 9/21/16)
PART 172 -- Food Additives Permitted For Direct Addition To Food For Human Consumption; Subpart I--Multipurpose Additives
Sec. 172.861 Cocoa butter substitute from coconut oil, palm kernel oil, or both oils.
The food additive, cocoa butter substitute from coconut oil, palm kernel oil, or both oils, may be safely used in food in accordance with the following conditions:
(a) Cocoa butter substitute from coconut oil, palm kernel oil (CAS Reg. No. 85665-33-4), or both oils is a mixture of triglycerides. It is manufactured by esterification of glycerol with food-grade fatty acids (complying with 172.860) derived from edible coconut oil, edible palm kernel oil, or both oils.
(b) The ingredient meets the following specifications:
Acid number: Not to exceed 0.5.
Saponification number: 220 to 260.
Iodine number: Not to exceed 3.
Melting range: 30 to 44 deg. C.
(c) The ingredient is used or intended for use as follows:
(1) As coating material for sugar, table salt, vitamins, citric acid, succinic acid, and spices; and
(2) In compound coatings, cocoa creams, cocoa-based sweets, toffees, caramel masses, and chewing sweets as defined in 170.3 (n)(9) and (n)(38) of this chapter, except that the ingredient may not be used in a standardized food unless permitted by the standard of identity.
(d) The ingredient is used in accordance with current good manufacturing practice and in an amount not to exceed that reasonably required to accomplish the intended effect.

Coconut Triglycerides: 21CFR176.210
PART 176 -- INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS
Subpart B--Substances for Use Only as Components of Paper and Paperboard
Sec. 176.210 Defoaming agents used in the manufacture of paper and paperboard.
(d) Substances permitted to be used in the formulation of defoaming agents include substances subject to prior sanctions or approval for such use and employed subject to the conditions of such sanctions or approvals, substances generally recognized as safe for use in food, substances generally recognized as safe for use in paper and paperboard, and substances listed in this paragraph, subject to the limitations, if any, prescribed.
(1) Fatty triglycerides, and the fatty acids, alcohols, and dimers derived therefrom: Coconut oil.

LINKS

online database (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
wINCI (to cite publicly) - http://webdictionary.personalcarecouncil.org
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed ;
Also search: PubMed Dietary Supplement Subset https://ods.od.nih.gov/Research/PubMed_Dietary_Supplement_Subset.aspx and
https://ods.od.nih.gov/Health_Information/IBIDS.aspx
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions http://ec.europa.eu/growth/tools-databases/cosing/
and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc

Note: ChemPortal can be used to search several of the above databases simultaneously - http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en

TRIHYDROXSTEARIN – ORIGINAL DELIBERATIONS

April 3-4, 1997 Meeting

Dr. Schroeter noted that the unpublished data received from Rheox, Inc., reviewed at the December 1996 Panel meeting, have been incorporated into the Draft Report. He said that after reviewing these data, his Team determined that the available data are now sufficient for evaluating the safety of Trihydroxystearin in the area of skin sensitization and, therefore, concluded that this ingredient is safe as used in cosmetics.

The Panel voted unanimously in favor of issuing a Tentative Report on Trihydroxystearin with a safe as used conclusion.

September 22-23, 1997 Meeting

Dr. Belsito noted that a comment to the Tentative Report on Trihydroxystearin had been received from Henkel, Inc. The comment is actually a query relating to how the Panel was able to arrive at a conclusion on the safety of Trihydroxystearin in cosmetics without sensitization data on this ingredient. Dr. Belsito noted that the Panel's assessment of the sensitization potential of Trihydroxystearin is based on negative sensitization data on Glyceryl Stearate (concentrations up to 20.0%) from human RIPTs involving a large number of subjects. These data are from the published CIR Final Report on Glyceryl Stearate.

Dr. Belsito proposed that receipt of the comment from Henkel, Inc. and the Panel's response to it should be indicated in the report discussion. He noted that the negative sensitization data on Glyceryl Stearate that were used to assess the sensitization potential of Trihydroxystearin should be mentioned in the Panel=s response.

The Panel adopted Dr. Belsito's proposal and voted unanimously in favor of issuing a Final Report with the following conclusion: Based on the available animal and clinical data in this report, which includes study summaries from CIR Safety Assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate/SE, the Expert Panel concludes that Trihydroxystearin is safe as used in cosmetic formulations.

TRILAURIN AND GLYCERYL ESTERS – ORIGINAL DELIBERATIONS

December 8-9, 1997 Meeting

Dr. Schroeter noted that, at the September 22-23, 1997 Panel meeting, his Team determined that the following data are needed for completion of this safety assessment:

1. Current concentration of use
2. Method of manufacture
3. Chemical and physical characterization, including impurities; e.g. pyridine, quinoline
4. Dermal absorption data; if there is significant absorption, a reproductive and developmental toxicity study will be needed
5. 28-day dermal toxicity data
6. Two genotoxicity studies on Glyceryl Laurate and Dilaurate, at least one in a mammalian system; if positive, a 2-year dermal carcinogenicity study usiing NTP methods may be needed
7. Dermal irritation and sensitization data on Glyceryl Dilaurate and Trilaurate
8. Ocular irritation, if available, on Glyceryl Dilaurate and Trilaurate
9. Immunological safety data on Glyceryl Laurate and Dilaurate.

Dr. Schroeter also noted that the Belsito Team's proposal to add other glyceryl fatty acid esters to this review was considered in Teams on the preceding day.

Dr. Belsito said that his Team had proposed tabling the report and adding all esters (listed in International Cosmetic Ingredient Dictionary) resulting from the esterification of glycerol with non-cyclic fatty acids. He added that upon completion of this project, any data needs could be determined.

Dr. Shank wanted to know why the esters of glycerol with cyclic fatty acids are being excluded.

Dr. Belsito said that these esters (with cyclic chains) should not be included because they may be light absorbers. He said that he was also thinking of some of the cyclic thio chains (e.g. Glyceryl Thioglycolate) that are strong sensitizers, whereas, the linear ones are not. Dr. Belsito said that it would be difficult for him to arrive at a conclusion on the safety of esters with cyclic chains, but that he would be more comfortable (in terms of sensitization or photosensitization data) with making decisions on branched or straight-chain fatty acids, that is, as long as they don=t contain cyclic rings.

Dr. McEwen said that saturated versus unsaturated fatty acids should also be taken into consideration. He noted that, when compared to saturated fatty acids, the unsaturated fatty acids are more likely to be phototoxic.

The Panel voted unanimously in favor of tabling the report on the Trilaurin ingredient family to allow inclusion of other glyceryl esters of non-cyclic fatty acids.

Sept 10, 1998 Meeting

Dr. Schroeter noted that of the 85 ingredients reviewed in this safety assessment, only 35 are being used and data are available only on 17. He also stated that his Team concluded that the Glyceryl Triesters being reviewed are safe as used in cosmetics, and that the Glyceryl Diesters and Monoesters should be deleted from the report and tabled for review at a future Panel meeting.

Assuming that the Glyceryl Triesters are mixtures of tri-, di-, and mono-esters, Dr. Schroeter also said that it may be that some of the data on Glyceryl Triesters may be applicable to the Glyceryl di- and mono-esters.

The Panel voted unanimously in favor of deleting the Glyceryl di- and mono- esters from the current report, developing separate reports on these two ingredient groups, and tabling the two reports that will be developed for review at a future Panel meeting.

The Panel also voted unanimously in favor of issuing a Tentative Report with a safe as used conclusion on the following Glyceryl Triesters: Trilaurin, Triarachidin, Tribehenin, Tricaprin, Tricaprylin, Trierucin, Triheptanoin, Triheptylundecanoin, Triisononanoin, Triisopalmitin, Triisostearin, Trilinolein, Trimyristin, Trioctanoin, Triolein, Tripalmitin, Tripalmitolein, Triricinolein, Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, and Glyceryl Triacetyl Ricinoleate.
Dr. Andersen noted that all editorial changes made by Panel members will be incorporated into the Tentative Report.

March 3-4, 1999 Meeting

Dr. Belsito said that his Team determined that these ingredients are safe as used in cosmetics. However, he noted that his Team had reservations about issuing this conclusion as a final recommendation because the skin irritation and sensitization data on which the conclusion is based are incomplete. Specifically, the conclusions of these studies were provided without details (see pages 48 and 72 of CIR report). Therefore, Dr. Belsito's Team proposed reissuing the Tentative Report with a safe as used conclusion, with the expectation that the details for the skin irritation and sensitization studies will be submitted during the 90-day comment period. The data could then be evaluated to determine whether they support the summaries and conclusions that were provided.

Dr. Schroeter recommended that the Panel issue a Final Report with a safe as used conclusion at this meeting, and that Dr. Andersen then proceed to obtain the skin irritation and sensitization study details referred to by Dr. Belsito. He emphasized that the Panel is merely seeking clarification of results that have been submitted.

Dr. Belsito said that his Team had determined that if the details are not provided, then the study summaries should be deleted from the report text. The report would then be classified as insufficient due to the need for skin irritation and sensitization data.

Dr. Andersen said that if the Panel chooses to approve issuance of a Final Report with a safe as used conclusion, contingent on the availability of details from the skin irritation and sensitization studies and the finding that there is nothing unusual that would lead to questioning of the data, a Final Report would then be issued. He also said that if the data are not provided, the report will be reviewed by the Panel at the June 14-15, 1999 Panel meeting.

Dr. Bergfeld summarized the Panel=s proposed action plan as follows: The ingredients are safe, with clarification of the data on human safety. If the data can be obtained, the document will become a Final Report. If the data are not obtained, the document will not become a Final Report and will be reevaluated at the June 14-15, 1999 Panel meeting.

The Panel voted unanimously in favor of the preceding proposal by Dr. Bergfeld as it relates to the following ingredients: Trilaurin, Triarachidin, Tribehenin, Tricaprin, Tricaprylin, Trierucin, Triheptanoin, Triheptylundecanoin, Triisononanoin, Triisopalmitin, Triisostearin, Trilinolein, Trimyristin, Trioctanoin, Triolein, Tripalmitin, Tripalmitolein, Triricinolein, Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, Glyceryl Triacetyl Ricinoleate, and Glyceryl Stearate Diacetate

Dr. Belstio said that the Panel's concern about skin penetration enhancement induced by glyceryl triesters should be stated in the report discussion. He noted that this finding may have an impact on ingredients previously reviewed by the Panel that were found to be safe because they were not absorbed through the skin.

Dr. Belsito recommended that whenever data on the skin penetration enhancement property of an ingredient are included in a CIR report, concern about this property should be addressed in the report discussion.

Amended Safety Assessment of Triglycerides as Used in Cosmetics

Status:	Re-Review for Panel Review
Release Date:	March 17, 2017
Panel Meeting Date:	April 10-11, 2017

The 2017 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, Chemist.

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

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published the Final Report on the Safety Assessment of Trihydroxystearin in 2000.[1] Based on the available animal and clinical data, which included summary data from the CIR safety assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, the Panel concluded that Trihydroxystearin is safe as used in cosmetics. In 2015, the Panel re-evaluated the safety of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, reaffirming that Hydroxystearic Acid is safe as a cosmetic ingredient in the present practices of use and concluding that Glyceryl Stearate and Glyceryl Stearate SE are safe in the present practices of use and concentration.[2] (In 1982, the conclusion issued for Glyceryl Stearate and Glyceryl Stearate SE was safe for topical application to humans.[3])

The Panel issued two additional reports on related ingredients. In 2001, the Panel published the Final Report on the Safety Assessment of Trilaurin and 22 additional glyceryl triesters.[4] In 1980, the Panel published the Final Report of the Safety Assessment for Caprylic/Capric Triglyceride.[5] In both safety assessments, the Panel reached the conclusion that the ingredients are safe as used in cosmetics. (In 2003, the Panel reaffirmed that conclusion for Caprylic/Capric Triglyceride.[6]) The 25 ingredients reviewed in the three reports are:

Caprylic/Capric Triglyceride
Glyceryl Stearate Diacetate
Glyceryl Triacetyl Hydroxystearate
Glyceryl Triacetyl Ricinoleate
Triarachidin
Tribehenin
Tricaprin
Tricaprylin
Trierucin
Triheptanoin
Triheptylundecanoin
Trihydroxystearin
Triisononanoin
Triisopalmitin
Triisostearin
Trilaurin
Trilinolein
Trimyristin
Trioctanoin (now, Triethylhexanoin)
Triolein
Tripalmitin
Tripalmitolein
Triricinolein
Tristearin
Triundecanoin

In accordance with its procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since these assessments have been issued. Because the three reports named above each comprise triglycerides, i.e., fatty acid triesters of glycerin, and because each report was reviewed 15+ years ago, the Panel determined these reports should be re-reviewed together in one report; this family is referred to as the triglycerides.

Also included in this assessment are 26 triglycerides named in the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*) and 3 named in the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database, but not the *Dictionary*, that have not been reviewed:

Acetic/Linoleic/Palmitic Triglyceride
C8-12 Acid Triglyceride
C12-18 Acid Triglyceride
C18-36 Acid Triglyceride
C18-38 Acid Triglyceride (in VCRP only)
Capric/Lauric/Myristic/Oleic Triglyceride
Caprylic/Capric/Lauric Triglyceride
Caprylic/Capric/Linoleic Triglyceride
Caprylic/Capric/Myristic/Stearic Triglyceride
Caprylic/Capric/Palmitic/Stearic Triglyceride
Caprylic/Capric/Stearic Triglyceride
C10-40 Isoalkyl Acid Triglyceride
Coconut Triglycerides (in VCRP only)
Cod Liver/Mink/Tallow Triglyceride
C10-18 Triglycerides
Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride
Glyceryl Tribehenate/Isostearate/Eicosandioate
Glyceryl Tri-Hydrogenated Rosinate
Glyceryl Tripalmate/Palm Kernelate/Olivate/Macadamiate/Rapeseedate
Hydrogenated C12-18 Triglycerides
Isomerized Safflower Glycerides
Jojoba Oil/Caprylic/Capric Triglyceride Esters
Lauric/Palmitic/Oleic Triglyceride
Oleic/Linoleic Triglyceride
Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride
Palmitic/Stearic Triglyceride
Ricinoleic/Caproic/Caprylic/Capric Triglyceride
Tallow Triglyceride (in VCRP only)
Trilinolenin

A consolidated list of the 54 ingredients included in this review is provided in Table 1.

According to the *Dictionary*, the majority of the ingredients named in this assessment have several functions, with most reported to function as skin conditioning agents (occlusive or emollient) and/or viscosity increasing agents in cosmetics; some are also reported to function as a fragrance or solvent.[7] An exception is Glyceryl Tri-Hydrogenated Rosinate, which is only reported to function as a surfactant – emulsifying agent. A reported function of Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride is skin bleaching agent; skin bleaching agent is not a cosmetic function, and therefore use in that manner is not being assessed in this report. A complete listing of all the functions for each ingredient (except those listed only in the VCRP and not the *Dictionary*) is given in Table 2.

Excerpts from the summaries of the reports on the previously reviewed ingredients (as provided in those reports) 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.) For complete and detailed information, please refer to the original documents, which are available on the CIR website (http://www.cir-safety.org/ingredients). Additionally, the Discussions from the Trihydroxystearin (2000) and Trilaurin (2001) assessments are also included in this document.

The triglycerides 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] Additionally, the Panel reviewed the safety of 44 monoglyceryl monoesters in 2015, concluding that those ingredients are safe in the present practices of use and concentration,[2] and of a group of diglycerides in 2007, concluding this family of ingredients is are safe in the present practices of use and concentration provided the content of 1,2-diesters is not high enough to induce epidermal hyperplasia.[9] Many of the acid components and related glyceryl esters of these triglycerides have also been reviewed by CIR. A listing of those that have been reviewed, and the associated conclusions, is provided in Table 3.

Finally, much of the new data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[10] 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 definitions and structures of the ingredients included in this triglyceride group are provided in Table 2, and are presented in order of increasing chain length, subdivided by chain type. (Toxicity data are presented following this order.).

Each of the ingredients in this report is a triglyceride; triglycerides are the fatty acid triesters of glycerin. Subsequently, each of the ingredient structures in this report contains a glycerin core, tri-substituted with fatty acid residues.

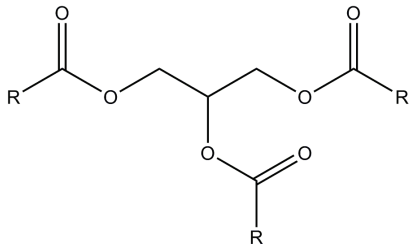


Figure 1. Triglycerides, wherein each "RC(O)-" is a fatty acid residue

For example, Tricaprylin is the triester of caprylic acids with glycerin.

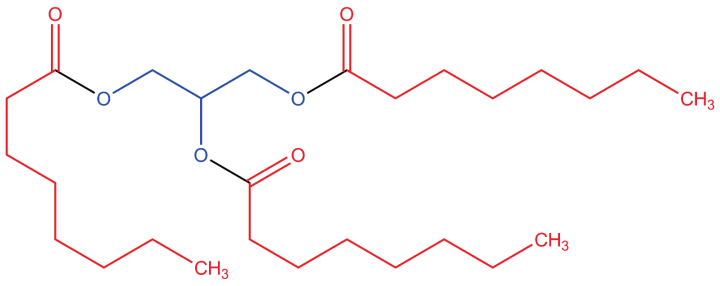


Figure 2. Tricaprylin (the triester of caprylic acids with glycerin)

Medium- and Long-Chain Triglycerides

Medium chain triglycerides (MCTs) are a unique class of lipids composed mainly of caprylic (C_8; 50-80%) and capric fatty acids (C_{10}; 20-50%) with a minor level of caproic (C_6; 1-2%) and lauric (C_{12}; 1-2%) fatty acids.[11,12] They are derived from common edible oils rich in free medium-chain fatty acids such as coconut or palm oil. Compositional analysis indicates that the fatty acids present are the type commonly found in other edible oils.

MCTs have only saturated fatty acids.[13] Long-chain triglycerides (LCT) can have both saturated and unsaturated fatty acids with a chain length greater than 12 carbons.

Medium- and long-chain triacylglycerol (MLCT)-oil is composed of a glycerol backbone with randomly bound medium- and long-chain fatty acids that are randomly attached via a food-grade lipase.[14] Six configurations are possible: L-L-L (L; long-chain fatty acid; 49.5-52.7%); L-L-M (M; medium-chain fatty acid) or L-M-L (37.3-39.6%); L-M-M or M-L-M (8.6-9.3%); M-M-M (0.1-0.2%). The typical fatty acid composition of MLCT-oil is presented in Table 4. The approximate fatty acid composition of a specific MLCT oil produced from MCT and edible vegetable oil is described in Table 5.[13]

Physical and Chemical Properties

Triglycerides are hydrophobic materials that range from oils, at the lowest molecular weights/shortest chain-lengths, to waxy solids, at the highest molecular weights/longest chain-lengths. Physical and chemical properties are presented in Table 6.

Reactivity

Triolein (major skin lipid) was irradiated with 300-nm ultraviolet (UV) light, and the conditions for exposure approximated those at the skin surface exposed to sunlight.[4] *Using gas chromatography, the irradiated samples were analyzed for the presence of acrolein, formaldehyde, and acetaldehyde. The maximum amount of acrolein (1.05 nmol/mg Triolein) was formed after 6 h of irradiation. Maximum amounts of formaldehyde (6 nmol/mg Triolein) and acetaldehyde (2.71 nmol/mg Triolein) were formed after 12 h of irradiation.*

Caprylic/Capric Triglyceride can undergo hydrolysis by enzymatic or chemical means to produce free fatty acids, partial glycerides, and glycerol.[5] *The free fatty acids may, in turn, undergo enzymatic β-oxidation. β-Oxidation of caprylic acid forms β-ketocaprylic acid and can be further oxidized to yield acetic acid and C_6,-acid. However, it is possible that the β-ketocaprylic may also be oxidized to form methyl-n-phenylketone by decarboxylation. In the case of capric acid, methyl-n-heptylketone may also be formed.*

Methods of Manufacture

One method of production of Trihydroxystearin involves the hydrogenation of castor oil, in the presence of the reagent nickel, at a temperature of 200ºC. Another method of production is the reduction of triricinolein.[1]

Trilaurin may be produced by reacting glycerol with lauric acid or glycerol with lauroyl chloride (reagent: pyridine or quinoline).[4] *The reaction of lauric acid with glycerine is another method of production. Triolein may be prepared by the esterification of oleic acid. Tripalmitin can be prepared from glycerol and palmitic acid in the presence of either Twitchell reagent or trifluoroacetic anhydride. Tristearin may be prepared from stearic acid and glycerol in the presence of Al_2O_3. Triundecanoin is produced by esterification of undecanoic acid and glycerine. The undecanoic acid is produced from castor oil, which is hydrolyzed to fatty acids and subjected to thermal degradation and fractionation. The resulting undecenoic acid is transformed to undecanoic acid and reesterified to the glycerol moiety. Deodorization, the final step, is accomplished using steam to remove components that give rise to unwanted flavors and odors.*

Caprylic/Capric Triglyceride is manufactured by hydrolyzing coconut oil, removing the free glycerine, and separating the medium chain length fatty acids by fractional distillation.[5] *The acids are then blended in the proper ratio and re-esterified with glycerine.*

Triglycerides (general)

Some of the triglycerides are produced synthetically via classical Fischer type esterification methods (i.e., reaction of carboxylic acids with a glycerin to produce carboxylic esters), although the reaction may be promoted by acid or base catalysis, or by the use of an acid chloride. However, some of these ingredients may be natural sourced and produced by transesterification (i.e., exchange of acid moieties to create a different ester product). For example, the triglycerides in natural oils can be reacted with intended length fatty acids to produce new triglycerides.

Medium- and Long-Chain Triglycerides

The following are method of manufacture schemes for MCT (Figure 3)[11] and MLCT-oil (Figure 4):[14]

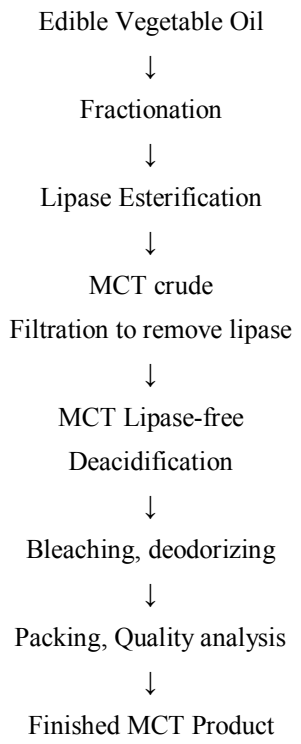


Figure 3. MCT production scheme

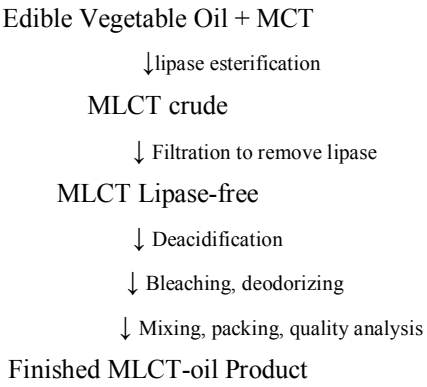


Figure 4. MLCT-oil production scheme

Impurities

Triundecanoin contains no impurities or residues of catalysts or solvents.[4] *1,4-Dioxane, ethylene oxide, free amines, and nitrosamines are not added or formed during the production process. Furthermore, volatile compounds are effectively removed, by the deodorization process, below detection limits (0.1 ppm). The deodorization process also has removed any organochlorine or organophosphorus pesticides that may be present in the crude oil used in the production process. It is also important to note that the total content of polycyclic aromatic hydrocarbons (PAHs), if present in the crude oil, is reduced below 10 ppb. Additionally, aflatoxins, if present in the raw materials, are reduced below detection limits (0.5 ppb) by neutralization and bleaching.*

The only known impurities of Caprylic/Capric Triglyceride are approximately 300 ppm free fatty acids and as much as 0.2% glycerol.[5] *The relatively low iodine number 5, which is determined in an arbitrary but standard method, indicates very little unsaturated material present.*

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this safety assessment is evaluated based on data received from the FDA and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in

cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA VCRP database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to information from the VCRP and that received from the Council, 32 ingredients assessed in this report are in use. Caprylic/Capric Triglyceride has the highest frequency of use; according to 2017 VCRP data, it is used in 6000 cosmetic formulations, with uses reported for all exposure types.[15] Tribehenin has the next highest frequency of use, with 723 reported uses, followed by Triethylhexanoin, with 601 reported uses. (Table 7; Table 8)

A use concentration survey was conducted in 2015 for some of the ingredients; a survey of the concentration of use of the remaining ingredients will be conducted soon. For those that were surveyed, the results indicate that Triethylhexanoin has the highest maximum use concentration in leave-on formulations, with concentrations of 100% reported for face and neck formulations and 63% in lipstick formulations (Table 7).[16]

Approximately half of the ingredients included in this safety assessment have been reviewed previously by the Panel. The frequency and maximum concentrations of use for the majority of these ingredients has increased when compared to the original review. The most remarkable increase is in the frequency of use of Caprylic/Capric Triglyceride; in 2003, this ingredient was reported to be used in 763 formulations and in 2017, it is reported to be used in 6000 formulations. A concentration of use survey has not yet been completed for this ingredient, so it is not known if the use concentrations have changed. However, in 2003, Caprylic/Capric Triglyceride was reported to be used at relatively high concentrations, including maximum concentrations of up to 84% in perfumes and up to 54% in lipsticks.[6]

The 22 triglycerides not currently reported to be in use, according to VCRP data, and currently-available industry survey results, are listed in Table 9.

Some of the triglycerides are used at relatively high concentrations in products that can be used near the eye, can possibly be ingested, or come in contact with mucous membranes; for example, Triethylhexanoin in used at up to 52% in eye make-up remover and Glyceryl Triacetyl Ricinoleate in used at up to 49.2% in eye shadows, and Triethylhexanoin is used at up to 63% in lipstick formulations. Additionally, some of these ingredients are used in cosmetic sprays and powders and could possibly be inhaled; for example, Triethylhexanoin and Triisostearin are reported to be used at maximum concentrations of 36% and 30%, respectively, in perfumes, and 14.7% and 10.4%, respectively, in face powders. 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.[17,18] 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.[19,20] Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[21-23]

All the triglycerides described in this safety assessment (and listed in the *Dictionary*) are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).[24] In Australia, Triethylhexanoin cannot be classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances*.[25]

Non-Cosmetic

Trihydroxystearin has been used as a thickening agent for peanut butter.[1] *FDA has listed the following indirect food additive uses in the Code of Federal Regulations (CFR): components of adhesives (21CFR 175.1 05), components of resinous and polymeric coatings (21 CFR 175.300), components of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170), components of paper and paperboard in contact with dry food (21 CFR 176.180), defoaming agents used in the manufacture of paper and paperboard (21 CFR 176.21 0), cellophane (21CFR 177.1200), closures with sealing gaskets for food containers (21 CFR 177.1210), polyester resins cross-linked (21 CFR177.2420), and textiles and textile fibers (21 CFR 177.2800).*

Trihydroxystearin is among the inert ingredients that are exempt from the requirement of a tolerance under the Federal Food, Drug, and Cosmetic Act when used in pesticide formulations that are applied to crops.[1]

Trilaurin has been detected in pharmaceutical excipients.[4] *Tricaprylin has been used as an energy source for bum patients and for patients having difficulty digesting long-chain fatty acids. Tristearin has been approved for use as a direct food additive (21 CFR 172.811). Additionally, the following glyceryl triesters have been approved for use as components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food (i.e., use as indirect food additives): Trilaurin, Trimyristin, Triolein, Tripalmitin, Tristearin (21 CFR 177.2800), and Glyceryl Triacetyl Hydroxystearate (21 CFR 178.3505).*

The following non-cosmetic uses of Tristearin have been reported: soap, candles, candies, adhesive pastes, metal polishes, waterproofing paper, textile sizes, leather stuffing, and manufacture of stearic acid.[4]

Letters issued by the FDA have attested to the safety of Caprylic/Capric Triglyceride when used as a food additive.[5] *In addition, it has also been marketed for consumption since 1962 as a nutritional supplement and blood lipid lowering agent.*

It has also been suggested for use in enteric drugs and rectal suppositories and as a vehicle for topically applied pharmaceuticals.

C10-18 Triglycerides and coconut triglycerides are approved for use as direct multipurpose food additives (21CFR172.861). Coconut triglycerides is also approved as an indirect food additive as a defoaming agent used in the manufacture of paper and paperboard (21CFR172.861).

Medium-Chain Triglycerides

The FDA received a GRAS (Generally Recognized as Safe) Notification request for MLCT for use as a food ingredient, such that the total daily consumption of MLCT-oil would not exceed 31 g/day.[14] The FDA responded that the tailored triglycerides ingredient (12% medium-chain fatty acids; 12% MCFAs) is GRAS under the intended conditions of use as an oil in home cooking, salad dressings, vegetable-oil spreads, and frozen dinners (including meat and poultry).[26] The agency has not, however, made its own determination regarding the GRAS status of the subject use of the tailored triglycerides (12 percent MCFAs) ingredient.

MCT are a component of a homogenous lipid emulsion approved for intravenous (i.v.) infusions indicated for use in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.[27] The lipid content of the infusion is 0.20 g/ml, and comprises a mixture of soybean oil, MCT, olive oil, and fish oil; recommended dosing is 1 to 2 grams/kg/day, not exceeding 2.5 grams/kg/day.

TOXICOKINETIC STUDIES

Dermal Penetration

In mice and guinea pigs, little skin penetration was observed, although Tricaprylin did enhance the skin penetration of drugs in vivo (Wistar rats) and in vitro (hairless mice).[4]

Penetration Enhancement

The skin penetration enhancement of drugs in the presence of Triolein has been reported.[4]

Absorption, Distribution, Metabolism, and Excretion

Metabolism data indicate that most triglycerides (or glyceryl triesters) are split into monoglycerides, free fatty acids, and glycerol in the small intestine and absorbed by the intestinal mucosa [4]

When absorbed from the digestive tract, Caprylic/Capric Triglyceride is hydrolyzed, and the fatty acids are catabolized to C_2 fragments which may be further metabolized either to CO_2 or to form long-chain fatty acids. [5]

Triglycerides (general)

Absorption and metabolism of LCT differ from MCT.[13] LCT are degraded by salivary, intestinal and pancreatic lipases into two fatty acids and a monoacyl glycerol; whereas, MCT are degraded by the same enzymes into three fatty acids and the simple glycerol backbone. Medium-chain fatty acids (MCFA) are readily absorbed from the small intestine directly into the bloodstream and transported to the liver for hepatic metabolism, while long-chain fatty acids (LCFA) are incorporated into chylomicrons and enter the lymphatic system. MCFA are readily broken down to carbon dioxide and two-carbon fragments, while LCFA are re-esterified to triacylglycerols and either metabolized for energy or stored in adipose tissue.

Triethylhexanoin

The primary metabolite of Triethylhexanoin, along with glycerol and monoglycerides, is 2-ethylhexanoic acid.[25]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

In acute oral toxicity studies in which Trihydroxystearin was tested using albino rats, the LD_{50} was not achieved at a dose of 5 g/kg and no deaths were reported. [1]

Acute oral LD_{50} values range from 5 g/kg in mice (Tribehenin) to > 20 g/kg in rats (Tristearin).[4] *In other acute oral toxicity studies, Trioctanoin was not toxic following oral administration to male mice at a dose of 50 ml/kg, and Triisostearin did not induce toxicity in rats at a dose of 2 g/kg.*

Acute oral LD_{50} values for Caprylic/Capric Triglyceride were > 25 ml/kg in mice and >5 g/kg in rats.[5] *Male rats and guinea pigs in groups of ten each were exposed for 6 h in a 40 L chamber containing an aerosol of Caprylic/Capric Triglyceride at a nominal concentration of 28.1 µl/l of air. The fraction of the aerosol with particles small enough to be inhaled into the lung, i.e., with a diameter of 5 µm or less, represented 1.97 µl/l of the test substance. No adverse effects were observed.*

The acute dermal and oral toxicity studies summarized below are described in Table 10.

The dermal LD_{50} in rats was >2 g/kg (the highest dose tested) for both Triheptanoin[28] and Tristearin.[29] The oral LD_{50} was >2 g/kg for Triisostearin in mice and rats,[30] >2 g/kg Triolein in mice,[31] >5 g/kg Triheptanoin in mice, and >48 g/kg Triethylhexanoin[32] in rats. The oral LD_{50} of an MLCT oil was >5 g/kg in rats.[13]

Short-Term Toxicity Studies

The short-term oral administration of Trilaurin, Tristearin, or Triolein to weanling rats did not result in gross or microscopic lesions.[4] *However, in another short-term study, significant differences in hematological and clinical chemistry parameters as well as organ weights were noted after administration of Tricaprylin to male and female Wistar rats.*

No signs of toxicity were observed in rabbits following 4 wks of applications of a tanning butter formulation containing 22% Caprylic/Capric Triglyceride at a dose of 2 g/kg, five times/wk for 4 wks, to intact and abraded skin.[5] *Two groups of 10 rats were dosed by gavage with 7.6 or 21.3 ml/kg undiluted Caprylic/Capric Triglyceride daily for 30 day.*[5] *With the exception of a few gross observations made in the high-dose group in the first week of the study, no adverse were observed.*

The short-term toxicity studies summarized below are described in Table 11.

In 28-day gavage studies in Han-Wistar rats, dosing with 33% Caprylic/Capric Triglyceride did not produce any signs of toxicity,[33] but undiluted test material produced some gastrointestinal effects, decreased thymic weight, caused inflammation in the lungs, and resulted in changes in some clinical pathology parameters.[34] These changes were reversible. In Göttingen minipigs, clinical signs of toxicity were observed with both 0.5 and 2 ml/kg/day Caprylic/Capric Triglyceride administered by gavage; no changes in organ weights or gross or microscopic lesions were observed.[35] In rats, a no-observed adverse effect level (NOAEL) of 10 mg/kg bw/day was reported in a 30 day study with MCT,[36] and a NOAEL of 3500 mg/kg/day was reported with MLCT.[13] In a human study, no adverse effects were observed in a placebo-controlled double-blind study in which healthy subjects ingested 42 g/day MLCT.[13]

Subchronic Toxicity Studies

Application of a perfumed skin softener formulation containing 4% Caprylic/Capric Triglyceride to the shaved skin of female rats at a dose of 2 ml/kg 5 days/wk for 13 wks did not produce any toxic effects.[5] *No toxic effects were noted in a 3-mos feeding study of 1 and 5% Caprylic/Capric Triglyceride in the diet of rats.*

The subchronic toxicity studies summarized below are described in Table 11.

Three-month feeding studies were performed with MCT in rats[36] and dogs.[37] The NOAELs were 50,000 ppm and 15%, respectively, and no toxicologically-relevant signs of toxicity were observed.

Chronic Toxicity Studies

No significant differences were found in growth rate or the incidence of lesions between groups of rats fed a mixture containing 0.0002% Trilaurin for 2 years and controls.[4] *In another chronic study, cardiac lipidosis and/or focal fibrosis was observed in rats fed a basal diet consisting of 30 cal % Trierucin for 24 weeks. Renal tubular dilatation, proteinaceous casts, or fibrosis were also reported. When the chronic oral toxicity of Tricaprylin was evaluated using groups of male rats, significant reductions in hematological/clinical chemistry parameters and significant increases in organ weight were noted after 26 weeks of dosing. Few lesions in the kidneys, myocardium, and aorta were noted when Tricaprylin was tested in another chronic oral toxicity study.*

In studies in which rats were fed a diet containing 19.6% of a MCT composed of about 75% caprylic acid and 25% capric acid for 47 weeks or an MCT at 20% in the diet, for 1 yr, nutritional effects resulting from long-term consumption of this ingredient were observed, but no effects were interpreted as adverse or toxic.[5]

In a 9-mos feeding study, an oil containing 64% Triheptanoin was not toxic in rats Table 11.[38]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Tricaprylin was not teratogenic in mice or rats when administered orally [4] *In another study on reproductive effects, Tricaprylin was effective in producing fusion of the endometrial epithelium (symplasma formation) and decidualization of the stroma in pseudopregnant New Zealand white rabbits. The oral administration of Trioctanoin to mice did not result in any significant differences in indices of potential developmental toxicity (i.e., litter size, birth weight, and neonatal growth and survival to postnatal day 3) between test and control groups. Test results for 291 fetuses from various strains of mice injected intraperitoneally with Trioctanoin (vehicle control) in a teratogenicity study indicated various kinds of eye abnormalities in 6.2% of the fetuses.*

In a reproduction study, young adult male and female rats were fed a balanced diet containing 19.6% of a triglyceride of 75% caprylic and 25% capric acid for three weeks before mating.[5] *Litter size and birth weight of the test animals were similar to those of rats on conventional or low fat diets, but mortality during lactation was somewhat higher, and there was less weight gain due to a smaller volume of milk secreted. After weaning, the F_1 generation was fed as the F_0 generation had been and showed a weight gain comparable to that of control rats.*

Tricaprylin

In a study evaluating the developmental toxicity of trichloroacetonitrile in which Tricaprylin was used as a vehicle, a possibly biologically significant effect (increased resorptions, reduced fetal weight, and anomalies) was observed in the Tricaprylin control group when compared to the water control group.[39] Therefore, the developmental toxicity of trichloroacetonitrile was reexamined using Tricaprylin and corn oil as vehicles. Groups of 20 gravid Long-Evans rats were dosed by

gavage on days 6-18 of gestation with 15 mg/kg/day trichloroacetonitrile in Tricaprylin and 15-75 mg/kg/day trichloroacetonitrile in corn oil; vehicle control groups were dosed with Tricaprylin, corn oil only, and water. The dosing volume was 10 ml/kg. All dams were killed on day 20 of gestation.

Statistically significant difference in some parameters was observed in the Tricaprylin control group compared to the water and/or corn oil control groups. There was a statistically significant increase in the percent implantation loss in the Tricaprylin group as compared to both the water and corn oil controls, and the total implants/litter was statistically significantly less when compared to the corn oil, but not the water, control group. Also, there were statistically significant decreases in fetal body weights and crown-rump length in the Tricaprylin control group as compared to the water and corn oil control groups. There was no difference in the incidence of fetal anomalies among the three control groups. In the dams, the maternal average kidney weight was statistically significantly increased in the Tricaprylin controls when compared to the water and corn oil controls; no effect on liver or spleen weight was reported.

The study authors postulated that the differences observed between the Tricaprylin group and the other two control groups may be attributable to potential changes in nutritional status. Dams of the Tricaprylin group gained significantly less weight than those of the corn oil group during days 15-18 of gestation. However, food and water consumption were not monitored. The stud y authors also stated that the differences in reproductive parameters could be due to normal variation for Long-Evans rats.

Additionally, the developmental toxicity of trichloroacetonitrile appeared to be vehicle-dependent; developmental effects caused by trichloroacetonitrile were seen at higher doses when administered in corn oil compared to those seen when Tricaprylin was used as the vehicle. The study authors suggested that trichloroacetonitrile and Tricaprylin "appear to interact in some way to potentiate effects of the cardiovascular system."

GENOTOXICITY STUDIES

In Vitro

Ames test results indicated that Trihydroxystearin was not mutagenic to the following Salmonella typhimurium strains, with or without metabolic activation, when tested at concentrations ranging from 3 to 1000 µg/plate: TA1535, TA1537, TA1538, TA98, and TA100.[1]

In the Ames test, Tricaprylin was mutagenic in one of four S. typhimurium strains tested.[4] *Negative test results were reported for Trilaurin in the following assays: dominant lethal test, host-mediated mitotic gene conversion assay, chromosomal aberrations assay, micronucleus test, sister chromatid exchange (SCE) assay, spot test for gene mutations, and cytogenetic assay for clastogenic activity. In the Ames test, Trilaurin, Trioctanoin, Triolein, Tristearin, and Triisostearin were not mutagenic in S. typhimurium strains. However, Trioctanoin was mutagenic in the spot test for gene mutations. In other tests, no clastogenic activity was noted when Trioctanoin was tested in a cytogenetics assay and results were negative in a sister chromatid exchanges mutagenicity assay.*

The genotoxicity studies summarized below are described in Table 12.

Tristearin (5000 µg/plate)[29] and Tricaprylin (concentration not stated)[32] were not mutagenic in the Ames test, Triethylhexanoin was not genotoxic in an Ames test (50-5000 µg/plate) or a mammalian chromosomal aberration assay (7.5-4000 µg/ml),[25] and Triisonanoin was not genotoxic in an Ames test (50-5000 µg/plate), chromosomal aberration assay (10-320 µg/ml), or a mammalian cell gene mutation assay (5-80 µg/ml).[40]

A lipid emulsion that comprises a mixture of soybean oil, MCT, olive oil, and fish oil (test concentrations not provided) was not genotoxic in an Ames test, a chromosomal aberration assay, or a hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay.[27] In vivo, the emulsion was not genotoxic in a bone marrow cytogenic study in rats.

CARCINOGENICITY STUDIES

Following intraperitoneal injection of Tricaprylin into 30 female mice in a tumorigenicity study, lung tumors were observed in 37% of the animals.[4] *In the untreated-control group of 30 mice, the lung tumor incidence was 23%. The results of an oral carcinogenicity study by the National Toxicology Program (NTP) indicated that Tricaprylin caused a statistically significant dose-related increase in the incidence of pancreatic acinar cell hyperplasia and adenoma in rats. Tricaprylin did not induce acinar cell carcinomas. Additionally, the incidence of squamous cell papilloma in the squamous portion of the stomach of rats in the highest dose group (10 ml/kg Tricaprylin) was significantly greater when compared to controls.*

ANTI-CARCINOGENICITY STUDIES

Trilaurin completely inhibited the formation of neoplasms initiated by 7,12-dimethylbenz[a]anthracene (DMBA) and promoted by croton oil.[4] *Additionally, extensive damage to tumor cells (lymphoma implants in the liver) was noted in rats after oral dosing with Tricaprylin.*

DERMAL IRRITATION AND SENSITIZATION STUDIES

Trihydroxystearin was not irritating to the skin of albino rabbits in 24-hour occlusive patch tests.[1] *In 48-hour occlusive patch tests, Trihydroxystearin did not induce skin irritation in any of the 103 subjects tested.*

Triisostearin and a 20% solution of Tribehenin in liquid paraffin were, at most, mildly irritating when applied to the skin of rabbits.[4] *However, Trioctanoin and an eyeliner containing 36.3% Trilaurin did not induce cutaneous irritation in rabbits. Neither Tribehenin nor Trioctanoin induced sensitization in the Magnusson-Kligman guinea pig maximization test. Triisostearin did not induce significant cutaneous reactions in a study evaluating the phototoxicity and photoallergenicity potential of this ingredient in guinea pigs.*

An eyeliner containing 36.3% Trilaurin did not induce skin irritation reactions in test subjects.[4] *Trioctanoin itself did not induce skin irritation. A lip enhancer cream containing 0.38% Tribehenin was not comedogenic and did not induce clinically significant skin irritation in any of the subjects evaluated in a 28-day test. Repeated insult patch test (RIPT) results (occlusive patches) for the following products were negative: eye enhancer cream containing 0.32% Tribehenin (198 subjects), hand cream containing 0.38% Tribehenin (at least 200 subjects), lip cream containing 0.38% Tribehenin (at least 200 subjects), and an eye defining pencil containing 1.68% Tristearin. None of these products induced clinically significant irritant or allergic contact dermatitis. In a skin sensitization test involving 91 subjects, there was no evidence of delayed contact hypersensitivity after repeated applications (occlusive patches) of an eyebrow pencil containing 40% Trilaurin. Also, reportedly, Trioctanoin did not induce sensitization in a contact allergy test.*

Undiluted Caprylic/Capric Triglyceride was not irritating to rabbit skin in primary skin irritation tests.[5] *Slight to moderate erythema was observed in the intact and abraded skin of rabbits following 4 wks of applications of a tanning butter formulation containing 22% Caprylic/Capric Triglyceride at a dose of 2 g/kg, five times/wk for 4 wks . Application of a perfumed skin softener formulation containing 4% Caprylic/Capric Triglyceride to the shaved skin of female rats at a dose of 2 ml/kg 5 days/wk for 13 wks did not result in any localized skin effects. Caprylic/Capric Triglyceride was not a sensitizer in guinea pigs. Undiluted Caprylic/Capric Triglyceride was not irritating when tested using groups of 12 (21-day patch test), or 40 (test methods not described), and it was not an irritant or sensitizer in 128, subjects (Draize repeated insult patch test).*

The dermal irritation and sensitization studies summarized below are described in Table 13.

Dermal effects were observed in 4-h semi-occlusive patch tests in rabbits with undiluted Triheptanoin; very slight to slight erythema was reported in 1-2 of 3 animals in one study, but in the other study, very slight to well-defined erythema was observed in all 6 animals 30-60 min after patch removal, moderate to severe erythema and severe edema, discoloration, and dryness with sanguineous lacerations and scaling was observed in 1 animal 24-72 h after dosing, and scaling was observed in all animals at day 6.[28] Triisostearin (test concentration not provided) produced well-defined erythema in all 3 rabbits at 1 and 24 h; all erythema was resolved by 72 h.[30] No irritation was observed in 4-h patch tests with undiluted Tristearin,[29] Caprylic/Capric Triglyceride,[36] or C8-C12 Acid Triglycerides.[36] Triheptanoin (100%)[28] and Tristearin (50%)[29] were not sensitizers in guinea pigs. Triisonanoin was predicted to be non-irritating in an EpiSkin™ in vitro test.[40] However, in a mouse local lymph node assay (LLNA), it was predicted that Triisonanoin may cause sensitization; results were negative with 25% and 50% Triisostearin but positive when tested at 100%.

In a human study, Triolein was not a sensitizer in a chamber test.[32] (Details were not provided.)

OCULAR IRRITATION STUDIES

Trihydroxystearin was classified as a mild, transient ocular irritant in albino rabbits.[1]

An eye enhancer cream containing 0.32% Tribehenin and a hand cream containing 0.38% Tribehenin were classified as non-irritants in an in vitro chorioallantoic membrane vascular assay for determining the ocular irritation potential of chemicals.[4] *An eyeliner containing 36.3% Trilaurin and a 20% solution of Tribehenin in liquid paraffin were, at most, mildly irritating to the eyes of rabbits. Trioctanoin and Triisostearin did not induce ocular irritation in rabbits.*

An eye enhancer cream containing 0.32% Tribehenin induced reactions ranging from mild to moderate ocular irritation in a group of 20 subjects, which resolved to either mild irritation or no irritation reactions at 2 hours post exposure.[4] *In a clinical in-use safety test of two eye enhancer creams containing 0.32% Tribehenin, neither ocular irritation nor clinically relevant alterations in visual acuity were observed after 4 consecutive weeks of daily product use. Similar results were reported after testing of another eye enhancer cream containing 0.32% Tribehenin and an eye defining pencil containing 1.68% Tristearin in separate studies according to the same procedure. All of the subjects tested in these studies were contact lens wearers.*

Caprylic/Capric Triglyceride was non-irritating, to at most very mildly irritating, to rabbit eyes.[5]

The ocular irritation studies summarized below are described in Table 14.

Undiluted Triheptanoin,[28] Tristearin,[29] Caprylic/Capric Triglyceride,[36] and C8-12 Acid Triglyceride,[36] as well as Triisostearin at an unspecified concentration,[30] were not irritating in rabbit eyes. Triisononanoin was predicted to be non-irritating in an in vitro eye irritation test using the SkinEthic™ reconstructed model.[40]

SUMMARY

In 2000, the Panel assessed the safety of Trihydroxystearin and concluded that, based on the available animal and clinical data, which included summary data from the CIR safety assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate SE, Trihydroxystearin is safe as used in cosmetics. The Panel published two additional reports on related ingredients; the Panel concluded that Caprylic/Capric Triglyceride (1980) and Trilaurin and 22 additional glyceryl triesters (2001) are safe as used in cosmetics. An additional 29 triglycerides that are cosmetic ingredients and have not been reviewed by the Panel have also been identified. This safety assessment is a compilation of these 54 triglycerides, most of which (but not all) function as skin conditioning agents and/or viscosity increasing agents in cosmetics.

Some of these triglycerides are produced synthetically via classical Fischer type esterification methods, although the reaction may be promoted by acid or base catalysis, or by the use of an acid chloride. Additionally, some of these ingredients may be natural sourced and produced by transesterification.

Thirty-two of the 54 ingredients included in this safety assessment are in use, and Caprylic/Capric Triglyceride has the highest frequency of use (6000 formulations). A use concentration survey has been completed for some, but not all, of the ingredients. According to the results for those surveyed, Triethylhexanoin has the highest maximum use concentration, with concentrations of 100% reported for face and neck formulations and 63% in lipstick formulations. Approximately half of the ingredients included in this safety assessment have been reviewed previously by the Panel. The frequency and maximum concentrations of use for the majority of these ingredients have generally increased since these ingredients were originally reviewed.

Many of the triglycerides are approved by the FDA for use as direct or indirect food additives.

In acute toxicity testing, the dermal LD_{50} in rats was >2 g/kg (the highest dose tested) for both Triheptanoin and Tristearin. The oral LD_{50} was >2 g/kg for Triisostearin in mice and rats, >2 g/kg Triolein in mice, >5 g/kg Triheptanoin in mice, and >48 g/kg Triethylhexanoin in rats. The oral LD_{50} of an MLCT oil was >5 g/kg in rats.

In 28-day gavage studies in Han-Wistar rats, dosing with 33% Caprylic/Capric Triglyceride did not produce any signs of toxicity, but undiluted test material produced some gastrointestinal effects, decreased thymic weight, caused inflammation in the lungs, and resulted in changes in some clinical pathology parameters. These changes were reversible. In Göttingen mini-pigs, clinical signs of toxicity were observed with both 0.5 and 2 ml/kg/day Caprylic/Capric Triglyceride administered by gavage; no changes in organ weights or gross or microscopic lesions were observed.

Short-term and subchronic feeding studies were conducted with MCT. In rats, a NOAEL of 10 mg/kg bw/day was reported in a 30 day study with MCT, and a NOAEL of 3500 mg/kg/day was reported with MLCT. In a human study, no adverse effects were observed in a placebo-controlled double-blind study in which healthy subjects ingested 42 g/day MLCT. Three-month feeding studies were performed with MCT in rats and dogs, and the NOAELs were 50,000 ppm and 15%, respectively; no toxicologically-relevant signs of toxicity were observed.

In a chronic (9-mos) feeding study, an oil containing 64% Triheptanoin was not toxic in rats.

Tricaprylin was used as a vehicle in a DART study of trichloroacetonitrile, and its effect on the test results was compared to other vehicles. Additionally, the potential developmental toxicity of Tricaprylin was evaluated in comparison to the two other vehicles (water and corn oil). There was a statistically significant increase in the percent implantation loss in the Tricaprylin group as compared to both the water and corn oil controls, and the total implants/litter was statistically significantly less when compared to the corn oil, but not the water, control group. Also, there were statistically significant decreases in fetal body weights and crown-rump length in the Tricaprylin control group as compared to the water and corn oil control groups. The study authors postulated that the differences observed between the Tricaprylin group and the other two control groups may be attributable to potential changes in nutritional status.

Additionally, the developmental toxicity of trichloroacetonitrile appeared to be vehicle-dependent; developmental effects caused by trichloroacetonitrile were seen at higher doses when administered in corn oil compared to those seen when Tricaprylin was used as the vehicle. The study authors suggested that trichloroacetonitrile and Tricaprylin "appear to interact in some way to potentiate effects of the cardiovascular system."

The genotoxicity of several triglycerides was evaluated, and all the results were negative. Tristearin (5000 µg/plate) and Tricaprylin (concentration not stated) were not mutagenic in the Ames test, Triethylhexanoin was not genotoxic in an Ames test (50-5000 µg/plate) or a mammalian chromosomal aberration assay (7.5-4000 µg/ml), and Triisonanoin was not genotoxic in an Ames test (50-5000 µg/plate), chromosomal aberration assay (10-320 µg/ml), or a mammalian cell gene mutation assay (5-80 µg/ml).

A lipid emulsion that comprises a mixture of soybean oil, MCT, olive oil, and fish oil (test concentrations not provided) was not genotoxic in an Ames test, a chromosomal aberration assay, or a hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay. In vivo, the emulsion was not genotoxic in a bone marrow cytogenic study in rats.

Mixed results were obtained in dermal irritation and sensitization studies. Dermal effects were observed in 4-h semi-occlusive patch tests in rabbits with undiluted Triheptanoin; very slight to slight erythema was reported in 1-2 of 3 animals in

one study, but in the other, very slight to well-defined erythema was observed in all 6 animals 30-60 min after patch removal, moderate to severe erythema and severe edema, discoloration, and dryness with sanguineous lacerations and scaling was observed in 1 animal 24-72 h after dosing, and scaling was observed in all animals at day 6. Triisostearin (test concentration not provided) produced well-defined erythema in all 3 rabbits at 1 and 24 h; all erythema was resolved by 72 h. No irritation was observed in 4-h patch tests with undiluted Tristearin, Caprylic/Capric Triglyceride, or C8-C12 Acid Triglycerides. Triheptanoin (100%) and Tristearin (50%) were not sensitizers in guinea pigs. Triisonanoin was predicted to be non-irritating in an EpiSkin™ in vitro test. However, in a mouse LLNA, it was predicted that Triisonanoin may cause sensitization; results were negative with 25% and 50% Triisostearin but positive when tested at 100%. In a human study, Triolein was not a sensitizer in a chamber test.

Several triglycerides were evaluated and found not to be ocular irritants. Undiluted Triheptanoin, Tristearin, Caprylic/Capric Triglyceride, and C8-12 Acid Triglyceride, as well as Triisostearin at an unspecified concentration, were not irritating in rabbit eyes. Triisononanoin was predicted to be non-irritating in an in vitro eye irritation test using the SkinEthic™ reconstructed model.

No new carcinogenicity data were discovered in an extensive search of the published literature.

DISCUSSION FROM THE FINAL REPORT ON TRIHYDROXSTEARIN[1]

Although the data on Trihydroxystearin are limited, the CIR Expert Panel had previously conducted a safety assessment of Glyceryl Stearate and Hydroxystearic Acid. These data indicate no mutagenic, carcinogenic, or teratogenic effects in animals, and no irritation or sensitization in clinical tests. The data on these two ingredients is considered relevant to the assessment of Trihydroxystearin because of the chemical similarity of the ingredients. The data on Glyceryl Stearate and Hydroxystearic Acid are also consistent with the limited data that are available on Trihydroxystearin itself.

During the open, public comment period on the Tentative Report, a comment was made regarding the absence of sensitization data. The CIR Expert Panel agrees that data on sensitization potential are important in assessing the safety of an ingredient. In this case, there are data on a related ingredient. When tested at concentrations up to 20.0% in human RIPTs involving a large number of subjects, Glyceryl Stearate was neither an irritant nor a sensitizer. Thus, in the absence of sensitization data on Trihydroxystearin, it was concluded that this ingredient is not likely a sensitizer based on data on a chemically similar ingredient. All of the available data suggest that Trihydroxystearin and its component chemical species are safe as used in cosmetic formulations.

DISCUSSION FROM THE FINAL REPORT ON TRILAURIN, AND OTHER GLYCERYL TRIESTERS[4]

The Panel noted that, as part of an effort to evaluate vehicles used in carcinogenicity studies, the NTP conducted a 2-year carcinogenicity study in rats given Tricaprylin by gavage. This treatment was associated with a statistically significant dose-related increase in pancreatic acinar cell hyperplasia and adenoma, but there were no acinar carcinomas, the incidence of mononuclear leukemia was less, and nephropathy findings were reduced, compared to com oil controls. The Panel agreed that, overall, the study concluded that Tricaprylin did not offer significant advantages over com oil as vehicles in carcinogenicity studies. Trilaurin was also found to inhibit the formation of neoplasms initiated by DMBA and promoted by croton oil.

The available short- and long-term toxicity test results (NTP oral carcinogenicity study on Tricaprylin included) summarized above, do not warrant any restrictions on the use of any of the Glyceryl Triesters included in this safety assessment in rinse-off or leave-on cosmetic products. The Expert Panel recognizes that some of the Glyceryl Triesters included in this review are not in use, but would be considered safe if used at concentrations similar to those of Glyceryl Triesters that are being used in cosmetic products.

Although minimal percutaneous absorption of Triolein has been demonstrated in vivo using guinea pigs (but not hairless mice) and in vitro using full-thickness skin from hairless mice, the Expert Panel recognizes that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals, and recommends that care should be exercised in using these and other Glyceryl Triesters in cosmetic products.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Triglycerides included in this report

Acetic/Linoleic/Palmitic Triglyceride	Glyceryl Triacetyl Hydroxystearate	Trierucin
C12-18 Acid Triglyceride	Glyceryl Triacetyl Ricinoleate	Triethylhexanoin
C18-36 Acid Triglyceride	Glyceryl Tribehenate/Isostearate/Eicosandioate	Triheptanoin
C18-38 Acid Triglyceride	Glyceryl Tri-Hydrogenated Rosinate	Triheptylundecanoin
C8-12 Acid Triglyceride	Glyceryl Tripalmate/Palm Kernelate/ Olivate/Macadamiate/Rapeseedate	Trihydroxystearin
Capric/Lauric/Myristic/Oleic Triglyceride	Hydrogenated C12-18 Triglycerides	Triisononanoin
Caprylic/Capric Triglyceride	Isomerized Safflower Glycerides	Triisopalmitin
Caprylic/Capric/Lauric Triglyceride	Jojoba Oil/Caprylic/Capric Triglyceride Esters	Triisostearin
Caprylic/Capric/Linoleic Triglyceride	Lauric/Palmitic/Oleic Triglyceride	Trilaurin
Caprylic/Capric/Myristic/Stearic Triglyceride	Oleic/Linoleic Triglyceride	Trilinolein
Caprylic/Capric/Palmitic/Stearic Triglyceride	Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride	Trilinolenin
Caprylic/Capric/Stearic Triglyceride	Palmitic/Stearic Triglyceride	Trimyristin
C10-40 Isoalkyl Acid Triglyceride	Ricinoleic/Caproic/Caprylic/Capric Triglyceride	Triolein
Coconut Triglycerides	Tallow Triglyceride	Tripalmitin
Cod Liver/Mink/Tallow Triglyceride	Triarachidin	Tripalmitolein
C10-18 Triglycerides	Tribehenin	Triricinolein
Docosahexenoic/Docosapentenoic/ Oleic/Palmitic Triglyceride	Tricaprin	Tristearin
Glyceryl Stearate Diacetate	Tricaprylin	Triundecanoin

Note: ingredients that were previously reviewed are indicated in blue;' ingredients that were found in the VCRP but not the *Dictionary* are indicated in green

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;[CIR Staff]]

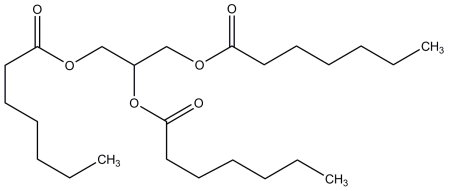
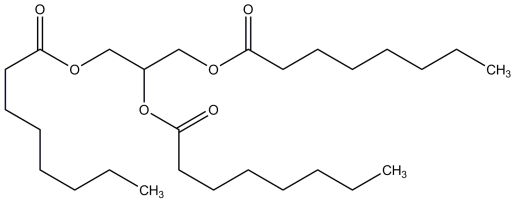
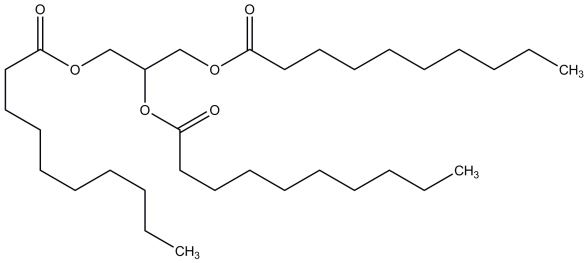
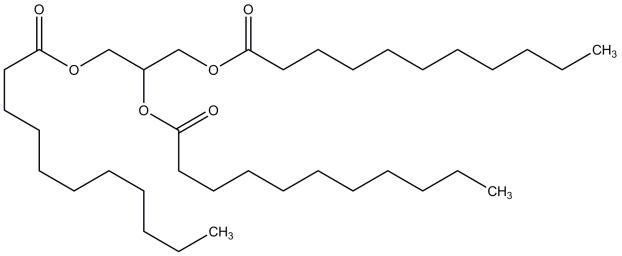
Ingredient/CAS No.	Definition & Structure	Function(s)
	Linear chain saturated triglycerides	
Triheptanoin 620-67-7	Triheptanoin is the triester of glycerin and heptanoic acid. It conforms to the formula 	skin conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Tricaprylin 538-23-8	Tricaprylin is the triester of glycerin and caprylic acid. It conforms to the formula: 	fragrance ingredient; skin conditioning agent – occlusive
Tricaprin 621-71-6	Tricaprin is the triester of glycerin and capric acid. It conforms to the formula: 	fragrance ingredient; skin conditioning agent – occlusive
Triundecanoin 13552-80-2	Triundecanoin is the triester of glycerin and undecanoic acid. It conforms to the formula: 	hair conditioning agent; skin conditioning agent – occlusive

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;|CIR Staff]

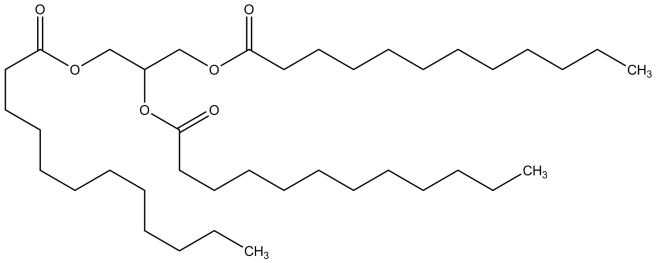
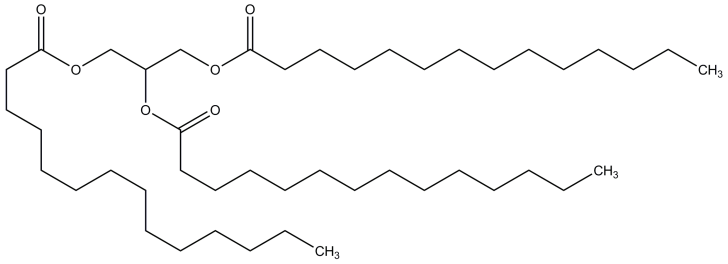
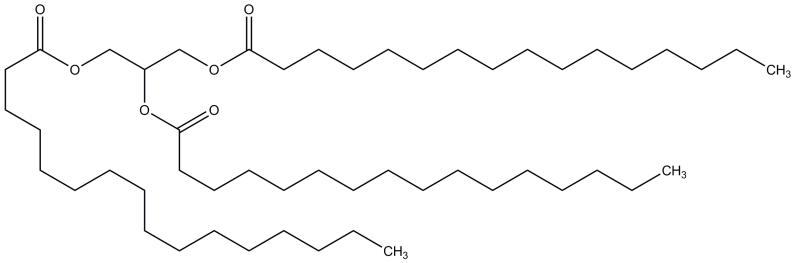
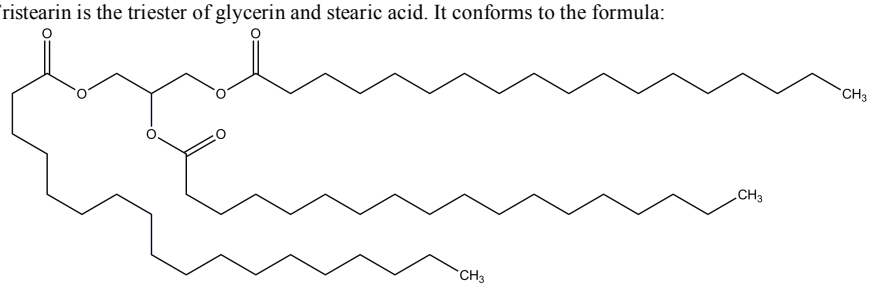
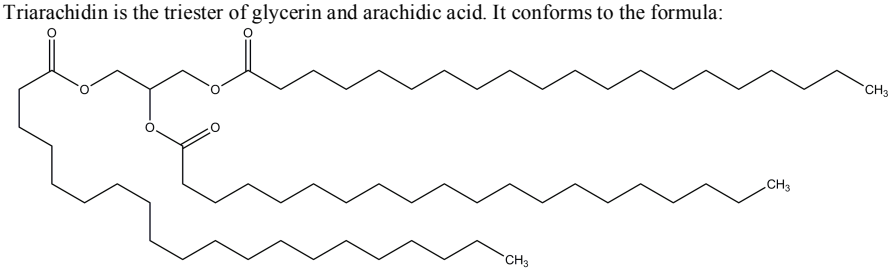
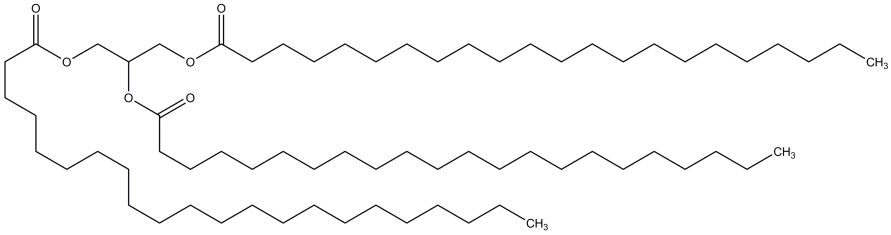
Ingredient/CAS No.	Definition & Structure	Function(s)
Trilaurin 538-24-9	Trilaurin is the triester of glycerin and lauric acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trimyristin 555-45-3	Trimyristin is the triester of glycerin and myristic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Tripalmitin 555-44-2	Tripalmitin is the triester of glycerin and palmitic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Tristearin 555-43-1	Tristearin is the triester of glycerin and stearic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triarachidin 620-64-4	Triarachidin is the triester of glycerin and arachidic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Tribehenin 18641-57-1	Tribehenin is the triester of glycerin and behenic acid. It conforms to the formula: 	skin conditioning agent – occlusive

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;|CIR Staff]

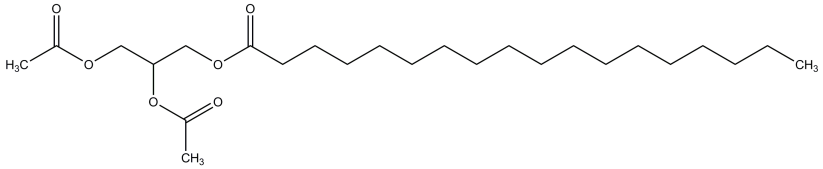
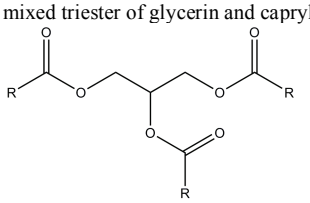
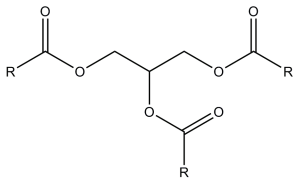
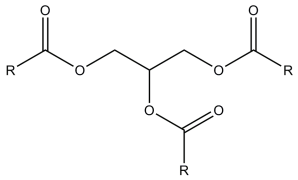
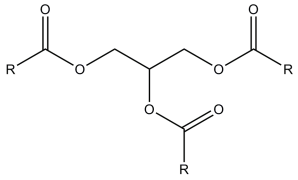
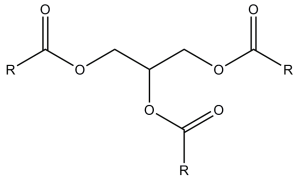
Ingredient/CAS No.	Definition & Structure	Function(s)
	Linear, mixed chain length saturated triglycerides	
Glyceryl Stearate Diacetate 84931-78-2	Glyceryl Stearate Diacetate is the organic compound that conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Caprylic/Capric Triglyceride 65381-09-1 73398-61-5	Caprylic/Capric Triglyceride is the mixed triester of glycerin and caprylic and capric acids.  [wherein RC(O)- is the residue of caprylic (C8) or capric (C10) acid.]	fragrance ingredient; skin conditioning agent – occlusive; solvent
Caprylic/Capric/Lauric Triglyceride 123465-33-8	Caprylic/Capric/Lauric Triglyceride is the mixed triester of glycerin with caprylic, capric and lauric acids.  [wherein RC(O)- is the residue of caprylic (C8), capric (C10), or lauric (C12) acid.]	skin conditioning agent – occlusive
C8-12 Acid Triglyceride	C8-12 Acid Triglyceride is the triester of glycerin and a mixture of saturated acids containing 8 to 12 carbons in the alkyl chain.  [wherein RC(O)- is the residue of a fatty acid 8, 10, or 12 carbons in length]	skin conditioning agent – occlusive; solvent; viscosity increasing agent - nonaqueous
Caprylic/Capric/Myristic/ Stearic Triglyceride	Caprylic/Capric/Myristic/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric, myristic and stearic acids.  [wherein RC(O)- is the residue of caprylic, capric, myristic or stearic acid.]	skin conditioning agent – occlusive
Caprylic/Capric/Palmitic/ Stearic Triglyceride	Caprylic/Capric/Palmitic/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric, palmitic and stearic acids.  [wherein RC(O)- is the residue of caprylic, capric, palmitic or stearic acid.]	skin conditioning agent – occlusive

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;[CIR Staff]]

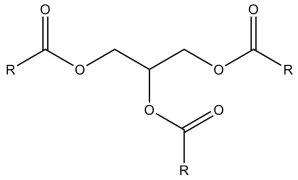
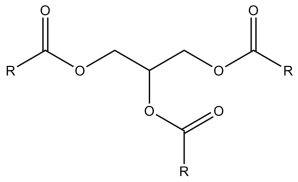
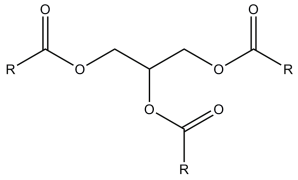
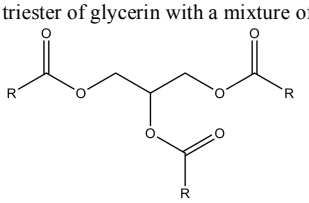
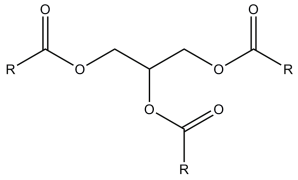
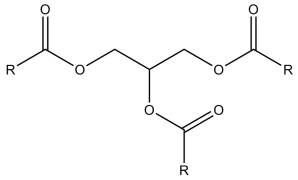
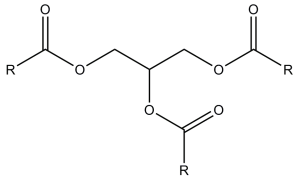
Ingredient/CAS No.	Definition & Structure	Function(s)
Caprylic/Capric/Stearic Triglyceride	Caprylic/Capric/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric and stearic acids.  [wherein RC(O)- is the residue of caprylic, capric, or stearic acid.]	skin conditioning agent – occlusive
C10-18 Triglycerides 85665-33-4	C10-18 Triglycerides is the triester of glycerin and a mixture of normal and branched chain C10-18 fatty acids.  [wherein RC(O)- is the residue of a fatty acid 10, 12, 14, 16, or 18 carbons in length]	skin conditioning agent – occlusive; solvents
C12-18 Acid Triglyceride	C12-18 Acid Triglyceride is the triester of glycerin and a synthetic mixture of saturated acids containing 12 to 18 carbons in the alkyl chain.  [wherein RC(O)- is the residue of a fatty acid 12, 14, 16, or 18 carbons in length]	skin conditioning agent – occlusive; solvent; viscosity increasing agent - nonaqueous
Palmitic/Stearic Triglyceride	Palmitic/Stearic Triglyceride is the triester of glycerin with a mixture of palmitic and stearic acids  [wherein RC(O)- is the residue of palmitic or stearic acid]	viscosity increasing agent - nonaqueous
C18-36 Acid Triglyceride 91052-08-3	C18-36 Acid Triglyceride is the triester of glycerin and C18-36 Acid. It conforms to the formula  [wherein RC(O)- is the residue of a fatty acid 18, 20, 22, 24, 26, 28, 30, 32, 34, or 36 carbons in length]	skin conditioning agent – occlusive
[C18-38 Acid Triglyceride] [not in the *Dictionary*]	[C18-38 Acid Triglyceride is the triester of glycerin and C18-38 acid. It conforms to the formula:]  [wherein RC(O)- is the residue of a fatty acid 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38 carbons in length]	
[Coconut Triglycerides] [T\this name is not in the Dictionary; potentially another name for Cocos Nucifera (Coconut) Oil]	[Coconut Triglycerides is a mixed triester of glycerin derived from coconut.]  [wherein RC(O)- is the residue of a fatty acid derived from coconut]	

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;|CIR Staff]

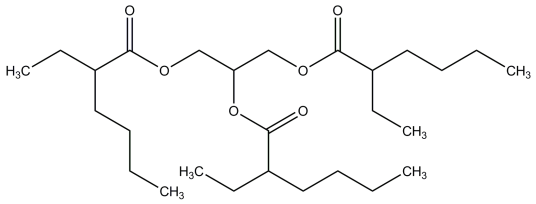
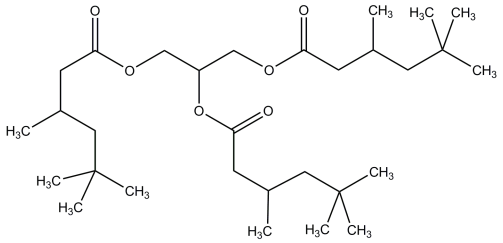
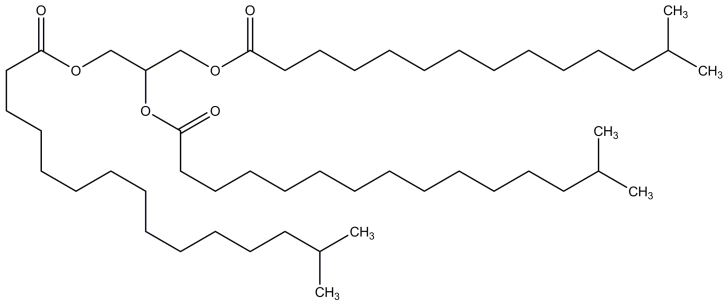
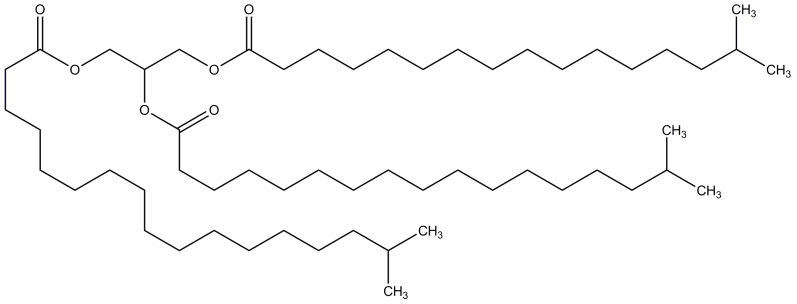
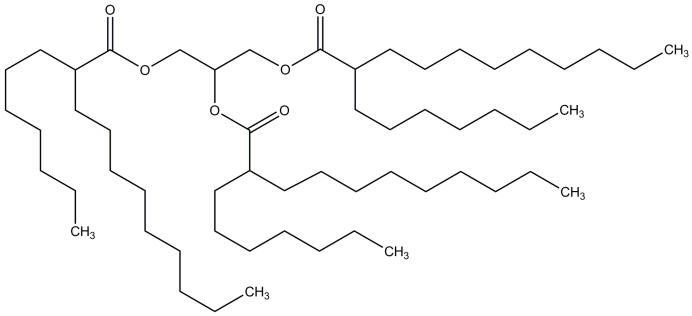
Ingredient/CAS No.	Definition & Structure	Function(s)
	Branched chain triglycerides	
Triethylhexanoin (previously named Trioctanoin) 7360-38-5	Triethylhexanoin is the triester of glycerin and 2-ethylhexanoic acid. It conforms generally to the formula: 	fragrance ingredient; hair conditioning agent; skin conditioning agent – occlusive
Triisononanoin 206354-95-2 56554-53-1	Triisononanoin is the triester of glycerin and a branched chain nonanoic acid. It conforms generally to the formula:  one example of an "iso"	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triisopalmitin 68957-79-9	Triisopalmitin is the triester of glycerin and a 16 carbon branched chain aliphatic acid. It conforms to the formula:  one example of an "iso"	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triisostearin 26942-95-0	Triisostearin is the triester of glycerin and isostearic acid. [It conforms to the structure:]  one example of an "iso"	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triheptylundecanoin 105214-66-2	Triheptylundecanoin is the triester of glycerin and heptylundecanoic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;|CIR Staff]

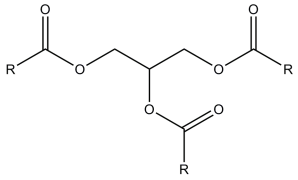
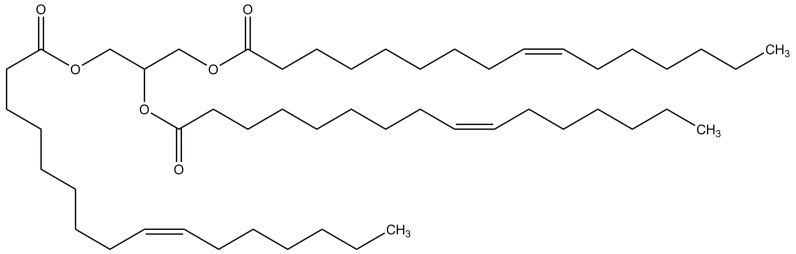
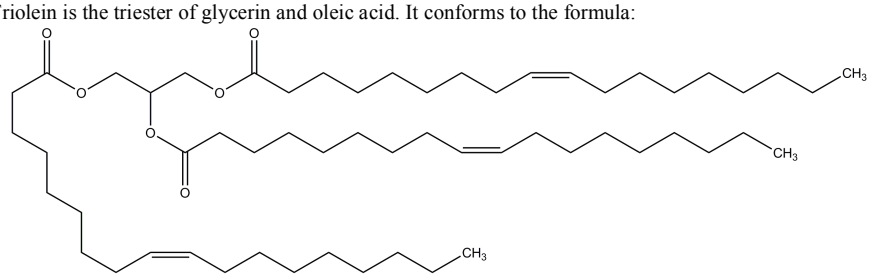
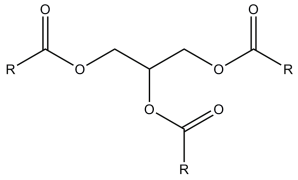
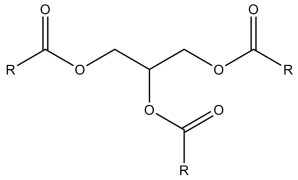
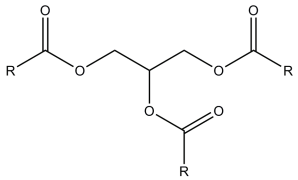
Ingredient/CAS No.	Definition & Structure	Function(s)
	Branched, mixed length chain triglyceride	
C10-40 Isoalkyl Acid Triglyceride	C10-40 Isoalkyl Acid Triglyceride is the triester of glycerin and C10-40 Isoalkyl Acid.  [wherein RC(O)- is the residue of a branched fatty acid 10 to 40 carbons in length]	hair conditioning agent; skin conditioning agent – emollient; viscosity increasing agent - nonaqueous
	Unsaturated chain & hydroxy acid triglycerides	
Tripalmitolein 129784-33-4 20246-55-3	Tripalmitolein is the triester of glycerin and palmitoleic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triolein 122-32-7 6915-08-8	Triolein is the triester of glycerin and oleic acid. It conforms to the formula: 	skin protectant; skin conditioning agent – emollient, occlusive, misc; viscosity increasing agent - nonaqueous
Oleic/Linoleic Triglyceride	Oleic/Linoleic Triglyceride is the mixed triester of glycerin with oleic and linoleic acids.  [wherein RC(O)- is the residue of oleic or linoleic acid]	skin conditioning agent – occlusive
Docosahexenoic/ Docosapentenoic/ Oleic/Palmitic Triglyceride	Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride is the mixed triester of glycerin with docosahexenoic, docosapentenoic, oleic, and palmitic acids.  [wherein RC(O)- is the residue of docosahexenoic, docosapentenoic, oleic, or palmitic acid.]	skin bleaching agent; skin protectant; skin conditioning agent – misc
Isomerized Safflower Glycerides 303101-61-3	Isomerized Safflower Glycerides is the product formed by the esterification of glycerin and isomerized safflower acid.  [wherein RC(O)- is the residue of a fatty acid derived from safflower oil, which is approximately 68% linoleic, 25% oleic, and 2% palmitic][41]	oral health care drug; skin conditioning agent - misc

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;|CIR Staff]

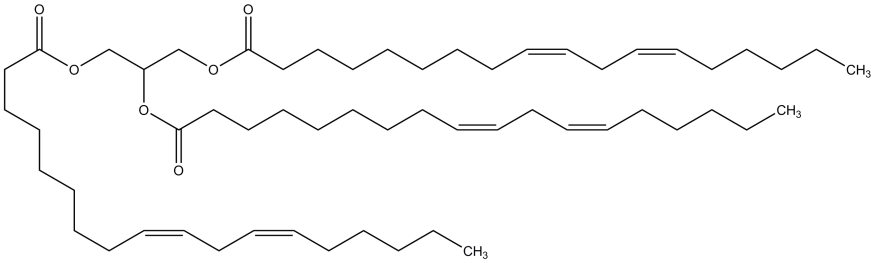
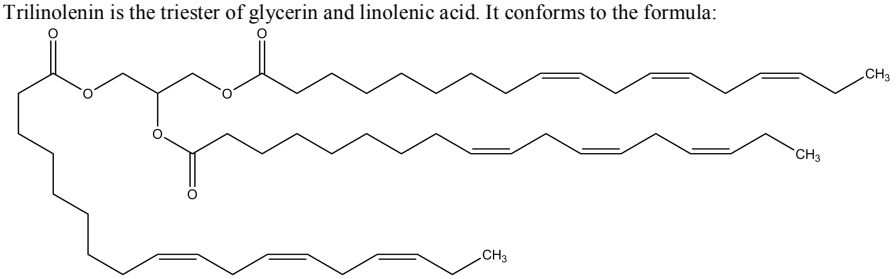
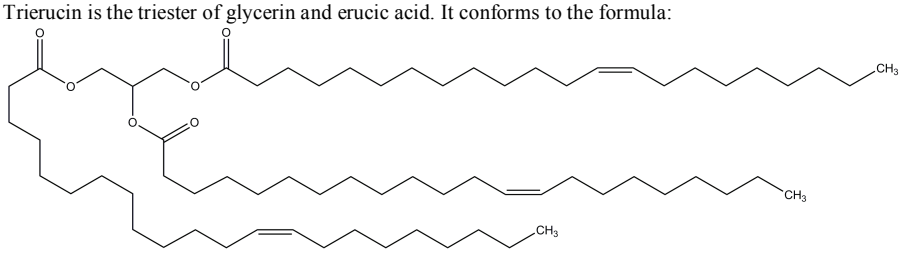
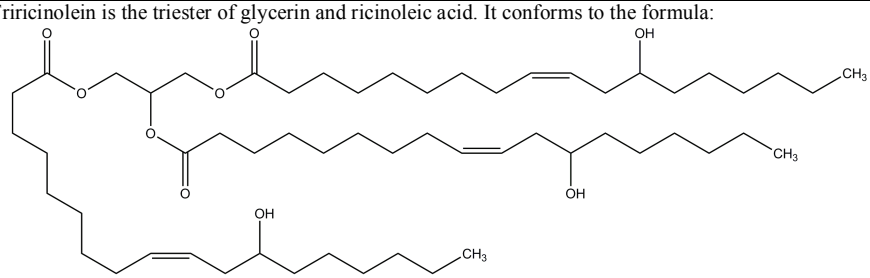
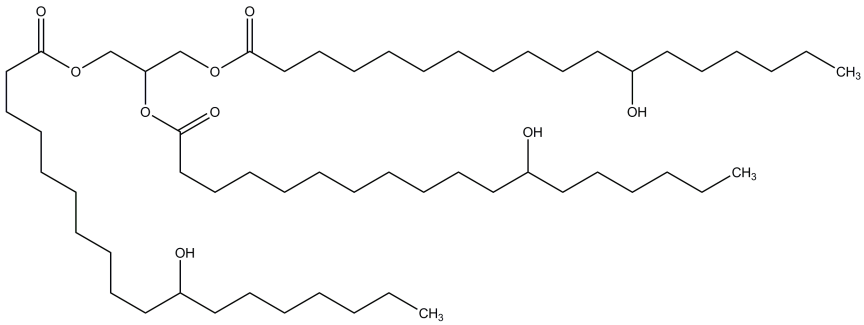
Ingredient/CAS No.	Definition & Structure	Function(s)
Trilinolein 537-40-6	Trilinolein is the triester of glycerin and linoleic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trilinolenin 14465-68-0	Trilinolenin is the triester of glycerin and linolenic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trierucin 2752-99-0	Trierucin is the triester of glycerin and erucic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triricinolein 15505-14-3 2540-54-7	Triricinolein is the triester of glycerin and ricinoleic acid. It conforms to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trihydroxystearin 139-44-6	Trihydroxystearin is the triester of glycerin and hydroxystearic acid. It conforms generally to the formula: 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;|CIR Staff]

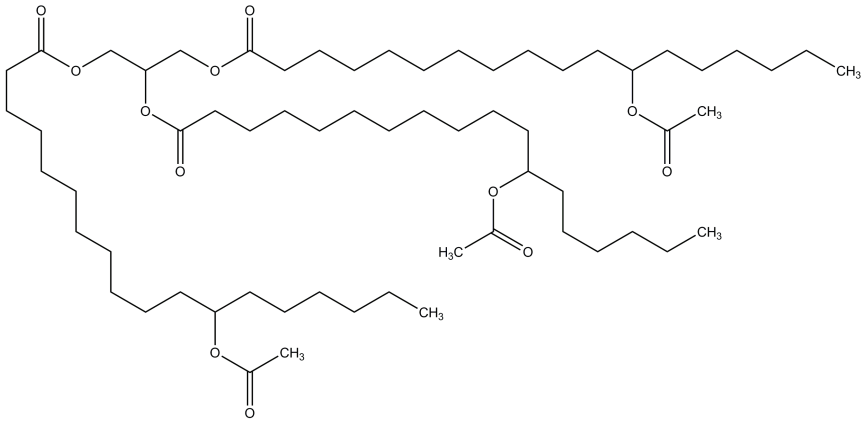
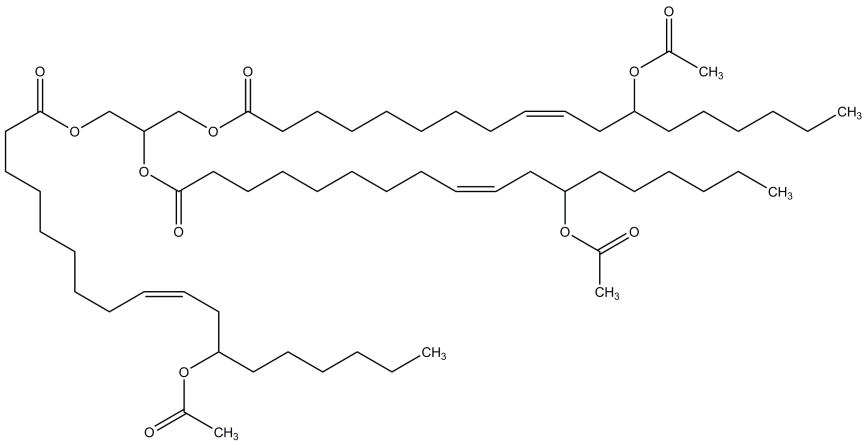
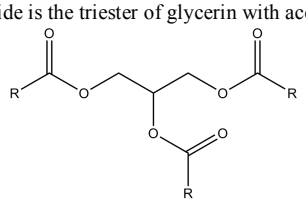
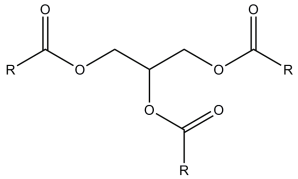
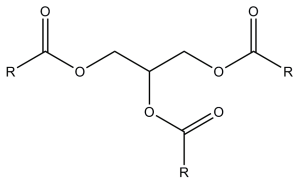
Ingredient/CAS No.	Definition & Structure	Function(s)
	Acetylated hydroxyacid triglycerides	
Glyceryl Triacetyl Hydroxystearate 27233-00-7	Glyceryl Triacetyl Hydroxystearate is the triester of glycerin and acetyl hydroxystearic acid. It conforms to the formula: 	skin conditioning agent - emollient
Glyceryl Triacetyl Ricinoleate 101-34-8	Glyceryl Triacetyl Ricinoleate is the triester of glycerin and acetyl ricinoleic acid. It conforms to the formula: 	skin conditioning agent - emollient
	Mixed chain – others (combinations of length, saturation, and branching variations)	
Acetic/Linoleic/Palmitic Triglyceride 221139-79-3	Acetic/Linoleic/Palmitic Triglyceride is the triester of glycerin with acetic, linoleic and palmitic acids.  [wherein RC(O)- is the residue of acetic, linoleic, or palmitic acid.]	skin conditioning agent – emollient; skin conditioning agent - humectant
Capric/Lauric/Myristic/ Oleic Triglyceride	Capric/Lauric/Myristic/Oleic Triglyceride is the mixed triester of glycerin with caprylic, capric, lauric, myristic and oleic acids.  [wherein RC(O)- is the residue of caprylic, capric, lauric, myristic, or oleic acid.]	skin protectant; skin conditioning agent – emollient; skin conditioning agent - misc
Caprylic/Capric/Linoleic Triglyceride	Caprylic/Capric/Linoleic Triglyceride is the mixed triester of glycerin with caprylic, capric and linoleic acids.  [wherein RC(O)- is the residue of caprylic, capric, or linoleic acid.]	skin conditioning agent - occlusive

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;|CIR Staff]

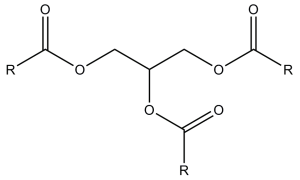
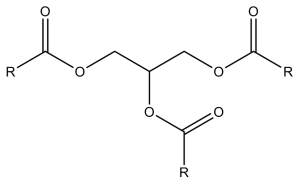
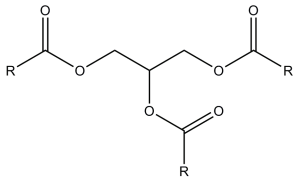
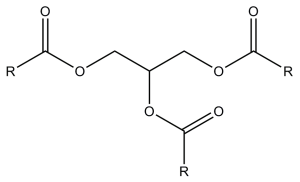
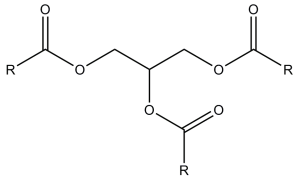
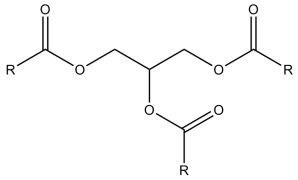
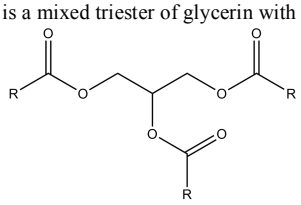
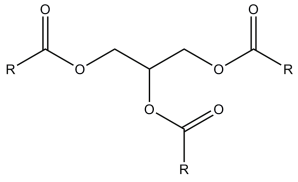
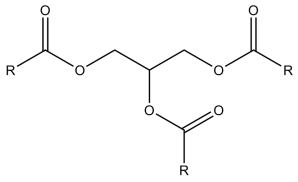
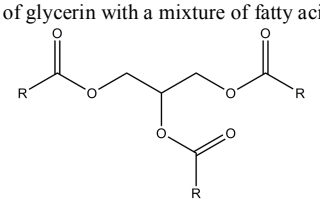
Ingredient/CAS No.	Definition & Structure	Function(s)
Cod Liver/Mink/Tallow Triglyceride	Cod Liver/Mink/Tallow Triglyceride is a mixed triester of glycerin with the fatty acids derived from cod liver oil, mink oil, and tallow  [wherein RC(O)- is the residue of a fatty acid derived from cod liver oil, mink oil (which is approximately 35-41% oleic acid, 17-28% palmitic acid (16/0), 13-17% palmitic acid (16/1), and 11-15% linoleic acid),[42] and tallow (which is approximately 37-43% oleic acid, 24-32% palmitic acid, 20-25% stearic acid, 3-6% myristic acid, and 2-3% linoleic acid)[43]].	skin conditioning agent – emollient; skin conditioning agent - occlusive
Glyceryl Tribehenate/ Isostearate/Eicosandioate 945031-36-7	Glyceryl Tribehenate/Isostearate/Eicosandioate is the triester of glycerin with a mixture of Behenic Acid, Isostearic Acid and eicosandioic acid.  [wherein RC(O)- is the residue of behenic, isostearic and eicosandioic acid.]	skin conditioning agent – emollient
Glyceryl Tri-Hydrogenated Rosinate	Glyceryl Tri-Hydrogenated Rosinate is a triester of glycerin and the partially hydrogenated acids derived from Rosin  [wherein RC(O)- is the residue of the partially hydrogenated acids derived from rosin.].	surfactant – emulsifying agent
Glyceryl Tripalmate/ Palm Kernelate/Olivate/ Macadamiate/ Rapeseedate	Glyceryl Tripalmate/Palm Kernelate/Olivate/Macadamiate/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 RC(O)- is the residue of a fatty acid derived from palm oil (which is approximately 44% palmitic acid, 39% oleic acid, and 10% linoleic acid), palm kernel oil (which is approximately 48% lauric acid, 16% myristic acid, and 15% oleic acid), olive oil (which is approximately 53-86% oleic acid and 7.5-20% palmitic acid,), macadamia oil (which is approximately 50-67% oleic acid, 12-25% palmitoleic acid, and 6-12% palmitic acid), and rapeseed oil (which is approximately 1-59% behenic acid, 12-57% oleic acid, 11-22% linoleic acid, and 8-12.5% linolenic acid)][41]	skin conditioning agent – emollient
Hydrogenated C12-18 Triglycerides	Hydrogenated C12-18 Triglycerides is the end-product of controlled hydrogenation of C12-18 triglycerides.  [wherein RC(O)- is the residue of hydrogenated of C12-18 acids]	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. [7;][CIR Staff]

Ingredient/CAS No.	Definition & Structure	Function(s)
Jojoba Oil/Caprylic/Capric Triglyceride Esters	Jojoba Oil/Caprylic/Capric Triglyceride Esters is the product obtained by the transesterification of Simmondsia Chinensis (Jojoba) Seed Oil with Caprylic/Capric Triglyceride.  [wherein RC(O)- is the residue of caprylic acid, capric acid, and a fatty acid derived from jojoba, which is approximately 83%as combinations of arachidic and behenic acids[44]]	skin protectant; skin conditioning agent – emollient
Lauric/Palmitic/Oleic Triglyceride	Lauric/Palmitic/Oleic Triglyceride is a mixed triester of glycerin with lauric, palmitic and oleic acids.  [wherein RC(O)- is the residue of lauric, palmitic, or oleic acid]	skin conditioning agent – occlusive
Oleic/Palmitic/Lauric/ Myristic/Linoleic Triglyceride	Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride is the mixed triester of glycerin with oleic, palmitic, lauric, myristic and linoleic acids.  [wherein RC(O)- is the residue of oleic, palmitic, lauric, myristic, or linoleic acid]	skin conditioning agent – occlusive
Ricinoleic/Caproic/ Caprylic/Capric Triglyceride	Ricinoleic/Caproic/Caprylic/Capric Triglyceride is the mixed triester of glycerin with ricinoleic, caproic, caprylic and capric acids.  [wherein RC(O)- is the residue of ricinoleic, caproic, caprylic, or capric acid]	skin conditioning agent – occlusive
[Tallow Triglyceride] [not in the *Dictionary*]	Tallow Triglyceride is the triester of glycerin with a mixture of fatty acids derived from tallow.  [wherein RC(O)- is the residue of a fatty acid derived from tallow, which is approximately 37-43% oleic acid, 24-32% palmitic acid, 20-25% stearic acid, 3-6% myristic acid, and 2-3% linoleic acid)[43]].	

Note: ingredients that were previously reviewed are indicated in blue;' ingredients that were found in the VCRP but not the *Dictionary* are indicated in green

Table 3. Previously Reviewed Components and Related Glyceryl Esters

Component	Conclusion	Reference
Glycerin	safe in cosmetics in the present practices of use and concentration	8
Monoglyceryl Monoesters, including Glyceryl Acetate, Glyceryl Arachidate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/ Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Erucate, Glyceryl Ethylhexanoate, Glyceryl Heptanoate, Glyceryl Hydrogenated Rapeseedate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxy-stearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isotridecanoate/Stearate/ Adipate, Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/ Oleate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Oleate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Olivate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Glyceryl Rosinate, Gly-ceryl Stearate , Glyceryl Stearate SE, Glyceryl Stearate/Malate, Glyceryl Tallowate, Glyceryl Undecylenate	safe in the present practices of use and concentration	2
Diglycerides, includes: Glyceryl Dilaurate, Glyceryl Diarachidate, Glyceryl Dibehenate, Glyceryl Dierucate, Glyceryl Dihydroxystearate, Glyceryl Diisopalmitate, Glyceryl Diisostearate, Glyceryl Dilinoleate, Glyceryl Dimyristate, Glyceryl Dioleate, Glyceryl Diricinoleate, Glyceryl Dipalmitate, Glyceryl Dipalmitoleate, Glyceryl Distearate	safe in the present practices of use and concentration, provided the content of 1,2-diesters is not high enough to induce epidermal hyperplasia	9
Acetic Acid	safe in the present practices of use and concentration	45
Caprylic/Capric/Coco Glycerides	safe for use as a cosmetic ingredient	46
Carthamus Tinctorius (Safflower) Seed Oil	safe in the present practices of use and concentration	41
Coconut Acid; Cocos Nucifera (Coconut) Oil	safe for use as a cosmetic ingredient	41
Cocoglycerides; Hydrogenated Coco-Glycerides	safe for use as a cosmetic ingredient	46
Elaeis Guineensis (Palm) Oil; Elaeis Guineensis (Palm) Kernel Oil	safe in the present practices of use and concentration	41
Hydroxystearic Acid	safe as a cosmetic ingredient in the present practices of use	47
Isostearic Acid	safe as a cosmetic ingredient in the present practices of use	47
Lauric Acid	safe in the present practices of use and concentration	48
Macadamia Nut Oil	safe in the present practices of use and concentration	41
Mink Oil	safe in the present practices of use and concentration	42
Myristic Acid Glyceryl Dimyristate Glyceryl Isostearate/Dimyristate	safe in the present practices of use and concentration	49
Oleic Acid	safe in the present practices of use and concentration	48
Olive Acid; Olea Europaea (Olive) Fruit Oil	safe in the present practices of use and concentration	41
Palmitic Acid	safe in the present practices of use and concentration	48
Pelargonic Acid	safe in the present practices of use and concentration	50
Rapeseed Acid; Hydrogenated Rapeseed Oil	safe in the present practices of use and concentration	41
Ricinoleic Acid; Ricinus Communis (Castor) Seed Oil; Hydrogenated Castor Oil	safe in the present practices of use and concentration	51
Simmondsia Chinensis (Jojoba) Seed Oil	safe in the present practices of use and concentration	52
Soy Acid; Hydrogenated Soybean Oil	safe in the present practices of use and concentration	41
Stearic Acid	safe in the present practices of use and concentration	48
Tallow; Tallow Glyceride; Hydrogenated Tallow Glyceride; Tallow Glycerides; Hydrogenated Tallow Glycerides	safe as a cosmetic ingredient in the present practices of use	43

Table 4. Fatty acid composition of MLCT-oil[14]

Fatty Acid	M/L	%*	Fatty Acid	M/L	%*
caprylic acid (C8:0)	M	8.5-9.1	linoleic acid (C18:2)	L	16.1-18.8
capric acid (C10:0)	M	2.7-2.8	linolenic acid (C18:3)	L	5.4-10.3
lauric acid (C12:0)	L	ND	arachidic acid (C20:0)	L	0.4-0.6
myristic acid (C14:0)	L	ND	gadoleic acid (C20:1)	L	0.9-1.2
palmitic acid ((C16:0)	L	3.2-4.0	benenic acid (C22:0)	L	0.2-0.4
palmitoleic acid (C16:1)	L	0.1-0.2	erucic acid (C22:1)	L	0.1-0.3
stearic acid (C18:0)	L	1.6-1.8	lignoceric acid (C24:0)	L	0.1-0.2
oleic acid (C18:1)	L	49.0-54.2	nervonic acid (C24:1)	L	0.1-0.3

*as a percent of the total fatty acid content;
Abbreviations: L – long-chain fatty acid; M – medium-chain fatty acid; ND – not detected

Table 5. Approximate fatty acid composition of a MLCT oil produced from MCT and edible vegetable oil

Fatty Acid	M/L	%*	Chain-length distribution	%*
caprylic acid (C8:0)	M	9.7	L-L-L	55.1
capric acid (C10:0)	M	3.3	L-L-M	35.2
palmitic acid ((C16:0)	L	3.8	L-M-M	9.1
stearic acid (C18:0)	L	1.7	M-M-M	0.6
oleic acid (C18:1)	L	51.2		
linoleic acid (C18:2)	L	18.4		
linolenic acid (C18:3)	L	9.0		
other fatty acids		2.9		

*as a percent of the total fatty acid content;
Abbreviations: L – long-chain fatty acid; M – medium-chain fatty acid

Table 6. Physical and Chemical Properties

	form	molecular weight	melting point (°C)	specific gravity	density	solubility	refractive index	partition coefficient	saponification value	acid value	hydroxyl value
Triheptanoin[28]	liquid	-25			0.964 (at 20°C)	water solubility - <0.05 mg/l		8.86			
Tricaprylin[4]		470.70	10 (stable); -22 (unstable)		0.9540 (at 20°C)	soluble in ethanol, diethyl ether, benzene, chloroform, and ligroin	1.4482 (at 20°C)				
Triundecanoin[4]	colorless to slightly amber liquid or white to off-white, waxy solid					Soluble in petroleum ether, chloroform, and hot alcohol; insoluble in water			265-290	10 max	25 max
Trilaurin[4]	needles (obtained from alcohol as solvent)	638.97	36		0.8986 (at 55°C)	insoluble in water; soluble in alcohol, ether, chloroform, and petroleum either; very soluble in acetone and benzene	1.4404 (at 60°C)		261		
Trimyristin[4]	polymorphic (crystallized from ethanol and diethyl ether)	768.28	56.5 (stable) 32 (unstable)			soluble in ether, acetone, benzene, and chloroform	1.4428 (at 60°C)				
Tripalmitin[4]	needles (obtained from ethanol as solvent)	807.35	66 (stable) 44.7 (unstable)		0.8752 (at 70°C)	soluble in ether, benzene, and chloroform	1.4381 (at 80°C)				
Tristearin[4]		891.51			0.8559 (at 90°C)	soluble in acetone	1.4395 (at 80°C)				
Caprylic/Capric Triglyceride[5]				0.92-0.96 (25°C/25°C)		soluble in ethanol to ~20% by weight	1.4480-1.4510	>3[32]	300-360	0.1 max	5.0 max
Triethylhexanoin[25]	colorless to pale yellow, transparent oily liquid	470	73.03 (estimated)			water solubility – 1.2 x 10^{-7} g/l (at 20°C; calculated)		>6.5[32] 8.98 (calc)			
Triisostearin[4]	Light yellow, oily substance								185-210	3 max	30 max
Triolein[4]	Colorless to yellowish oily liquid polymorphic	885.47	-32[32]		0.8988 (at 60°C)	Practically insoluble in water; slightly soluble in alcohol; soluble in chloro-form, ether, petroleum ether, and carbon tetrachloride	1.4621 (at 40°C)		192-202	5 max	10 max
Trihydroxystearin[1]	white, finely divided powder	939.49	85-86	1.023 (at 25°C)	8.51						

Table 7. Current and historical frequency and concentration of use of triglycerides according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Caprylic/Capric Triglyceride				**Glyceryl Triacetyl Hydroxystearate**			
	2017	**2003**	**2017**	**2003**	**2017**	**1998**	**2015**	**1998**
Totals*	**6000**	**763**	**NS**	**0.00001-84**	**20**	**3**	**1-19.6**	**9**
Duration of Use								
Leave-On	*5403*	*704*	*NS*	*0.00001-84*	*20*	*3*	*1-19.6*	*9*
Rinse-Off	*574*	*59*	*NS*	*0.002-10*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*23*	*NR*	*NS*	*7-78*	*NR*	*NR*	*NR*	*NR*
Eye Area	1063	207	NS	0.008-49	NR	NR	NR	NR
Incidental Ingestion	585	75	NS	0.002-54	20	2	1-19.6	9
Incidental Inhalation-Spray	122; 1446[a]; 1356[b]	30; 150[a]; 104[b]	NS	0.00005-84; 0.0001-19[a]; 0.06-48[b]	NR	1[a]	NR	NR
Incidental Inhalation-Powder	77; 1356[b]; 25[c]	11; 104[b]; 2[c]	NS	0.01-22; 0.06-48[b]; 0.8[c]	NR	NR	NR	NR
Dermal Contact	5195	672	NS	0.00005-84	NR	NR	NR	NR
Deodorant (underarm)	6[b]	1[b]	NS	0.00005-5[b]	NR	NR	NR	NR
Hair - Non-Coloring	161	10	NS	0.00005-18	NR	1	NR	NR
Hair-Coloring	22	1	NS	NR	NR	NR	NR	NR
Nail	17	5	NS	0.2-15	NR	NR	1-19.6	NR
Mucous Membrane	698	75	NS	0.002-78	20	2	NR	9
Baby Products	37	5	NS	0.8	NR	NR	NR	NR
	Glyceryl Triacetyl Ricinoleate				**Tribehenin**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**17**	**32**	**1-49.2**	**8**	**723**	**42**	**0.002-50.6**	**0.31-6**
Duration of Use								
Leave-On	*17*	*32*	*1-49.2*	*8*	*695*	*38*	*0.002-50.6*	*0.31-6*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*28*	*4*	*0.002-7*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	3	NR	27.1-49.2	NR	95	3	0.04-15	0.32
Incidental Ingestion	7	31	1-8	8	249	NR	0.01-5.6	0.38
Incidental Inhalation-Spray	1[a]	NR	NR	NR	9; 77[a]; 53[b]	4[a]; 3[b]	0.002-8[a]	3[a]; 0.38[b]
Incidental Inhalation-Powder	NR	NR	6.3	NR	2; 53[b]; 1[c]	3[b]	0.015-5.4; 0.002-4.8[c]	0.38[b]
Dermal Contact	10	1	6.3.-49.2	NR	409	38	0.002-50.6	0.32-6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	50.6	3-6[b]
Hair - Non-Coloring	NR	NR	NR	NR	28	4	0.015-8	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	4	NR	NR	NR
Mucous Membrane	7	31	1-8	8	255	NR	0.01-7	0.38
Baby Products	NR	NR	NR	NR	1	NR	NR	NR
	Tricaprin[d]				**Tricaprylin**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**51**	**NR**	**0.75**	**NR**	**262** **47[e]**	**70**	**0.0002-12.7**	**0.5-10**
Leave-On	*47*	*NR*	*0.75*	*NR*	*256* *47*	*66*	*0.0002-11*	*0.5-10*
Rinse-Off	*4*	*NR*	*0.75*	*NR*	*6* *NR*	*4*	*0.25-12.7*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR* *NR*	*NR*	*NR*	*NR*
Eye Area	5	NR	NR	NR	111 3	5	2-8	NR
Incidental Ingestion	3	NR	NR	NR	37 11	15	0.035-5	NR
Incidental Inhalation-Spray	6[a]; 17[b]	NR	NR	NR	1; 23[a]; 23[b] 9[a]; 23[b]	10[a]; 6[b]	4.1; 7[a]	2[a]; 2[b]
Incidental Inhalation-Powder	17[B]	NR	0.75[c]	NR	39; 23[a]; 1[c] 23[b]	2; 6[b]	1.5-2.3; 0.0002-7.5[c]	5; 2[b]
Dermal Contact	47	NR	0.75	NR	221 34	51	0.0002-11	0.5-10
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	4 NR	3	0.25-7	NR
Hair-Coloring	NR	NR	0.75	NR	NR 2	NR	12.7	NR
Nail	NR	NR	NR	NR	NR NR	1	NR	NR
Mucous Membrane	3	NR	NR	NR	37 11	15	0.035-5	NR
Baby Products	NR	NR	NR	NR	1 NR	NR	NR	NR

Table 7. Current and historical frequency and concentration of use of triglycerides according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Triethylhexanoin (previously Trioctanoin)				**Triheptanoin**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**601**	**27**	**0.002-100**	**0.1-50**	**26**	**NR**	**4-5.3**	**12-15**
Leave-On	*574*	*25*	*0.002-100*	*0.2-46*	*22*	*NR*	*4-5.3*	*12*
Rinse-Off	*27*	*2*	*0.1-61.1*	*0.1-50*	*4*	*NR*	*NR*	*15*
Diluted for (Bath) Use	*NR*	*NR*	*52.8*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	131	3	0.002-52	2-17	NR	NR	4.5	NR
Incidental Ingestion	116	6	8-63	46	2	NR	5.3	12
Incidental Inhalation-Spray	11[a]; 133[b]	4[a];3[b]	0.035-36; 5[a]	1-8[a]; 3-6[b]	13[a]; 6[b]	NR	NR	NR
Incidental Inhalation-Powder	26; 133[b]	3[b]	0.83-14.7; 0.6-100[c]	3-6[b]	6[b]	NR	4-5[c]	NR
Dermal Contact	481	20	0.002-100	0.1-50	24	NR	4-5	15
Deodorant (underarm)	1[b]	NR	0.8-9	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	0.035-30	0.2--1	NR	NR	NR	NR
Hair-Coloring	NR	NR	10	NR	NR	NR	NR	NR
Nail	1	NR	8-46	3	NR	NR	NR	NR
Mucous Membrane	117	6	8-63	46	3	NR	5.3	12
Baby Products	1	NR	NR	NR	NR	NR	NR	NR
	Trihydroxystearin				**Triisononanoin**			
	2017	**1997**	**2015**	**1997**	**2017**	**1998**	**2015**	**1998**
Totals*	**273**	**41**	**0.01-14.7**	**0.5-5[#]**	**15**	**8**	**1-25.3**	**25**
Leave-On	*238*	*38*	*0.01-14.7*	*NR*	*11*	*8*	*1-25.3*	*25*
Rinse-Off	*35*	*3*	*0.25-6.6*	*NR*	*4*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	80	10	0.3-14.7	NR	NR	NR	NR	NR
Incidental Ingestion	64	6	0.5-8	NR	1	NR	25.3	25
Incidental Inhalation-Spray	11[a]; 8[b]	4[a]; 1[b]	1.5-4[a]	NR	4[a]; 4[b]	1[a]; 6[b]	NR	NR
Incidental Inhalation-Powder	2; 8[b]	4; 1[b]	1-2; 1.7-4[c]	NR	4[b]	6[b]	1-10[c]	NR
Dermal Contact	154	30	0.01-14.7	NR	14	8	1-10	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	24	NR	0.25-4	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	74	6	0.5-8	NR	5	NR	25.3	25
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Triisostearin				**Trilaurin**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**291**	**5**	**0.05-45**	**36**	**125**	**197**	**0.00005-46.3**	**0.003-46**
Leave-On	*290*	*5*	*0.3-45*	*36*	*123*	*195*	*0.00005-46.3*	*0.003-46*
Rinse-Off	*1*	*NR*	*0.05-30*	*NR*	*2*	*2*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*1*
Eye Area	27	1	2-35	NR	107	145	0.2-36.3	0.003-46
Incidental Ingestion	161	4	8.3-45	36	1	14	46.3	0.2-46
Incidental Inhalation-Spray	5[a]; 10[b]	NR	6-30	NR	1; 3[a]; 3[b]	1; 2[a]; 4[b]	NR	0.96-3[a]; 0.4-3[b]
Incidental Inhalation-Powder	12; 10[b]	NR	3-10.4; 2.5-11[c]	NR	3[b]	4[b]	0.00005[c]	0.4-3[b]
Dermal Contact	130	1	0.05-35	NR	124	183	0.00005-36.3	0.003-46
Deodorant (underarm)	NR	NR	NR	NR	5[b]	NR	NR	NR
Hair - Non-Coloring	NR	NR	1-6	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	0.05-3	NR	NR	NR	NR	NR
Nail	NR	NR	45	NR	NR	NR	NR	NR
Mucous Membrane	160	4	0.8-45	36	2	14	46.3	0.2-46
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 7. Current and historical frequency and concentration of use of triglycerides according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Trilinolein				**Trimyristin**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**27**	**2**	**0.005-0.017**	**NR**	**27**	**10**	**0.12-8**	**1-2**
Leave-On	*12*	*2*	*0.005-0.017*	*NR*	*27*	*10*	*0.12-8*	*1-2*
Rinse-Off	*15*	*NR*	*0.005*	*NR*	*NR*	*NR*	*2*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*0.005*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	NR	NR	NR	NR	3	1	0.2-8	2
Incidental Ingestion	NR	NR	0.005	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	4[a]; 1[b]	1[a]	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	1[b]	NR	0.0048-0.017[c]	NR	10	5	0.5[c]	1
Dermal Contact	27	2	0.005-0.017	NR	27	10	0.12	1-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	0.12-8	NR
Hair - Non-Coloring	NR	NR	0.005	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	15	NR	0.005	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Triolein				**Tripalmitin**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**107**	**NR**	**0.005-0.14**	**NR**	**12**	**1**	**0.094-19.3**	**2**
Leave-On	*92*	*NR*	*0.0008-0.14*	*NR*	*10*	*NR*	*0.094-19.3*	*NR*
Rinse-Off	*15*	*NR*	*0.005-0.025*	*NR*	*2*	*1*	*1*	*2*
Diluted for (Bath) Use	*NR*	*NR*	*0.005*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	3	NR	0.005-14	NR	8	NR	0.094-19.3	NR
Incidental Ingestion	68	NR	0.008-0.0053	NR	NR	NR	15.6	NR
Incidental Inhalation-Spray	3[a]; 1[b]	NR	NR	NR	1[b]	NR	NR	NR
Incidental Inhalation-Powder	1[b]	NR	0.0053-0.025[c]	NR	NR	NR	0.7[c]	NR
Dermal Contact	39	NR	0.0005-0.14	NR	12	1	0.094-19.3	2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	0.0005	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	1	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	83	NR	0.005-0.0053	NR	1	NR	15.6	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Tristearin				**Triundecanoin[f]**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**66**	**46**	**0.004-24**	**3**	**4**	**NR**	**1.5**	**NR**
Leave-On	*54*	*42*	*0.004-24*	*3*	*3*	*NR*	*NR*	*NR*
Rinse-Off	*12*	*4*	*NR*	*NR*	*1*	*NR*	*1.5*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	9	22	0.004-24	2	NR	NR	NR	NR
Incidental Ingestion	3	4	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2; 14[a]; 14[b]	2; 3[a]; 5[b]	NR	NR	2[a]; 1[b]	NR	NR	NR
Incidental Inhalation-Powder	14[b]	5[b]	NR	NR	1[b]	NR	NR	NR
Dermal Contact	63	42	0.004-24	0.1-3	4	NR	1.5	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	12	4	NR	NR	NR	NR	1.5	NR
Baby Products	NR	NR	NR	NR	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.
**at the time of the original safety assessment, concentration of use data were not reported by the FDA.
[#] a concentration range was specified, but not details were provided
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays..
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
[d] as Capric Triglyceride in VCRP
[e] as Caprylic Triglyceride in VCRP
[f] as Glyceryl Triundecanoate in VCRP
NR – no reported use
NS – not yet surveyed

Table 8. Frequency (2017) and concentration of use (2015) previously unreviewed triglycerides

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	C12-18 Triglyceride		**C18-36 Triglyceride**		**C18-38 Triglyceride[d]**	
Totals*	**18**	**NS**	**216**	**NS**	**1**	**NS**
Duration of Use						
Leave-On	*18*	*NS*	*216*	*NS*	*1*	*NS*
Rinse-Off	*NR*	*NS*	*NR*	*NS*	*NR*	*NS*
Diluted for (Bath) Use	*NR*	*NS*	*NR*	*NS*	*NR*	*NS*
Exposure Type						
Eye Area	2	NS	92	NS	1	NS
Incidental Ingestion	14	NS	NR	NS	NR	NS
Incidental Inhalation-Spray	1[a]	NS	3; 1[a]; 5[b];	NS	NR	NS
Incidental Inhalation-Powder	1; 1[a]	NS	1[a]	NS	NR	NS
Dermal Contact	4	NS	134	NS	1	NS
Deodorant (underarm)	NR	NS	NR	NS	NR	NS
Hair - Non-Coloring	NR	NS	3	NS	NR	NS
Hair-Coloring	NR	NS	NR	NS	NR	NS
Nail	NR	NS	1	NS	NR	NS
Mucous Membrane	14	NS	NR	NS	NR	NS
Baby Products	NR	NS	NR	NS	NR	NS

	Caprylic/Capric/Lauric Triglyceride		**Caprylic/Capric/Myristic/Stearic Triglyceride**		**Caprylic/Capric/Stearic Triglyceride**	
Totals*	**4**	**NS**	**229**	**NS**	**22**	**NS**
Duration of Use						
Leave-On	4	*NS*	217	*NS*	21	*NS*
Rinse Off	NR	*NS*	12	*NS*	1	*NS*
Diluted for (Bath) Use	NR	*NS*	NR	*NS*	NR	*NS*
Exposure Type						
Eye Area	NR	NS	29	NS	3	NS
Incidental Ingestion	NR	NS	7	NS	1	NS
Incidental Inhalation-Spray	2[a]; 2[b]	NS	1; 156[a]; 18[b]	NS	6; 7[a]; 2[b]	NS
Incidental Inhalation-Powder	2[a]	NS	156[a]	NS	7[a]	NS
Dermal Contact	3	NS	221	NS	18	NS
Deodorant (underarm)	NR	NS	NR	NS	NR	NS
Hair - Non-Coloring	1	NS	1	NS	3	NS
Hair-Coloring	NR	NS	NR	NS	NR	NS
Nail	NR	NS	NR	NS	NR	NS
Mucous Membrane	NR	NS	12	NS	2	NS
Baby Products	NR	NS	NR	NS	NR	NS

	C10-40 Isoalkyl Acid Triglyceride		**Coconut Triglycerides[d]**		**C10-18 Triglyceride**	
Totals*	**1**	**NS**	**7**	**NS**	**93**	**NS**
Duration of Use						
Leave-On	*1*	*NS*	*5*	*NS*	*91*	*NS*
Rinse-Off	*NR*	*NS*	*1*	*NS*	*1*	*NS*
Diluted for (Bath) Use	*NR*	*NS*	*1*	*NS*	*1*	*NS*
Exposure Type						
Eye Area	NR	NS	NR	NS	23	NS
Incidental Ingestion	1	NS	NR	NS	11	NS
Incidental Inhalation-Spray	NR	NS	4[a]; 1[b]	NS	22[a]; 22[b]	NS
Incidental Inhalation-Powder	NR	NS	4[a]	NS	1; 22[a]; 1[c]	NS
Dermal Contact	NR	NS	7	NS	82	NS
Deodorant (underarm)	NR	NS	NR	NS	NR	NS
Hair - Non-Coloring	NR	NS	NR	NS	NR	NS
Hair-Coloring	NR	NS	NR	NS	NR	NS
Nail	NR	NS	NR	NS	NR	NS
Mucous Membrane	1	NS	1	NS	12	NS
Baby Products	NR	NS	NR	NS	1	NS

Table 8. Frequency (2017) and concentration of use (2015) previously unreviewed triglycerides

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Glyceryl Tribehenate/Isostearate/Eicosandioate		**Hydrogenated C12-18 Triglycerides**		**Palmitic/Stearic Triglyceride**	
Totals*	**10**	**NS**	**12**	**NS**	**6**	**NS**
Duration of Use						
Leave-On	*9*	*NS*	*10*	*NS*	*6*	*NS*
Rinse-Off	*1*	*NS*	*2*	*NS*	*NR*	*NS*
Diluted for (Bath) Use	*NR*	*NS*	*NR*	*NS*	*NR*	*NS*
Exposure Type						
Eye Area	6	NS	NR	NS	NR	NS
Incidental Ingestion	NR	NS	NR	NS	NR	NS
Incidental Inhalation-Spray	1[a]; 2[b]	NS	1[a]; 5[b]	NS	2[a]; 3[b]	NS
Incidental Inhalation-Powder	1[a]	NS	1[a]	NS	2[a]; 1[c]	NS
Dermal Contact	7	NS	12	NS	6	NS
Deodorant (underarm)	NR	NS	NR	NS	NR	NS
Hair - Non-Coloring	2	NS	NR	NS	NR	NS
Hair-Coloring	NR	NS	NR	NS	NR	NS
Nail	NR	NS	NR	NS	NR	NS
Mucous Membrane	NR	NS	1	NS	NR	NS
Baby Products	NR	NS	NR	NS	1	NS

	Tallow Triglyceride[d]		**Trilinolenin[e]**		
Totals*	**1**	**NS**	**2**	**NR**	
Duration of Use					
Leave-On	*1*	*NS*	*2*	*NR*	
Rinse-Off	*NR*	*NS*	*NR*	*NR*	
Diluted for (Bath) Use	*NR*	*NS*	*NR*	*NR*	
Exposure Type					
Eye Area	NR	NS	NR	NR	
Incidental Ingestion	NR	NS	NR	NR	
Incidental Inhalation-Spray	NR	NS	2[a]	NR	
Incidental Inhalation-Powder	1	NS	2[a]	NR	
Dermal Contact	NR	NS	2	NR	
Deodorant (underarm)	NR	NS	NR	NR	
Hair - Non-Coloring	NR	NS	NR	NR	
Hair-Coloring	NR	NS	NR	NR	
Nail	NR	NS	NR	NR	
Mucous Membrane	NR	NS	NR	NR	
Baby Products	NR	NS	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] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays..
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
[d] listed in the VCRP, but not the *Dictionary*.
[e] as Linoleic Acid Triglyceride in VCRP
NR – no reported use
NS – not yet surveyed

Table 9. Ingredients not reported to be in use

Acetic/Linoleic/Palmitic Triglyceride	Glyceryl Tri-Hydrogenated Rosinate	Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride
C8-12 Acid Triglyceride	Glyceryl Stearate Diacetate	Ricinoleic/Caproic/Caprylic/Capric Triglyceride
Capric/Lauric/Myristic/Oleic Triglyceride	Glyceryl Tripalmate/Palm Kernelate/Olivate/ Macadamiate/Rapeseedate	Triarachidin
Caprylic/Capric/Linoleic Triglyceride		Trierucin
Caprylic/Capric/Palmitic/Stearic Triglyceride	Isomerized Safflower Glycerides	Triheptylundecanoin
Cod Liver/Mink/Tallow Triglyceride	Jojoba Oil/Caprylic/Capric Triglyceride Esters	Triisopalmitin
Docahexenoic/Docosapentenoic/Oleic/ Palmitic Triglyceride	Lauric/Palmitic/Oleic Triglyceride	Tripalmitolein
	Oleic/Linoleic Triglyceride	Triricinolein

Table 10. Acute Toxicity Studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Procedure	LD_{50}	Reference
DERMAL						
Triheptanoin	rats	5/sex	none	24 h semi-occlusive patch with 2 g/kg	>2 g/kg	[28]
Tristearin	rats	5/sex	corn oil	24 h semi-occlusive patch with 2 g/kg	>2 g/kg	[29]
ORAL						
Triheptanoin	NMRI mice	5 males	none	5 g/kg by gavage	>5 g/kg	[28]
Triethylhexanoin	rats	not provided	not provided	not specified	>48 g/kg	[32]
Triisostearin	Swiss mice	5 females	none	2 g/kg by gavage	>2 g/kg	[30]
Triisostearin	Sprague-Dawley rats	5/sex	none	2 g/kg by gavage	>2 g/kg	[30]
Triolein	Wistar rats	5/sex	none	2 g/kg by gavage	>2 g/kg	[31]
MLCT (see Table 5)	Wistar rats	5/sex	none	5 g/kg MLCT oil or mixed rapeseed and soybean oils (7:3; control) by gavage	>5 g/kg	[13]

Abbreviations: MCT – medium-chain triglycerides; MLCT – medium- and long-chain triacylglycerol

Table 11. Short-Term, Subchronic, and Chronic Oral Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
SHORT-TERM TOXICITY STUDIES							
ANIMAL							
Caprylic/Capric Triglyceride, 33% (v/v)	Han-Wistar rats, 3/sex	28 days (1/sex was dosed for 32 days)	water	0 or 3.12 g/kg	animals were dosed orally (assumed by gavage), 1x/day, with a dose volume of 10 ml/kg	no clinical signs of toxicity were observed; no differences in clinical pathology parameters, cytochrome P450 induction, or gross or microscopic lesions were observed	33
Caprylic/Capric Triglyceride	Han-Wistar rats, 15/sex	28 days	none	undiluted	Animals were dosed daily by gavage (dose vol 0.5 and 2 ml/kg/day) Controls were dosed with 0.5% carboxy-methylcellulose/0.1% Tween 80 in water (2 ml/kg/day) Ten animals/sex were killed at the termination of dosing; a recovery group of 5 animals/sex were killed after a subsequent 4-wk non-treatment period	Soft and/or mucoid stools were observed in 12 male and 11 female test animals Absolute and relative thymic weights were decreased in males and females without histological alterations; histopathology revealed increased alveolar histio-cytosis with focal interstitial inflammation in lungs in 5/10 test males and 7/10 test females, compared to 1/10 male and 1/10 female controls; all effects were reversible during the recovery period Statistically significant changes noted in clinical chemistry and urinalysis parameters were reversible	34
Caprylic/Capric Triglyceride	Göttingen mini-pigs; 3/sex	6 wks	none	undiluted; 0.5 or 2 ml/kg/day	Animals were dosed daily by gavage Controls were dosed with 0.5% methyl-cellulose/0.1% Tween 80 in water (2 ml/kg/day)	0.5 and 2 ml/kg/day: transient tremors, abnormal feces color, and increased triglycerides. 2 ml/kg/day: also, reduced motor activity, decreased food intake, respiratory signs (2/6 animals) and in-creased total and LDL-cholesterol; at necropsy, the lung of 3/6 animals presented abnormal color and/or irregular surface correlated with a chronic bronchio-lo-alveolar inflammation (attributed by the research-ers to aspiration pneumonia) No changes in organ weights or gross or microscopic lesions were observed, and no toxicologically-rele-vant changes in hematology or urinalysis parameters were noted	35
MCT	Wistar rats, 10 males/group	30 days	none	10.2 – 20.1 g/kg bw/day	animals were dosed once daily by gavage, in accord with OECD TG 407	NOAEL = 10 mg/kg bw/day reduced food consumption, softened feces, ruffled fur were observed in the high dose group during the first days of the study	36
MLCT (see Table 5)	Wistar rats; 20 males/group	6 wks	none	diet containing 7% MLCT or rapeseed oil (control) (equiv to 3500 mg/kg/day)	6-wk dietary study	NOAEL = 3500 mg/kg/day no adverse effects were observed feed consumption, total carcass protein, and serum cholesterol values were statistically significantly in-creased; total body fat was statistically significantly decreased	13
HUMAN							
MLCT (see Table 5)	20 healthy males and females	4 wks		bread containing MLCT or mixed rapeseed and soybean oils (7:3; controls); 42 g/day	placebo-controlled double blind study	no adverse effects	13

Table 11. Short-Term, Subchronic, and Chronic Oral Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
SUBCHRONIC TOXICITY STUDIES							
MCT	Wistar rats, 20/sex	90 days	none	10,000 and 50,000 ppm	dietary study, in accord with OECD TG 408	NOAEL = 50,000 ppm no signs of systemic toxicity; all animals survived until study termination; no effects on body weight gain, hematology, clinical chemistry, urinalysis, or gross pathology	[36]
MCT	Beagle dogs, 4/sex	91 days	dry dog food with beef tallow	0, 5, 10, and 15%	3-h feeding regimen for the course of the study	NOAEL = 15% No toxicologically-significant clinical signs of toxicity; no mortality; no test article-related changes in hematology parameters; some changes in clinical chemistry parameters may have been related to the test article; decreased urine volume with increased specific gravity was reported in the mid- and high-dose group	[37]
CHRONIC TOXICITY STUDIES							
oil consisting of: 64% Triheptanoin 34% diheptanoin 2% monoheptanoin	Wistar rats, 10 males	9 mos	AIN3 diet	control diet with either 30% or 50% substitution of soybean oil with test oil	animals were exposed to *ad* libitum; controls were fed A"IM3 diet	no toxic effects were observed	[38]

Abbreviations: MCT – medium-chain triglycerides; MLCT – medium- and long-chain triacylglycerol; NOAEL – no-observable adverse effect level; OECD – Organisation for Economic Cooperation and Development; TG – test guideline

Table 12. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Tristearin	5000 µg/plate	95% ethanol	*S. typhimurium* TA1535, TA1537, TA98, TA100	Ames test, in accord with OECD TG 471, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[29]
Caprylic/Capric Triglyceride	not stated	not stated	not stated	Ames test	negative	[32]
Triethylhexanoin	50-5000 µg/plate	DMSO	*S. typhimurium* TA1535, TA1537, TA98, TA100, TA102	Ames test, in accord with OECD TG 471, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[25]
Triethylhexanoin	7.5-4000 µg/ml	ethanol	human lymphocytes	mammalian chromosomal aberration assay, in accord with OECD TG 473; with and without metabolic activation; solvent and appropriate positive controls were tested	negative	[25]
Triisonanoin	50-5000 µg/plate	acetone	*S. typhimurium* TA1535, TA1537, TA98, TA100 *Escherichia coli* WP2uvrA	Ames test, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[40]
Triisonanoin	10-320 µg/ml	acetone	cultured peripheral human lymphocytes	chromosomal aberration assay, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[40]
Triisonanoin	5-80 µg/ml	acetone	mouse lymphoma L5178Y cells	mammalian cell gene mutation assay, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[40]
lipid emulsion comprised of soybean oil, MCTs, olive oil, and fish oil	not provided	not provided	*S. typhimurium*	Ames test (details not provided)	negative	[27]
lipid emulsion comprised of soybean oil, MCTs, olive oil, and fish oil	not provided	not provided	human lymphocytes	chromosomal aberration assay (details not provided)	negative	[27]
lipid emulsion comprised of soybean oil, MCTs, olive oil, and fish oil	not provided	not provided	V79 cells	HPRT gene mutation assay (details not provided)	negative	[27]
MLCT (see Table 5)	313-5000 µg/plate	sodium phosphate buffer	*S. typhimurium* TA1535, TA1537, TA98, TA100 *E. coli* WP2uvrA	Ames test, with and without metabolic activation; solvent and appropriate positive controls were used	negative	[13]
IN VIVO						
lipid emulsion comprised of soybean oil, MCTs, olive oil, and fish oil	not provided	not provided	rats	bone marrow cytogenic study (details not provided)	negative	[27]

Abbreviations: DMSO – dimethyl sulfoxide; HPRT - hypoxanthine phosphoribosyl transferase; MCT – medium-chain triglycerides; MLCT – medium- and long-chain triacylglycerol; OECD – Organisation for Economic Cooperation and Development; TG – test guideline

Table 13. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO		
Triisonanoin	undiluted, 10 µl	EpiSkin™ reconstructed human epidermis model	EPISKIN™ in vitro test, in accord with OECD TG 439; appropriate negative and positive controls were used	predicted to be not irritating	[40]
			ANIMAL		
Triheptanoin	undiluted, 0.5 ml	White Russian rabbits, 6 male	4- h semi-occlusive patches were applied to a 6 cm^2 area performed in accord with OECD TG 404	mean erythema score – 2.22/4; mean edema score – 1.94/4 30-60 min: very slight to well-defined erythema in all animals 24-72 h: moderate to severe erythema and severe edema with brown discolorations and dryness, with sanguineous lacerations and scaling in 1 animal 72 h: 1 animal showed moderate redness of the skin, with dry skin and severe extensive subcutaneous hemorrhage 6 days: scaling was observed in all animals 10-14 days: all animals were normal	[28]
Triheptanoin	undiluted, 0.5 ml	NZW rabbits, 3 males	4- h semi-occlusive patches were applied in accord with OECD TG 404	1 h: very slight and slight erythema in 1 and 2 animals, respectively. 24 h: very slight edema in one of the latter animals very slight and slight erythema in 2 and 1 animals, respectively. 48 h: very slight edema in the latter. 48 and 72 h: very slight erythema in 2 animals, with very slight edema in one	[28]
Triheptanoin	100% for induction and challenge	female Dunkin Hartley guinea pigs, 20 test animals and 10 controls	Buehler test using occlusive patches at induction and challenge	not a sensitizer	[28]
Tristearin	undiluted, 0.5 ml	NZW rabbits, 3 males	4- h semi-occlusive patches were applied to a 6 cm^2 area in accord with OECD TG 404	not irritating no erythema or edema were observed	[29]
Tristearin	50% in petrolatum for induction and challenge	Dunkin Hartley guinea pigs, 20 test animals and 10 controls	Buehler test using occlusive patches at induction and challenge	not a sensitizer	[29]
Caprylic/Capric Triglyceride	undiluted, 0.5 ml	NZW rabbits, 6	4-h semi-occlusive patches	not irritating no erythema or edema were observed	[36]
C8-C12 Acid Triglycerides	undiluted, 0.5 ml	albino rabbits, 3	24-, 48-, and 72-h semi-occlusive application using pieces of soaked "Molton" in accord with OECD TG 404; the application site was 2.5 cm x 2.5 cm	not irritating no erythema or edema were observed	[36]
Triisonanoin	25 and 50% in acetone/oil (4:1 v/v), and undiluted	CBA mice, 4 females	LLNA in accord with OECD TG 429	negative at 25 and 50% (SI = 2.1 and 2.16, respectively) positive at 100% (SI = 4.27); may cause sensitization EC_3 = 70	[40]
Triisostearin	concentration and vehicle not stated	NZW rabbits, 3 males	4- h semi-occlusive patches were applied to a 6 cm^2 area in accord with OECD TG 404	1 and 24 h: well-defined erythema observed in 3/3 animals 48 h: slight erythema persisted in 2/3 animals 72 h: erythema cleared completely no edema was observed in any animal at any time point	[30]
			HUMAN		
Triolein	not stated	human subjects; number not stated	chamber test; details not provided	not a sensitizer	[32]

Abbreviations: LLNA – local lymph node assay; NZW – New Zealand White; OECD – Organisation for Economic Cooperation and Development; SI – stimulation index; TG – test guideline

Table 14. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO		
Triisononanoin	undiluted, 30 µl	HCE model	In vitro eye irritation test using the SkinEthic™ reconstructed model	predicted to be non-irritating	40
			ANIMAL		
Triheptanoin	undiluted, 0.1 ml	rabbits, 3 males	24 h instillation into one eye	non-irritating	28
Tristearin	undiluted, 0.1 ml	rabbits, 3 males	24 h instillation into one eye in accord with OECD TG 405	non-irritating any effects observed were resolved by day 6	29
Caprylic/Capric Triglyceride	undiluted, 0.1 ml	NZW rabbits, 6	single instillation into one eye; 72-h observation period	non-irritating	36
C8-C12 Acid Triglyceride	undiluted, 0.05 ml	albino rabbits, 3	6 instillations were made on 6 consecutive days; animals were observed for 10 days	non-irritating	36
Triisostearin	concentration and vehicle not stated	NZW rabbits, 3 males	24 h instillation into one eye in accord with OECD TG 405	non-irritating any effects observed were resolved within 48 h	30

Abbreviations: HCE - Human Corneal Epithelium; NZW - New Zealand White; OECD – Organisation for Economic Cooperation and Development; TG – test guideline

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Final Report on the Safety Assessment of Trihydroxystearin[1]

Trihydroxystearin is the triester of glycerin and hydroxystearic acid. It is used as a skin conditioning agent, a solvent, and as a viscosity increasing agent in cosmetic formulations at concentrations up to 5%. In acute oral toxicity studies in rats, no deaths were reported at a dose of 5 g/kg. Trihydroxystearin was reported to be a mild ocular irritant, but not a skin irritant in animal tests. Ames test results indicate that the ingredient is not mutagenic. Clinical testing found no skin irritation. Although the data on Trihydroxystearin are limited, the Cosmetic Ingredient Review (CIR) Expert Panel had previously conducted a safety assessment of Glyderyl Stearate and Hydroxystearic Acid. These data indicate no mutagenic, carcinogenic, or teratogenic effects in animals, and no irritation or sensitization in clinical tests. The data on these two ingredients are considered relevant to the assessment of Trihydroxystearin because of the chemical similarity of the ingredients. The data on Glyceryl Stearate and Hydroxystearic Acid are also consistent with the limited data that are available on Trihydroxystearin itself. Therefore, based on the available animal and clinical data in this report, which includes study summaries from earlier safety assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate/SE, the Expert Panel concludes that Trihydroxystearin is safe as used in cosmetic formulations.

INTRODUCTION

Trihydroxystearin is the triester of glycerin and hydroxystearic acid that is used as a skin-conditioning agent—occlusive, a solvent, and a viscosity increasing agent—nonaqueous in cosmetics. Although safety test data were not found in the published literature for this ingredient, unpublished data were provided and are described in this report. In addition, the Cosmetic Ingredient Review (CIR) Expert Panel considered that data on Hydroxystearic Acid and Glyceryl Stearate are relevant to the safety assessment of Trihydroxystearin. Hydroxystearic Acid is one of the chemical building blocks of Trihydroxystearin. Glyceryl Stearate is the esterification product of glycerine and stearic acid, making it closely related to Trihydroxystearin. Both Hydroxystearic Acid (Andersen 1999) and Glyceryl Stearate (Elder 1982) were previously reviewed by the Expert Panel and found to be safe as used in cosmetic products. A summary of the findings of each of those reports is provided in the summary section. The Panel relied upon those findings in this safety assessment.

CHEMISTRY

Chemical And Physical Properties

Trihydroxystearin (CAS No. 139-44-6) is the triester of glycerin and hydroxystearic acid that conforms generally to the formula shown in Figure 1 (Wenninger, Canterbery, and McEwen 2000).

Other names for this chemical are as follows: Glyceryl Tri(12-Hydroxystearate; 12-Hydroxyoctadecanoic Acid, 1,2,3-Propanetriyl Ester; Octadecanoic Acid, 12-Hydroxy-, 1,2,3-Propanetriyl Ester; and 1,2,3-Propanetriol Tri(12-Hydroxystearate) (Wenninger, Canterbery, and McEwen 2000); and Glycerol, Tris(12-Hydroxyoctadecanoate); Octadecanoic Acid, 12-Hydroxy-, triester with glycerol; 12-Hydroxystearic Acid Triglyceride; Glycerol 12-Hydroxystearate; Glycerol Tris(12-Hydroxystearate); Glyceryl Tris(12-Hydroxystearate); and Tri-12-Hydroxystearin (Scientific & Technical Information Network International 1996a).

Trihydroxystearin has a formula weight of 939.49 and a melting point of 86°C (Scientific & Technical Information Network International 1996b). Properties of two commercial grades of Trihydroxystearin are summarized in Tables 1 and 2, respectively. The commercial grade noted in Table 2 (Thixcin® E) is another grade of Thixcin® R that has a larger particle size (Rheox, Inc. 1996a).

Methods Of Production

One method of production of Trihydroxystearin involved the hydrogenation of castor oil, in the presence of the reagent nickel, at a temperature of 200°C. Another method of production is the reduction of triricinolein (Scientific & Technical Information Network International 1996b).

Reactivity

Regarding the reactivity of Trihydroxystearin, sources of ignition and strong oxidizers should be avoided (Rheox, Inc. 1995b; 1996b).

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Wilbur Johnson, Senior Scientific Analyst, prepared this report.

Address correspondence to him at Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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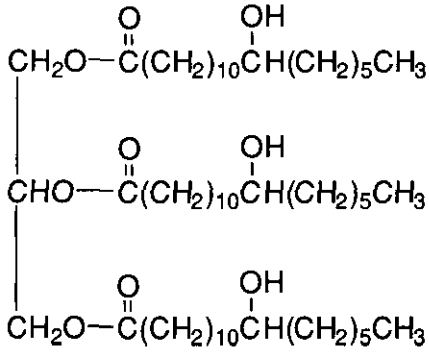

FIGURE 1
Chemical formula for Trihydroxystearin (Wenninger, Canterbery, and McEwen 2000).

USE

Purpose in Cosmetics

Trihydroxystearin has the following functions in cosmetics: Skin-conditioning agent—occlusive; solvent; and viscosity increasing agent—nonaqueous (Wenninger, Canterbery, and McEwen 2000)

Scope and Extent of Use in Cosmetics

United States

The product formulation data submitted to the Food and Drug Administration (FDA) in 1997 indicated that Trihydroxystearin was used in as many as 41 cosmetic product formulations (Table 3) (FDA 1997).

Concentration of use values are no longer reported to FDA by the cosmetics industry (FDA 1992). However, 1984 product formulation data submitted to the FDA indicated that the highest reported use concentration range for Trihydroxystearin was 5% to 10% (FDA 1984). Current concentration of use data indicate that Trihydroxystearin is typically used at concentrations of 0.5% to 5.0% (Rheox, Inc. 1996a).

Cosmetic products containing Trihydroxystearin are applied to the skin, hair, and most parts of the body, and could come in contact with the ocular and nasal mucosae. These products could be used on a daily basis, and have the potential for being applied frequently over a period of several years.

TABLE 1
Properties of Trihydroxystearin—THIXCIN® R (Rheox, Inc. 1995a)

Property	Description
Composition	An organic derivative of castor oil
Form and color	Finely divided white powder
Specific gravity, 250°C/250°C	1.023
Density, 250°C, lb/U.S. gal	8.51
Bulking value, U.S. gal/lb	0.1175
Melting point, °C	86
Fineness, through No. 200 sieve, %	99.8 min
Ash content, %	None
Processing temperature, °F	95–130 (35°–55°C)
Recommended solvent	Aliphatic only

TABLE 2
Properties of Trihydroxystearin—THIXCIN® E (Rheox, Inc. 1994)

Property	Description
Color	White
Form	Finely divided powder
Melting point, °C	85
Density (lbs./U.S. gallon)	8.51
Passing #200 screen, %	100
Ash content	None
Specific Gravity at 25°C	1.023

TABLE 3
Product formulation data on Trihydroxystearin (FDA 1997)

Product category	Total no. of formulations in category	Total no. containing ingredient
Eye shadow	501	1
Eye makeup remover	80	1
Mascara	158	5
Other eye makeup preparations	116	3
Blushers (all types)	229	1
Face powders	245	4
Foundations	283	9
Lipstick	758	6
Makeup bases	125	1
Body and hand skin care preparations (excluding shaving preparations)	776	1
Moisturizing skin care preparations	743	2
Paste masks (mud packs)	247	2
Other skin care preparations	683	3
Suntan gels, creams, and liquids	134	1
Other suntan preparations	43	1
1997 Totals		**41**

International

Trihydroxystearin is listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci 1997). This ingredient, which conforms to the specifications of the *Japanese Cosmetic Ingredients Codex*, has precedent for use without restriction in most CLS categories. It is not used in the following four CLS categories: eyeliner, lip, oral, and bath preparations.

Trihydroxystearin also is not included among the substances listed as prohibited from use in cosmetic products marketed in the European Union (European Economic Community 1995).

Noncosmetic Use

Trihydroxystearin has been used as a thickening agent for peanut butter (Elliger, Guadagni, and Dunlap 1972). FDA has listed the following indirect food additive uses in the Code of Federal Regulations (CFR): components of adhesives (21 CFR 175.105), components of resinous and polymeric coatings (21 CFR 175.300), components of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170), components of paper and paperboard in contact with dry food (21 CFR 176.180), defoaming agents used in the manufacture of paper and paperboard (21 CFR 176.210), cellophane (21 CFR 177.1200), closures with sealing gaskets for food containers (21 CFR 177.1210), polyester resins cross-linked (21 CFR 177.2420), and textiles and textile fibers (21 CFR 177.2800).

Trihydroxystearin is among the inert ingredients that are exempt from the requirement of a tolerance under the Federal Food, Drug, and Cosmetic Act when used in pesticide formulations that are applied to crops (FDA 1975).

TOXICOLOGY

Acute Oral Toxicity

The acute oral toxicity of Trihydroxystearin (Thixcin® R) was evaluated using 10 Wistar-derived, young albino rats (5 males, 5 females; weights = 200–300 g). The animals were fasted prior to administration of a single oral dose (intragastric intubation) of 5 g/kg. The test substance was administered as a 25% corn oil solution. Dosing was followed by a 14-day nontreatment period. The LD_{50} was not achieved at the administered dose of 5 g/kg; no deaths were reported (Food and Drug Research Laboratories, Inc. 1975a). Identical results were reported in another study in which Trihydroxystearin (Thixcin® E, another grade of Thixcin® R) was administered to 10 albino rats (same weights) according to the same procedure (Food and Drug Research Laboratories, Inc. 1975b).

Ocular Irritation

The ocular irritation potential of Trihydroxystearin (Thixcin® R) was evaluated using six young adult, albino rabbits according to the procedure described in 16 CFR 1500.42. The test substance (0.1 ml or 0.1 g) was instilled into the conjunctival sac of one eye of each animal. Untreated eyes served as controls. Reactions were scored at 24, 48, and 72 hours and at 7 days postinstillation according to the Draize scale: 0 to 110. Ocular irritation (score = 1) was observed in five rabbits, and all reactions cleared during the 7-day observation period. It was concluded that Trihydroxystearin (Thixcin® R) was a mild, transient ocular irritant (Food and Drug Research Laboratories, Inc. 1975c). Identical results were reported in another study in which Trihydroxystearin (Thixcin® E) was instilled into the conjunctival sac of the eyes of six albino rabbits according to the same experimental procedure (Food and Drug Research Laboratories, Inc. 1975d).

Skin Irritation

The skin irritation potential of Trihydroxystearin (Thixcin® R) was evaluated using six adult albino rabbits. The test substance (0.5 ml or 0.5 g) was applied to shaved and abraded sites, respectively, on the back of each animal. An occlusive patch was applied to each test site for 24 hours; reactions were scored at the time of patch removal. Erythema was observed at intact and abraded sites on one animal, and only at the abraded site in another; edema was not observed. It was concluded that Trihydroxystearin (Thixcin® R) was not irritating to the skin of rabbits (primary irritation index = 0.17) (Food and Drug Research Laboratories, Inc. 1975e). Identical results were reported in another study in which Trihydroxystearin (Thixcin® E) was applied to six albino rabbits according to the same test procedure (Food and Drug Laboratories, Inc. 1975f).

GENOTOXICITY

The mutagenicity of Trihydroxystearin (Thixcin® R) was evaluated in the Ames test (Ames, McCann, and Yamasaki 1975) using the following strains of *Salmonella typhimurium*: TA 1535, TA 1537, TA 1538, TA 98, and TA 100. Two independent mutation tests were conducted. The test substance (suspension in ethanol) was tested at concentrations of 3, 10, 33, 100, 333, and 1000 μg per plate with and without metabolic activation. Control cultures were treated with ethanol and the following substances served as positive controls: 2-Aminoanthracene, sodium azide, 9-aminoacridine, and 2-nitrofluorene. Except for sodium azide (dissolved in sterile, ultrapure water), all positive controls were dissolved in DMSO. 2-Aminoanthracene served as the positive control for metabolically activated cultures, and the remaining chemicals served as positive controls for cultures without metabolic activation. The results noted in the positive-control cultures were within the normal ranges expected for each bacterial strain and activation condition. Vehicle-control values were generally within the normal ranges experienced at the testing facility and reported in the literature for the bacterial strains tested. Thixcin® R was not toxic or mutagenic, with or without metabolic activation, to any of the bacterial strains when tested (in ethanol) to the limit of its solubility over the range

of concentrations tested. Precipitation of the test substance was noted at a concentration of 1000 μg/plate (Inveresk Research International Limited 1995).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

The skin irritation potential of Trihydroxystearin (Thixcin® R) was evaluated using 106 subjects (17 males, 89 females; ages = 11–65). Three subjects did not complete the study (reasons not stated). An occlusive patch containing a small amount of the test substance (volume not stated) was applied either to the inner aspect of the upper arm or to the back of each subject. Patches (secured with occlusive tape) remained in place for 48 hours. Reactions were scored 48 and 72 hours after patch removal according to the Schwartz-Peck scale: 0 (no erythema) to 4+ (erythema and edema with vesiculation and ulceration). Skin irritation was not observed in any of the 103 subjects who completed the study. It was concluded that Trihydroxystearin (Thixcin® R) is not a primary irritant as long as the conditions of contact do not exceed those indicated in this study (Food and Drug Research Laboratories, Inc. 1975g). The results were identical for the same 103 subjects patch-tested with Trihydroxystearin (Thixcin® E) according to the same test procedure (Food and Drug Research Laboratories, Inc. 1975 h).

SUMMARY

Hydroxystearic Acid Report (Andersen 1999)

Hydroxystearic Acid is a fatty acid that is used as a surfactant–cleansing agent in cosmetic products. One method of production involves the catalytic hydrogenation of castor oil.

Product formulation data submitted to FDA in 1996 indicated that Hydroxystearic Acid was used in two cosmetic products categorized as body and hand skin care preparations (excluding shaving preparations).

In male rats fed a diet containing hydrogenated castor oil, Hydroxystearic Acid was deposited in abdominal fat, as well as other body lipids, along with its metabolites (hydroxypalmitic acid, hydroxymyristic acid, and hydroxylauric acid). Hydroxystearic Acid has also been detected in the feces of twelve subjects who presumably ate a normal mixture of foods.

Reduced growth rate was noted in rats fed diets containing 8.7% and 17.3% 12-Hydroxystearic Acid, but not in rats fed 4.3% Hydroxystearic Acid, in a 90-day subchronic oral toxicity study. The results of a second 90-day experiment (no reduction in growth rate) confirmed that the reduction in growth rate previously observed was due to the lower caloric density of diets consisting of 8.7% and 17.3% Hydroxystearic Acid. In both experiments, the results of hematological and microscopic evaluations were unremarkable.

In an in vitro study, Hydroxystearic Acid interfered with oxidative phosphorylation in rat liver mitochondria. Oxidative phosphorylation was uncoupled and mitochondria were damaged.

Hydroxystearic Acid was not mutagenic in strains TA1535, TA100, TA1537, TA1538, and TA98 of *S. typhimurium*. However, Hydroxystearic Acid was classified as mutagenic in strain Hs30 of *Escherichia coli*.

Hydroxystearic Acid was not mutagenic in the L5178Y TK+/− mouse lymphoma assay, with or without metabolic activation; nor did it produce chromosome aberrations in Chinese hamster ovary cells, with or without metabolic activation.

In an 18-month carcinogenicity study (subcutaneous study), Hydroxystearic Acid was classified as tentatively carcinogenic in Swiss-Webster mice. Subcutaneous sarcomas were observed at the site of injection in 9 of the 28 mice (14 per dose group) that were alive at 6 months. All of the sarcomas were observed in the low-dose group (total dose of 4 mg delivered in a total of 8 ml tricaprylin for 80 weeks). The high dose group received a total dose of 80 mg delivered in a total of 8 ml of tricaprylin.

In a second study in which nine A/He male mice received a total intraperitoneal dose of 60 mg Hydroxystearic Acid over a period of 4 weeks, the frequency of lung tumors was within the spontaneous occurrence.

The dermal teratogenicity of two antiperspirant prototype formulations containing 7% Hydroxystearic Acid was evaluated using two groups of 30 Charles River Crl:CD VAF/Plus female rats. There were no test article-related or statistically significant differences in the incidence of fetal malformations or fetal developmental variations between experimental and control groups. Skin irritation reactions, however, were observed in greater than 50% of the dams in both experimental groups. No deaths were reported during the study.

Skin irritation reactions to each of three antiperspirant prototype formulations, each containing 7% Hydroxystearic Acid, were observed in a human primary irritation patch test using 35 volunteers. Semiocclusive patches produced reactions in as many as nine of the subjects, whereas occlusive patches produced reactions in as many as 17 individuals. Only two reactions were noted in the semiocclusive patch controls and only one in the occlusive patch controls. Although the formulations reportedly contained the same concentration of Hydroxystearic Acid, there were small differences in the numbers of individuals reacting to each.

Glyceryl Stearate Report (Elder 1982)

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 waxlike 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% to 50%; Glyceryl Stearate/SE is used in over 200 cosmetic products at concentrations of ≥0.1% to 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 a Generally Recognized as Safe (GRAS) ingredient, an indirect food additive, a direct food additive, and as an over-the-counter (OTC) substance.

In acute oral toxicity studies in rats, Glyceryl Stearate and Glyceryl Stearate/SE at concentrations up to 100% were mildly toxic. In chronic studies, 15% to 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 2 years developed renal calcifications.

Glyceryl Stearate and Glyceryl Stearate/SE at concentrations of up to 100% were mildly irritating or nonirritating to the skin of rabbits. In subchronic and chronic dermal toxicity tests, 4% to 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 into the conjunctival sac of the eyes of rabbits.

Glyceryl Stearate, fed to mice in doses of 50 to 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.

Results of single and repeated insult patch tests (RIPTs) used to evaluate human skin irritation and sensitization potential of Glyceryl Stearate and Glyceryl Stearate/SE confirmed that both ingredients were nonsensitizing and nonirritating. Glyceryl Stearate was tested at concentrations up to 20% in RIPTs. Products containing 2% Glyceryl Stearate were nonphototoxic and nonphotoallergenic. Worker experience was that Glyceryl Stearate and Glyceryl Stearate/SE are nonirritating to human skin.

Trihydroxystearin

Trihydroxystearin is the triester of glycerin and hydroxystearic acid that is used as a skin-conditioning agent—occlusive, a solvent, and a viscosity increasing agent—nonaqueous in cosmetics. According to one source, the typical use concentration range for this ingredient (marketed as Thixcin® R and Thixcin® E grades that differ only in particle size) in cosmetics is 0.5% to 5.0%. Frequency of use data submitted to FDA in 1997 indicated that Trihydroxystearin has been used in as many as 41 cosmetic products.

In acute oral toxicity studies in which Trihydroxystearin (Thixcin® R and Thixcin® E grades) was tested using albino rats, the LD_{50} was not achieved at a dose of 5 g/kg and no deaths were reported.

Trihydroxystearin (Thixcin® R and Thixcin® E grades tested) was classified as a mild, transient ocular irritant in albino rabbits, but was not irritating to the skin of albino rabbits in 24-hour occlusive patch tests.

Ames test results indicated that Trihydroxystearin (Thixcin® R grade) was not mutagenic to the following *S. typhimurium* strains, with or without metabolic activation, when tested at concentrations ranging from 3 to 1000 μg/plate: TA1535, TA1537, TA1538, TA98, and TA100.

In 48-hour occlusive patch tests, Trihydroxystearin (Thixcin® R and Thixcin® E grades tested) did not induce skin irritation in any of the 103 subjects tested.

DISCUSSION

Although the data on Trihydroxystearin are limited, the CIR Expert Panel had previously conducted a safety assessment of Glyceryl Stearate and Hydroxystearic Acid. These data indicate *no mutagenic, carcinogenic, or teratogenic effects in animals,* and no irritation or sensitization in clinical tests. The data on these two ingredients is considered relevant to the assessment of Trihydroxystearin because of the chemical similarity of the ingredients. The data on Glyceryl Stearate and Hydroxystearic Acid are also consistent with the limited data that are available on Trihydroxystearin itself.

During the open, public comment period on the Tentative Report, a comment was made regarding the absence of sensitization data. The CIR Expert Panel agrees that data on sensitization potential are important in assessing the safety of an ingredient. In this case, there are data on a related ingredient. When tested at concentrations up to 20.0% in human RIPTs involving a large number of subjects, Glyceryl Stearate was neither an irritant nor a sensitizer. Thus, in the absence of sensitization data on Trihydroxystearin, it was concluded that this ingredient is not likely a sensitizer based on data on a chemically similar ingredient. All of the available data suggest that Trihydroxystearin and its component chemical species are safe as used in cosmetic formulations.

CONCLUSION

Based on the available animal and clinical data in this report, *which includes study summaries from CIR Safety* Assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate/SE, the Expert Panel concludes that Trihydroxystearin is safe as used in cosmetic formulations.

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[2]Available for review from Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

Final Report on the Safety Assessment of Trilaurin, Triarachidin, Tribehenin, Tricaprin, Tricaprylin, Trierucin, Triheptanoin, Triheptylundecanoin, Triisononanoin, Triisopalmitin, Triisostearin, Trilinolein, Trimyristin, Trioctanoin, Triolein, Tripalmitin, Tripalmitolein, Triricinolein, Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, Glyceryl Triacetyl Ricinoleate, and Glyceryl Stearate Diacetate[1]

Triesters of glycerin and aliphatic acids, known generically as glyceryl triesters and specifically as Trilaurin, etc., are used in cosmetic products as occlusive skin-conditioning agents and/or nonaqueous viscosity-increasing agents. Hundreds of glyceryl triesters are used in a wide variety of cosmetic products at concentrations ranging from a few tenths of a percent to 46%. Glyceryl triesters are also known as triglycerides; ingested triglycerides are metabolized to monoglycerides, free fatty acids, and glycerol, all of which are absorbed in the intestinal mucosa and undergo further metabolism. Dermal absorption of Triolein in mice was nil; the oil remained at the application site. Only slight absorption was seen in guinea pig skin. Tricaprylin and other glyceryl triesters have been shown to increase the skin penetration of drugs. Little or no acute, subchronic, or chronic oral toxicity was seen in animal studies unless levels approached a significant percentage of caloric intake. Subcutaneous injections of Tricaprylin in rats over a period of 5 weeks caused a granulomatous reaction characterized by oil deposits surrounded by macrophages. Dermal application was not associated with significant irritation in rabbit skin. Ocular exposures were, at most, mildly irritating to rabbit eyes. No evidence of sensitization or photosensitization was seen in a guinea pig maximization test. Most of the genotoxicity test systems were negative. Tricaprylin, Trioctanoin, and Triolein have historically been used as vehicles in carcinogenicity testing of other chemicals. In one study, subcutaneous injection of Tricaprylin in newborn mice produced more tumors in lymphoid tissue than were seen in untreated animals, whereas neither subcutaneous or intraperitoneal injection in 4- to 6-week-old female mice produced any tumors in another study. Trioctanoin injected subcutaneously in hamsters produced no tumors. Trioctanoin injected intraperitoneally in pregnant rats was associated with an increase in mammary tumors in the offspring compared to that seen in offspring of untreated animals, but similar studies in pregnant hamsters and rabbits showed no tumors in the offspring. One study of Triolein injected subcutaneously in rats showed no tumors at the injection site. As part of an effort to evaluate vehicles used in carcinogenicity studies, the National Toxicology Program conducted a 2-year carcinogenicity study in rats given Tricaprylin by gavage. This treatment was associated with a statistically significant dose-related increase in pancreatic acinar cell hyperplasia and adenoma, but there were no acinar carcinomas, the incidence of mononuclear leukemia was less, and nephropathy findings were reduced, all compared to corn oil controls. Overall, the study concluded that Tricaprylin did not offer significant advantages over corn oil as vehicles in carcinogenicity studies. Trilaurin was found to inhibit the formation of neoplasms initiated by dimethylbenzanthracene (DMBA) and promoted by croton oil. Tricaprylin was not teratogenic in mice or rats, but some reproductive effects were seen in rabbits. A low level of fetal eye abnormalities and a small percentage of abnormal sperm were reported in mice injected with Trioctanoin as a vehicle control. Clinical tests of Trilaurin at 36.3% in a commercial product applied to the skin produced no irritation reactions. Trilaurin, Tristearin, and Tribehenin at 40%, 1.68%, and 0.38%, respectively, in commercial products were also negative in repeated-insult patch tests. Tristearin at 0.32% in a commercial product induced transient, mild to moderate, ocular irritation after instillation into the eyes of human subjects. Based on the enhancement of penetration of other chemicals by skin treatment with glyceryl triesters, it is recommended that care be exercised in using them in cosmetic products. On the basis of the available data, the following 23 glyceryl triesters are considered safe as used in cosmetics: Trilaurin, Triarachidin, Tribehenin, Tricaprin, Tricaprylin, Trierucin, Triheptanoin, Triheptylundecanoin, Triisononanoin, Triisopalmitin, Triisostearin, Trilinolein, Trimyristin, Trioctanoin, Triolein, Tripalmitin, Tripalmitolein, Triricinolein, Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, Glyceryl Triacetyl Ricinoleate, and Glyceryl Stearate Diacetate. Some of these are not currently in use, but would be considered safe if used at concentrations similar to those glyceryl triesters that are in use as cosmetic ingredients.

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

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INTRODUCTION

The safety of glyceryl triesters, triesters of glycerin and aliphatic acids, is reviewed in this report. These ingredients are used mostly as skin-conditioning agents—occlusive and/or viscosity-increasing agents—nonaqueous in cosmetic products.

Of the ingredients reviewed in this safety assessment, toxicity data are available only on Trilaurin, Triarachidin, Tribehenin, Tricaprylin, Trierucin, Triisostearin, Trilinolein, Trioctanoin, Triolein, Tripalmitin, and Tristearin. Only 11 ingredients in this safety assessment are being used in cosmetics, including Tribehenin, Triisononanoin, Triisostearin, Trilaurin, Trilinolein, Trimyristin, Trioctanoin, Tripalmitin, Tristearin, Glyceryl Triacetyl Hydroxystearate, and Glyceryl Triacetyl Ricinoleate.

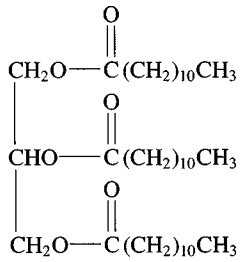
Information is available on the constituent chemicals and on related cosmetic ingredients. Glycerin is classified as a generally recognized as safe (GRAS) food ingredient based on a literature review published in 1973 (Informatics, Inc., 1973). The Cosmetic Ingredient Review (CIR) Expert Panel concluded that the glyceryl triesters Caprylic/Capric Triglyceride (Elder 1980), and Trihydroxystearin (CIR 1997) are safe in the present practices of use and concentration in cosmetics.

CHEMISTRY

Chemical and Physical Properties

Physical and chemical properties of Trilaurin and other glyceryl triesters are included in Table 1. Trilaurin has a saponification value of 261 (Mattson, Baur, and Beck 1951). Descriptions/specifications for cosmetic grade glyceryl triesters are included in Table 2.

Trilaurin (CAS No. 538-24-9) is the triester of glycerin and lauric acid that conforms generally to the formula (Wenninger and McEwen 1997):



It has also been defined as a crystalline glyceride synthesized from palm-nut, coconut, and bayberry oils (Grant 1972). Other names (Wenninger and McEwen 1997; Scientific & Technical

TABLE 1
Physical and chemical properties of Glyceryl Triesters

Properties	Trilaurin*	Tricaprylin**	Trimyristin**	Triolein**	Tripalmitin**	Tristearin**
Form	Needles (obtained from alcohol as solvent)	—	Polymorphic (crystallized from ethanol and diethyl ether)	Polymorphic	Needles obtained from ethanol as solvent	—
Molecular weight	638.97	470.70	768.28	885.47	807.35	891.51
Dipole moment	2.59 D					
Boiling point(s)	15°C, 35°C, and 46.4°C	233.1°C	311°C	235–240°C	310–320°C	—
Melting point	36°C	10°C (stable); −22°C (unstable)	56.5°C (stable); 32°C (unstable)	—	66°C (stable); 44.7°C (unstable)	55°C (α); 73°C (β)
Density	0.8986 at 55°C	0.9540 (density of liquid at 20°C relative to density of water at 4°C)	0.08848 (density of liquid at 60°C relative to density of water at 4°C)	0.8988 g/ml at 60°C	0.8752 (density of liquid at 70°C relative to density of water at 4°C)	0.8559 (density of liquid at 90°C relative to density of water at 4°C)
Refractive index	1.4404 at 60°C	1.4482 at 20°C	1.4428 at 60°C	1.4621 at 40°C	1.4381 at 80°C	1.4395 at 80°C
Solubility	Insoluble in water; soluble in alcohol, ether, chloroform, and petroleum ether; very soluble in acetone and benzene	Soluble in ethanol, diethyl ether, benzene, chloroform, and ligroin (volatile, flammable fraction of petroleum)	Soluble in ether, acetone, benzene, and chloroform	Soluble in ether, chloroform, and petroleum ether	Soluble in ether, benzene, and chloroform	Soluble in acetone

*STN International (1997b, 1997c).
**Lide and Frederikse (1993).

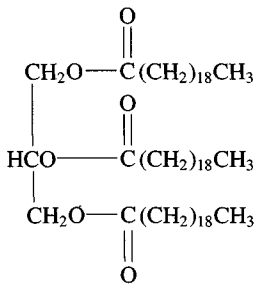
TABLE 2
Descriptions/specifications of Glyceryl Triesters

Properties	Triolein (Nikitakis and McEwen 1990)	Triundecanoin (Nikitakis and McEwen 1990)	Triisostearin (CTFA 1998a)
Form	Colorless to yellowish oily liquid with a slight characteristic odor and taste	Colorless to slightly amber liquid or white to off-white, waxy solid, depending on ambient temperature	Light yellow, oily substance with a faint, characteristic odor
Acid value	5 maximum	10 maximum	Not more than 3
Saponification value	192 to 202	265 to 290	185 to 210
Hydroxyl value	10 maximum	25 maximum	Not more than 30
Moisture	0.3% maximum	—	—
Loss on drying	—	—	Not more than 1%
Residue on ignition	—	—	Not more than 0.5 g
Identification	Positive: Close match to a standard IR spectrum with no indication of foreign materials	Positive: Close match to a standard IR spectrum with no indication of foreign materials	—
Solubility	Practically insoluble in water; slightly soluble in alcohol; soluble in chloroform, ether, and carbon tetrachloride	Soluble in petroleum ether, chloroform, and hot alcohol; insoluble in water	—

Information Network [STN] International 1997a) for this chemical include:

- Dodecanoic Acid, 1,2,3-Propanetriyl Ester
- Glyceryl Trilaurate
- 1,2,3-Propanetriol Tridodecanoate
- Laurin, Tri-
- Glycerin Tridodecanoate
- Glycerin Trilaurate
- Glycerol Trilaurate
- Glyceryl Tridodecanoate
- Lauric Acid Triglyceride
- Lauric Acid Triglycerin Ester
- Lauric Triglyceride
- Tridodecanoin
- Tridodecanoyl Glycerol
- Trilauroylglycerol

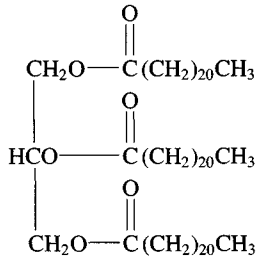
Triarachidin (CAS No. 620-64-4) is the triester of glycerin and arachidic acid (q.v.) that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for Triarachidin include:

- Eicosanoic Acid, 1,2,3,-Propanetriyl Ester
- Glyceryl Triarachidate
- 1,2,3-Propanetriol Trieicosanoate

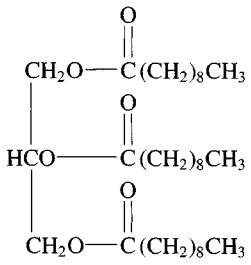
Tribehenin (CAS No. 18641-57-1) is a cream-colored solid with a faint odor (Unichema International 1992). It is the triester of glycerin and behenic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names for Tribehenin include:

- Behenic Acid, 1,2,3-Propanetriyl Ester
- Docosanoic Acid, 1,2,3-Propanetriyl Ester
- Glyceryl Tribehenate
- 1,2,3-Propanetriol Tridocosanoate (Wenninger and McEwen 1997)

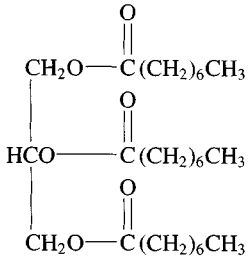
Tricaprin (CAS No. 621-71-6) is the triester of glycerin and capric acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for this chemical include:

- Decanoic Acid, 1,2,3-Propanetriyl Ester
- 3,6,9,12,15,18,21,24,27,30-Decaoxadotriacontan-1-ol, 32-[4-(1,1,3,3,-Tetramethylbutyl)Phenoxy]-
- Glyceryl Tricaprate
- Glyceryl Tridecanoate
- 1,2,3-Propanol Tridecanoate

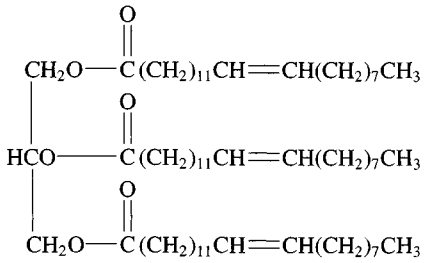
Tricaprylin (CAS No. 538-23-8) is the triester of glycerin and caprylic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Unichema International 1996; Wenninger and McEwen 1997) for Tricaprylin include:

- Caprylic Acid, 1,2,3-Propanetriyl Ester
- Glyceryl Tricaprylate
- Octanoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Trioctanoate
- Glycerol Trioctanoate

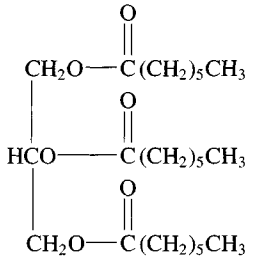
Trierucin (CAS No. 2752-99-0) is the triester of glycerin and erucic acid that conforms to the following formula:



Other names (Wenninger and McEwen 1997) for this chemical include:

- 13-Docosenoic Acid, 1,2,3-Propanetriyl Ester
- Glyceryl Trierucate
- 1,2,3-Propanetriol Tri(13-Docosenoate)

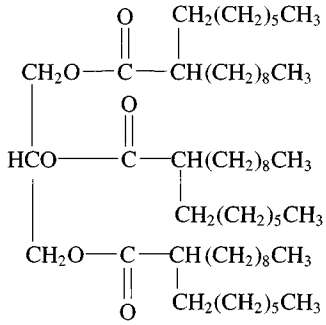
Triheptanoin (CAS No. 620-67-7) is the triester of glycerin and heptanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for Triheptanoin include:

- Glyceryl Triheptanoate
- Heptanoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Triheptanoate

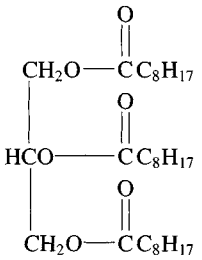
Triheptylundecanoin (CAS No. 105214-66-2) is the triester of glycerin and heptylundecanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for this chemical include:

- Glyceryl Triheptylundecanoate
- 2-Heptylundecanoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Triheptylundecanoate
- Triheptylundecanoic Acid, 1,2,3-Propanetriyl Ester
- Undecanoic Acid, 2-Heptyl-, 1,2,3-Propanetriyl Ester

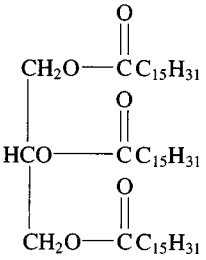
Triisononanoin is the triester of glycerin and a branched-chain nonanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for this chemical include:

- 1,2,3-Propanetriol Triisononoate
- Isononanoic Acid, 1,2,3-Propanetriyl Ester

Triisopalmitin (CAS No. 68957-79-9) is the triester of glycerin and a 16-carbon branched-chain aliphatic acid that conforms to the following formula (Wenninger and McEwen 1997):



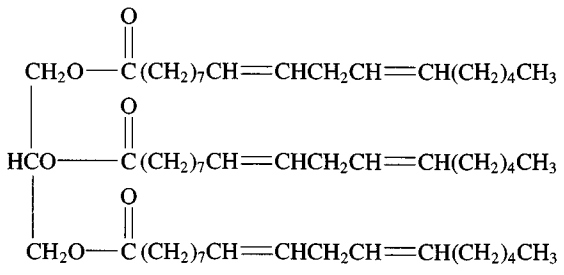
Other names (Wenninger and McEwen 1997) for Triisopalmitin include:

- Glyceryl Triisopalmitate
- Isohexadecanoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Triisohexadecanoate
- Triisohexadecanoic Acid, 1,2,3-Propanetriyl Ester

Triisostearin (CAS No. 26942-95-0) is the triester of glycerin and isostearic acid (q.v.). Other names (Wenninger and McEwen 1997) for this chemical include:

- Glyceryl Triisostearate
- Isooctadecanoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Triisooctadecanoate

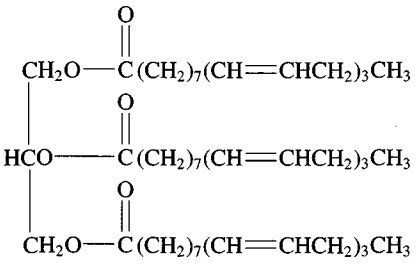
Trilinolein (CAS No. 537-40-6) is the triester of glycerin and linoleic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for this chemical include:

- Glyceryl Trilinoleate
- Linoleic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Trilinoleate
- 9,12-Octadecadienoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Tri(9,12-Octadecaienoate)

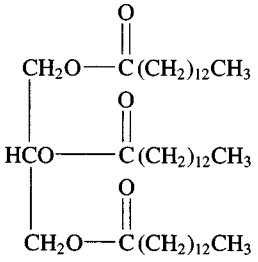
Trilinolenin (CAS No. 14465-68-0) is the triester of glycerin and linolenic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for Trilinolenin include:

- Glyceryl Trilinolenate
- Linolenic Acid, 1,2,3-Propanetriyl Ester
- 9,12,15-Octadecatrienoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriyl Linolenate
- 1,2,3-Propanetriyl-9,12,15-Octadecatrienoate

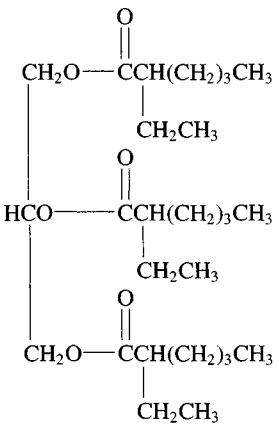
Trimyristin (CAS No. 555-45-3) is present in many vegetable fats and oils, notably in coconut oil and nutmeg butter (Budavari 1989). It is the triester of glycerin and myristic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for this chemical include:

- Glyceryl Trimyristate
- 1,2,3-Propanetriol Tritetradecanoate
- Tetradecanoic Acid, 1,2,3-Propanetriyl Ester

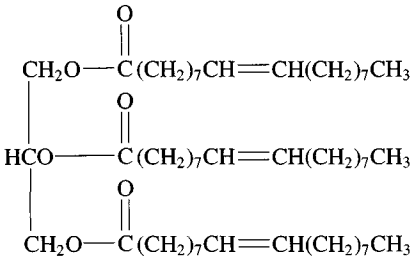
Trioctanoin (CAS No. 7360-38-5) is a colorless to pale yellow, transparent oily liquid with negligible odor (Unichema International 1996). It is the triester of glycerin and 2-ethylhexanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for Trioctanoin include:

- 2-Ethylhexanoic Acid, 1,2,3-Propanetriyl Ester
- Glyceryl Tri(2-Ethylhexanoate); Glyceryl Trioctanoate
- Hexanoic Acid, 2-Ethyl-, 1,2,3-Propanetriyl Ester
- Octanoic Acid, 1,2,3-Propanetriyl Ester

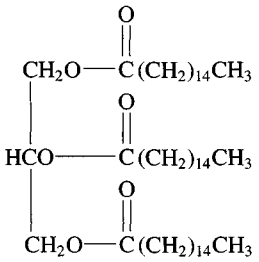
Triolein (CAS No. 122-32-7) is the predominating constituent in expressed almond oil, lard, and many of the more fluid animal oils and those of vegetable origin (Gennaro 1990). It is the triester of glycerin and oleic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for this chemical include:

- Glyceryl Trioleate
- 9-Octadecenoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Tri(9-Octandecenoate)

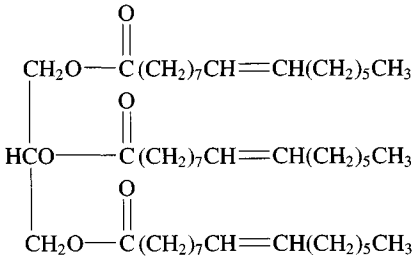
Tripalmitin (CAS No. 555-44-2) predominates in palm oil and coconut oil (Gennaro 1990). It is the triester of glycerin and palmitic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for Tripalmitin include:

- Glyceryl Tripalmitate
- 1,2,3-Propanetriol Trihexadecanoate
- Hexadecanoic Acid, 1,2,3-Propanetriyl Ester

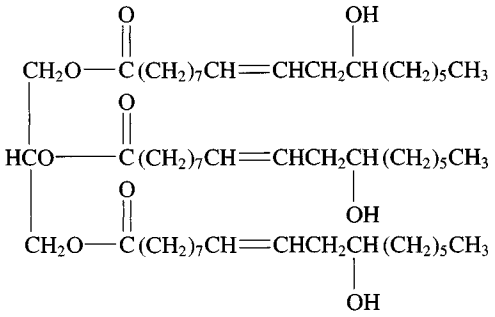
Tripalmitolein (CAS Nos. 20246-55-3 and 129784-33-4) is the triester of glycerin and palmitoleic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for this chemical include:

- Glyceryl Tripalmitoleate
- 9-Hexadecenoic Acid, 1,2,3-Propanetriyl Ester
- Palmitoleic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Tri(9-Hexadecenoate)
- 1,2,3-Propanetriol Tripalmitoleate

Triricinolein (CAS No. 2540-54-7) constitutes approximately 80% of castor oil (Lewis 1993). Triricinolein is the triester of glycerin and ricinoleic acid that conforms to the following formula (Wenninger and McEwen 1997):

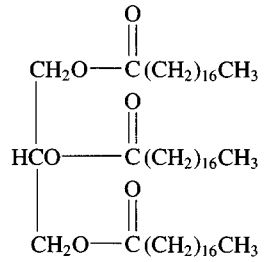


Other names (Wenninger and McEwen 1997) for Triricinolein include:

- Glyceryl Triricinoleate
- 12-Hydroxy-9-Octadecenoic Acid, 1,2,3-Propanetriyl Ester
- 9-Octadecenoic Acid, 12-Hydroxy-, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Tri(12-Hydroxy-9-Octadecenoate)

Tristearin (CAS No. 555-43-1) is present in many animal and vegetable fats, especially the hard ones (e.g. cacao butter and tallow) (Budavari 1989). It is the triester of glycerin and

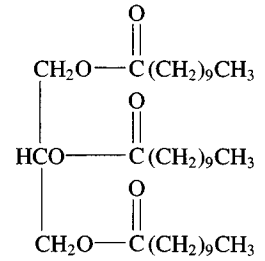
stearic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for this chemical include:

- Glyceryl Tristearate
- Octadecanoic Acid, 1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriol Trioctadecanoate

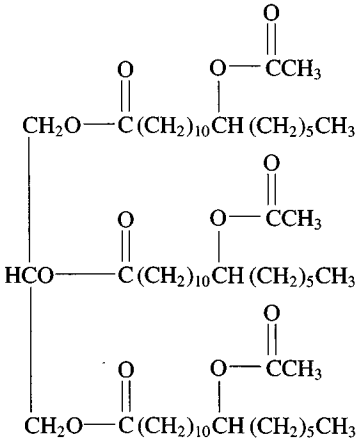
Triundecanoin (CAS No. 13552-80-2) is the triester of glycerin and undecanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for Triundecanoin include:

- Glyceryl Triundecanoate
- Undecanoic Acid, 1,2,3-Propanetriyl Ester

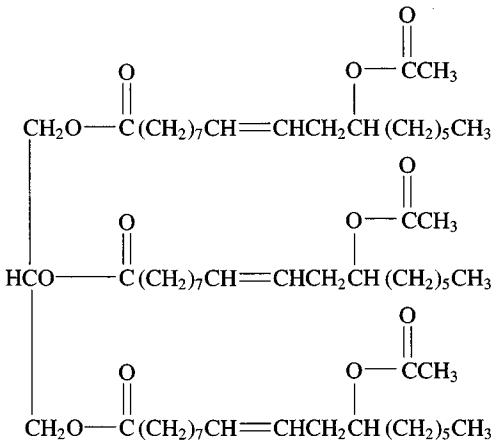
Glyceryl Triacetyl Hydroxystearate (CAS No. 27233-00-7) is the triester of glycerin and acetyl hydroxystearic acid that conforms to the following formula (Wenninger and McEwen 1997):



Two other names (Wenninger and McEwen 1997) for this chemical are:

- Octadecanoic Acid, (Acetyloxy)-1,2,3-Propanetriyl Ester
- Octadecanoic Acid, 12-Hydroxy-, 1,2,3-Propanetriyl Ester

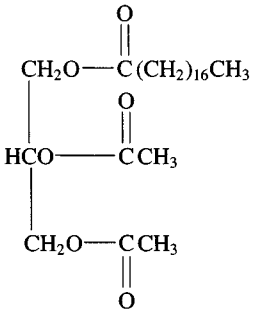
Glyceryl Triacetyl Ricinoleate (CAS No. 101-34-8) is the triester of glycerin and acetyl ricinoleic acid that conforms to the following formula (Wenninger and McEwen, 1997):



Two other names (Wenninger and McEwen 1997) for Glyceryl Triacetyl Ricinoleate are:

- 9-Octadecenoic Acid, 12-(Acetyloxy)-,1,2,3-Propanetriyl Ester
- 1,2,3-Propanetriyl 12-(Acetyloxy)-9-Octadecenoate

Glyceryl Stearate Diacetate is the organic compound that conforms to the following formula (Wenninger and McEwen 1997):



Glyceryl Diacetate Monostearate and Glyceryl Monostearate Acetate are other names for this chemical (Wenninger and McEwen 1997).

Analytical Methods

Trilaurin has been analyzed/identified using the following methods: infrared (IR) spectroscopy (Deman and Deman 1982);

mass spectroscopy (STN International 1997b); nuclear magnetic resonance (NMR) spectroscopy (STN International 1997c); capillary supercritical fluid chromatography (Giron, Link, and Bouissel 1992); nonaqueous reverse phase, high-performance liquid chromatography (Fabien, Craske, and Wootton 1993); and high-performance size-exclusion chromatography (Lubke, Le Quere, and Barron 1996).

Trimyristin has been analyzed by thin-layer chromatography (Frank et al. 1971).

Tricaprin has been analyzed by gas-liquid chromatography (Mingrone et al. 1995).

Tricaprylin has been analyzed by IR and NMR spectroscopy (NTP 1994).

Tribehenin has been analyzed by IR spectroscopy (Abramovici et al. 1991).

Tripalmitin has been analyzed using the thin-layer chromatography/flame-ionization detection system (Rao, Riley, and Larkin 1985) and liquid chromatography–mass spectrometry (Erdahl and Privett 1977).

Trilinolein, Trilinolenin. Triolein, and Tristearin have been analyzed by gas-liquid chromatography (Watts and Dils 1968). Additionally, Triolein has been analyzed using reverse-phase high-performance liquid chromatography (Castilho, Silveira, and Pena 1989) and thin-layer chromatography (Padley 1969). Trilinolein has also been analyzed by reversed phase high performance liquid chromatography (Castilho, Silveira, and Pena 1989).

Methods of Production

Trilaurin may be produced by reacting glycerol with lauric acid or glycerol with lauroyl chloride (reagent: pyridine or quinoline). The reaction of lauric acid with glycerine is another method of production (STN International 1997c).

Triolein may be prepared by the esterification of oleic acid (Budavari 1989).

Tripalmitin can be prepared from glycerol and palmitic acid in the presence of either Twitchell reagent or trifluoroacetic anhydride (Budavari 1989).

Tristearin may be prepared from stearic acid and glycerol in the presence of Al_2O_3 (Budavari 1989).

Triundecanoin is produced by esterification of undecanoic acid and glycerine. The undecanoic acid is produced from castor oil, which is hydrolyzed to fatty acids and subjected to thermal degradation and fractionation. The resulting undecenoic acid is transformed to undecanoic acid and reesterified to the glycerol moiety. Deodorization, the final step, is accomplished using steam to remove components that give rise to unwanted flavors and odors (Karlshamns Sweden AB 1997).

Impurities

Triisostearin contains not more than 20 ppm heavy metals and not more than 2 ppm arsenic (CTFA 1998a).

Triundecanoin contains no impurities or residues of catalysts or solvents. 1,4-Dioxane, ethylene oxide, free amines, and nitrosamines are not added or formed during the production process. Furthermore, volatile compounds are effectively removed, by the deodorization process, below detection limits (0.1 ppm). The deodorization process also has removed any organochlorine or organophosphorus pesticides that may be present in the crude oil used in the production process. It is also important to note that the total content of polycyclic aromatic hydrocarbons (PAHs), if present in the crude oil, is reduced below 10 ppb. Additionally, aflatoxins, if present in the raw materials, are reduced below detection limits (0.5 ppb) by neutralization and bleaching (Karlshamns Sweden AB 1997). The specifications for heavy metals are as follows: As (<0.1 ppm), Cd (<0.001 ppm), Pb (<0.1 ppm), Hg (<0.01 ppm), Cr (<0.05 ppm), Ni (<0.1 ppm), Cu (<0.1 ppm), and Fe (<1.5 ppm) (Karlshamns Sweden AB 1997).

Reactivity

Tripalmitin, Tristearin, and Triolein

Glycerol chlorohydrins and their esters have been identified as products of the hydrolysis of Tripalmitin, Tristearin, and Triolein with hydrochloric acid. Column chromatography and IR, NMR, and mass spectrometry were the analytical methods used. The main reaction products were the corresponding diesters of 3-chloro-propane-1,2-diol, followed by monoesters of 3-chloropropane-1,2-diol and esters of 1,3-dichloropropan-2-ol (Davidek et al. 1980).

After Triolein was heated under simulated deep-fat frying conditions (at 185°C for 72 hours), thermally oxidized Triolein was converted into methyl esters by transesterification using sodium methoxide as a catalyst. The methyl esters were fractionated by urea exclusion. The urea adduct-forming ester, methyl oleate (89.2%), predominated (Paulose and Chang 1978).

Triolein (major skin lipid) was irradiated with 300-nm ultraviolet (UV) light, and the conditions for exposure approximated those at the skin surface exposed to sunlight. Using gas chromatography, the irradiated samples were analyzed for the presence of acrolein, formaldehyde, and acetaldehyde. The maximum amount of acrolein (1.05 nmol/mg Triolein) was formed after 6 hours of irradiation. Maximum amounts of formaldehyde (6 nmol/mg Triolein) and acetaldehyde (2.71 nmol/mg Triolein) were formed after 12 hours of irradiation (Nihati-Shirkhodaee and Shibamoto 1992).

USE

Purpose in Cosmetics

Information on the functions of glyceryl trIesters in cosmetics is summarized in Table 3. The glyceryl triesters are used mostly as skin-conditioning agents—occlusive and/or viscosity-increasing agents—nonaqueous (Wenninger and McEwen 1997).

TABLE 3
Functions of Glyceryl Triesters in cosmetics (Wenninger and McEwen 1997)

Ingredient	Function(s)
Trilaurin	Skin-conditioning agent—occlusive and/or viscosity-increasing agent
Triarachidin	as above
Tribehenin	as above
Tricaprin	as above
Tricaprylin	as above
Trierucin	as above
Triheptanoin	as above
Triheptylundecanoin	as above
Triisononanoin	as above
Triisopalmitin	as above
Triisostearin	as above
Trilinolein	as above
Trimyristin	as above
Triolein	as above
Tripalmitin	as above
Tripalmitolein	as above
Triricinolein	as above
Tristearin	as above
Trioctanoin	Hair conditioning agent; skin-conditioning agent—occlusive
Triundecanoin	as above
Glyceryl Triacetyl Hydroxystearate	Skin-conditioning agent—emollient
Glyceryl Triacetyl Ricinoleate	as above
Glyceryl Stearate Diacetate	Skin-conditioning agent—occlusive; viscosity-increasing agent—nonaqueous

Frequency of use data submitted to the Food and Drug Administration (FDA) in 1998 indicate that only 12 of the 23 ingredients in this safety assessment are being used in cosmetics. These include: Tricaprylin, Tribehenin, Triisononanoin, Triisostearin, Trilaurin, Trilinolein, Trimyristin, Trioctanoin, Tripalmitin, Tristearin, Glyceryl Triacetyl Hydroxystearate, and Glyceryl Triacetyl Ricinoleate. FDA frequency of use data on these ingredients are summarized in Table 4 (FDA 1998).

Concentration of use values are no longer reported to FDA by the cosmetics industry (FDA 1992). However, current concentration of use data received from the cosmetics industry are included in Table 5.

International Use

Eleven of the 23 ingredients reviewed in this report are listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category* (*CLS*) (Rempe and Santucci 1997). The following ingredients, which conform to the specifications of the *Japanese Cosmetic Ingredients Codex*, have precedent for use without restriction in all *CLS* categories: Trilaurin, Tribehenin, Trioctanoin, Trimyristin, Tripalmitin, and Tristearin.

Noncosmetic Use

Trilaurin has been detected in pharmaceutical excipients (Giron, Link, and Bouissel 1992).

Tricaprylin has been used as an energy source for burn patients and for patients having difficulty digesting long-chain fatty acids (NTP 1994).

Tristearin has been approved for use as a direct food additive (21 CFR 172.811). Additionally, the following Glyceryl Triesters have been approved for use as components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food (i.e., use as indirect food additives): Trilaurin, Trimyristin, Triolein, Tripalmitin, Tristearin (21 CFR 177.2800), and Glyceryl Triacetyl Hydroxystearate (21 CFR 178.3505). The following noncosmetic uses of Tristearin have been reported: soap, candles, candies, adhesive pastes, metal polishes, waterproofing paper, textile sizes, leather stuffing, and manufacture of stearic acid (Lewis 1993).

TABLE 4
Product formulation data on Glyceryl Triesters (FDA 1998)

Product category	Total no. of formulations in category	Total no. containing ingredient
Trilaurin		
Eyebrow pencil	91	6
Eyeliner	514	128
Eye shadow	506	9
Other eye makeup preparations	120	2
Other fragrance preparations	148	1
Blushers (all types)	238	1
Foundations	287	25
Lipstick	790	14
Other makeup preparations	135	2
Cleansing skin care preparations (creams, lotions, powders, sprays)	653	2
Body and hand skin care (excluding shaving) preparations (creams, lotions, powders, sprays)	796	4
Moisturizing skin care preparations (creams, lotions, powders, sprays)	769	1
Night skin care preparations (creams, lotions, powders, sprays)	188	1
Other skin care preparations (creams, lotions, powders, sprays)	692	1
1998 Trilaurin totals		**197**
Trilinolein		
Night skin care preparations (creams, lotions, powders, sprays)	188	1
Other skin care preparations (creams, lotions, powders, sprays)	692	1
1998 Trilinolein totals		**2**
Trimyristin		
Eye shadow	506	1
Blushers (all types)	238	4
Face powders	250	5
1998 Trimyristin totals		**10**
Tripalmitin		
Cleansing skin care preparations (creams, lotions, powders, sprays)	653	1
1998 Tripalmitin totals		**1**
Tristearin		
Eyeliner	514	21
Eye shadow	506	1
Other fragrance preparations	148	2
Foundations	287	1
Lipstick	790	4
Cleansing skin care preparations (creams, lotions, powders, sprays)	653	3
Face and neck (excluding shaving) skin care preparations (creams, lotions, powders, sprays)	263	1
Body and hand skin care (excluding shaving) preparations (creams, lotions, powders, sprays)	796	4
Moisturizing skin care preparations (creams, lotions, powders, sprays)	769	3
Paste masks (mud packs)	255	1
Other skin care preparations (creams, lotions, powders, sprays)	692	5
1998 Tristearin totals		**46**
Triisostearin		
Eye shadow	506	1
Lipstick	790	4
1998 Triisostearin totals		**5**
Triisononanoin		
Face and neck (excluding shaving) skin care preparations (creams, lotions, powders, sprays)	263	2
Body and hand skin care (excluding shaving) preparations (creams, lotions, powders, sprays)	796	4
Night skin care preparations (creams, lotions, powders, sprays)	188	1
Other skin care preparations (creams, lotions, powders, sprays)	692	1
1998 Triisononanoin totals		**8**

(Continued on next page)

TABLE 4
Product formulation data on Glyceryl Triesters (FDA 1998) (*Continued*)

Product category	Total no. of formulations in category	Total no. containing ingredient
Tribehenin (Glyceryl Tribehenate)		
Eyebrow pencil	91	1
Other eye makeup preparations	120	2
Hair conditioners (noncoloring)	636	4
Blushers (all types)	238	8
Foundations	287	12
Makeup bases	132	2
Other makeup preparations	135	6
Body and hand skin care (excluding shaving) preparations (creams, lotions, powders, sprays)	796	3
Moisturizing skin care preparations (creams, lotions, powders, and sprays)	769	3
Other suntan preparations	38	1
1998 Tribehenin totals		**42**
Tricaprylin (Glyceryl Tricaprylate)		
Eyebrow pencil	91	2
Eyeliner	514	1
Eye shadow	506	1
Other eye makeup preparations	120	1
Tonics, dressings, and other hair-grooming aids (noncoloring)	549	3
Face powders	250	2
Foundations	287	24
Lipstick	790	15
Makeup bases	132	1
Makeup fixatives	11	1
Other makeup preparations	135	1
Nail polish and enamel removers	34	1
Cleansing skin care preparations (creams, lotions, powders, and sprays)	653	2
Body and hand skin care (excluding shaving) preparations (creams, lotions, powders, and sprays)	796	5
Foot powders and sprays	35	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays)	769	6
Paste masks (mud packs)	255	1
Other skin care preparations (creams, lotions, powders, and sprays)	692	1
Suntan gels, creams, and liquids	136	1
1998 Tricaprylin totals		**70**
Trioctanoin (Glycerol Tris-(2-Ethylhexanoate))		
Eye shadow	506	2
Mascara	167	1
Blushers (all types)	238	1
Foundations	287	1
Lipstick	790	6
Other makeup preparations	135	2
Cleansing skin care preparations (creams, lotions, powders, and sprays)	653	2
Body and hand skin care (excluding shaving) preparations (creams, lotions, powders, and sprays)	796	3
Moisturizing skin care preparations (creams, lotions, powders, and sprays)	769	4
Other skin care preparations (creams, lotions, powders, and sprays)	692	5
1998 Trioctanoin totals		**27**
Glyceryl Triacetyl Hydroxystearate		
Tonics, dressings, and other hair grooming aids	549	1
Lipstick	790	2
1998 Glyceryl Triacetyl Hydroxystearate totals		**3**
Glyceryl Triacetyl Ricinoleate		
Lipstick	790	31
Other skin care preparations (creams, lotions, powders, and sprays)	692	1
1998 Glyceryl Triacetyl Ricinoleate totals		**32**

TABLE 5
Use concentration data on Glyceryl Triesters (CTFA 1998a,* 1998b,** 1998c,*** 1999)

Product type	Maximum use concentrations
Trilaurin	
Other bath preparations	1%
Eyebrow pencil	20%
Eyeliner	5%–36%
Eye shadow	0.003%–46%
Foundations	2%
Lipstick	0.2%–46%
Lip liner	46.3%**
Makeup fixatives	0.8%
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations)	0.4%–3%
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations)	3%
Moisturizing creams, lotions, powders, and sprays	3%
Night creams, lotions, powders, and sprays (excluding shaving preparations)	0.9%
Tribehenin	
Deodorants (underarm)	3%–6%
Suntan gels, creams, and liquids	3%
Eye cream	0.32%*** (not a maximum value)
Lip cream	0.38%*** (not a maximum value)
Hand cream	0.38%*** (not a maximum value)
Tricaprylin	
Blushers (all types)	5%
Face powders	5%
Foundations	0.5%–2%
Other makeup preparations	10%
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations)	2%
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations)	2%
Indoor tanning preparations	2%
Triheptanoin	
Lipstick	12%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	15%
Triisononanoin	
Lipstick	25%
Triisostearin	
Lipstick	36%
All product types	<40%*
Trimyristin	
Eye shadow	2%
Powders (dusting and talcum) (excluding aftershave talc)	1%
Blushers (all types)	1%
Face powders	1%
Trioctanoin	
Eyebrow pencil	10%
Eyeliner	17%
Eye shadow	2%–5%
Hair conditioners	0.2%
Tonics, dressings, and other hair-grooming aids	1%
Blushers (all types)	3%
Foundations	7%–14%
Lipstick	46%

(Continued on next page)

TABLE 5

Use concentration data on Glyceryl Triesters (CTFA 1998a,* 1998b,** 1998c,*** 1999) (*Continued*)

Product type	Maximum use concentrations
Makeup bases	4%
Nail polish and enamel	3%
Aftershave lotions	0.2%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	50%
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations)	6%
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations)	3%
Moisturizing creams, lotions, powders, and sprays	2%-5%
Night creams, lotions, powders, and sprays (excluding shaving preparations)	8%
Paste masks (mud packs)	0.1%
Suntan gels, creams, and liquids	2%
Indoor tanning preparations	4%
Tripalmitin	
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	2%
Tristearin	
Eyeliner	2%
Eye pencils	~2%***
Foundations	0.1%–3%
Glyceryl Triacetyl Hydroxystearate	
Lipstick	9%
Glyceryl Triacetyl Ricinoleate	
Lipstick	8%

BIOLOGICAL PROPERTIES

Absorption, Distribution, and Metabolism

The following summary of triglyceride absorption, metabolism, and distribution is included in the NTP (National Toxicology Program) report on the comparative toxicology of corn oil, safflower oil, and tricaprylin (NTP 1994); Johnson et al. (1990) is the original source:

> In the small intestine, most triglycerides are split into monoglycerides, free fatty acids, and glycerol, which are absorbed by the intestinal mucosa. Within the epithelial cells, resynthesized triglycerides collect into globules along with cholesterol and phospholipids and are encased in a protein coat as chylomicrons. Chylomicrons are transported in the lymph to the thoracic duct and eventually to the venous system. The chylomicrons are removed from the blood as they pass through the capillaries of adipose tissue. Fat is stored in adipose cells until it is transported to other tissues as free fatty acids which are used for cellular energy or incorporated into cell membranes. When ^{14}C-labeled long-chain triglycerides are administered intravenously, 25% to 30% of the radiolabel is found in the liver within 30 to 60 minutes, with less than 5% remaining after 24 hours. Lesser amounts of radiolabel are found in the spleen and lungs. After 24 hours, nearly 50% of the radiolabel has been expired in carbon dioxide, with 1% of the carbon label remaining in the brown fat. The concentration of radioactivity in the epididymal fat is less than half that of the brown fat.

In addition to the preceding information, there are also data indicating that, after absorption, long-chain saturated fatty acids are transported mainly via the intestinal lymph as triglycerides. Fatty acids with 10 or less carbon atoms are transported mainly from the intestine via the portal blood vessels. There are also data indicating that unsaturated long-chain fatty acids are absorbed mainly via the lymph vessels (Bergstrom, Blomstrand, and Borgstrom 1954).

It is also important to note that there are data indicating a difference in the rate of metabolism of long- versus medium-chain triglycerides. (Medium-chain triglycerides is the term used to describe one form of neutral lipid, triglyceride that contains fatty acid molecules with a chain length varying from 6 to 12 carbon atoms.) Specifically, in one experiment, ^{14}C-Trioctanoin (8 carbons in fatty acid chain) and ^{14}C-Tripalmitin (16 carbons) were injected into isolated intestinal loops of rats. At 15 minutes after ^{14}C-Trioctanoin injection, mostly all of the lipid remaining in the luminal contents (92%) was present as fatty acid. However, after the injection of ^{14}C-Tripalmitin, only 29% of the residual ^{14}C-labeled lipid had been hydrolyzed to fatty acid (Greenberger, Rodgers, and Isselbacher 1966).

In Vivo Studies

Trilaurin

Three rats were placed under light anesthesia and dosed with olive oil (dose = 0.12 ml per 100 g of body weight) containing Glyceryl Trilaurate-1-C^{14} (0.5 μC$_i$). Doses were administered by gastric probe after 15 to 18 hours of fasting. Cumulative $^{14}CO_2$ elimination curves of the percentage of radioactive carbon dioxide relative to the dose ingested indicated that the amount of $^{14}CO_2$ exhaled over a period of 7 hours was 73%. Furthermore,

the absorption rate for Glyceryl Trilaurate-1-C^{14} was 5.4% per minute and its utilization rate was 0.91% per minute (Metais, Bach, and Warter 1967). Studies conducted prior to 1970 have indicated that triglycerides (e.g., Trilaurin) are metabolized to mono- and diglycerides in the body during the process of fat digestion. Pancreatic enzymes are primarily responsible for hydrolysis of the triglyceride to monoglyceride and free fatty acid, which are absorbed into the intestinal wall and used to resynthesize triglycerides (Kabara 1984). According to another source, the triglycerides are hydrolyzed by intracellular lipases to yield fatty acids and glycerol. Glycerol is converted directly to glucose, whereas the fatty acids are metabolized into two-carbon units that contribute to the formation of citric acid (Informatics, Inc. 1973).

Tricaprin

After Tricaprin was fed to white mice, capric acid (15%) was found in the depot fat along with caprylic acid (trace amounts), lauric acid (as high as 25%), and myristic acid (as high as 17.5%) (Powell 1932).

Tricaprylin

Tricaprylin and Triolein are normal body constituents found in fat cells and in chylomicrons (Bryson and Bischoff 1969).

Triolein, Tripalmitin, and Tristearin

Suzuki et al. (1978) evaluated the percutaneous absorption of Glyceryl Tri-(oleate-1-^{14}C) (a.k.a. ^{14}C-Triolein) using male hr/hr strain hairless mice (average weight = 25 g) and male Hartley guinea pigs (average weight = 340 g). In each experiment, the radioactive oil was applied (0.01 ml on 2.0 cm diameter Japanese papers backed with Lumirror film) to dorsal skin. The oil was applied either undiluted or in a hydrophilic ointment. The hydrophilic ointment had the following composition: 5% ^{14}C-labelled oil, 30% white petrolatum, 15% stearyl alcohol, 12% propylene glycol, 2% sodium lauryl sulfate, and 36% distilled water. Mice were killed at 1, 6, 24, and 48 hours post application, and guinea pigs were killed at 6 and 24 hours post application. Whole body autoradiography was the technique used in the experiment with hairless mice and microautoradiography was used in the experiment with guinea pigs.

As determined by whole body autoradiography, ^{14}C-Triolein (undiluted or in hydrophilic ointment) did not penetrate into the body organs of mice. The oil remained localized at the application site at 48 hours post application. The results of the microautoradiography study using guinea pigs are summarized as follows: After 6 hours, the silver grains were distributed from the stratum corneum to the sebaceous glands. After 24 hours, the grains had spread up to the hair bulges and concentrated considerably in the sebaceous glands. The grains were also observed slightly in the dermis under the basal layer and around the hair follicles and the sebaceous glands (Suzuki et al. 1978).

Rats were fed an emulsion diet (via stomach tube) consisting of 95 parts Triolein (Glycerol Trioleate) and 5 parts Glycerol 1-^{14}C-Trioleate. The percentage of administered Glycerol 1-^{14}C-Trioleate that was identified in the lymph in 24 hours was 88% (Mattson and Volpenhein 1972). In an earlier study four male rats (weights $\approx$ 250 g) were dosed orally with [1-^{14}C]Triolein. The percentage of radioactivity that was absorbed in 24 hours ranged from 57% to 92% (mean = 78.2%). The percentage of absorbed activity that was recovered in the lymph fat from the thoracic duct ranged from 51% to 83% (mean = 65.5%) (Bergstrom, Blomstrand, and Borgstrom 1954).

After a single dose of [1-^{14}C]Triolein was administered intravenously into fasted rats, a high rate of uptake was noted within the first hour in the following organs: liver, myocardium, gastric mucosa, and diaphragm. However, after 24 hours, radioactivity in these tissues had decreased markedly. A similar pattern of distribution was noted in mice; however, large amounts of radioactivity were also noted in the brown fat, white adipose tissue, and spleen, even after 24 hours (Becker and Bruce 1985). In an earlier study, a ^{14}C-oleic acid–labeled Triolein emulsion was administered intravenously to rats. Following injection, an initial rapid drop in the serum concentration of Triolein was noted ($t_{1/2} = 4.5$ minutes). Approximately 95% of the administered dose disappeared within 30 minutes. Radioactivity was increased in the liver (maximum at 10 to 20 minutes), followed by a subsequent decline. As much as 8% of the administered radioactivity was detected in the epidermal fat pads (Procter & Gamble Company 1973).

In another study, rats were fed Triolein in which the fatty acids occupying specific positions in the glyceride molecule had been labeled. The recovery of labeled glycerol and oleic acid and the location of labeled acid in the triglyceride molecules of the lymph were determined. It was concluded that approximately 75% of the glycerol of dietary triglyceride was absorbed as monoglyceride, and 75% of the fatty acids of dietary triglyceride were absorbed as free acids (Mattson and Volpenhein 1964).

The absorption of [I-^{14}C]Tristearin was evaluated using groups consisting of six to seven male Wistar rats (weights = 200 to 250 g). The rats were prepared either with an external bile fistula or a sham operation (control group), and then allowed to recover for 6 to 12 hours. Weighed doses of [I-^{14}C]Tristearin were fed in a pellet of bran. Doses of 25, 50, 100, and 200 mg were administered to four groups, respectively. The rats were killed after 16 hours and lipid from the stomach, small gut, and colon (with feces) was extracted. Absorption was expressed as the percentage of the dose that had left the stomach. Only rats in which 80% or more of the dose had left the stomach were used. Tristearin absorption was classified as poor at all administered doses. Significantly lower absorption of Tristearin was noted only in the 200 mg dose group ($p < .02$, $n = 6$) (Hamilton, Webb, and Dawson 1969). Results for [1-^{14}C]Triolein and [1-^{14}C]Tripalmitin are summarized below:

When groups of rats were dosed with [I-^{14}C]Triolein according to the same procedure, the absorption of 25 mg and

200 mg doses was almost complete (95% and 96%, respectively) (Hamilton et al. 1969).

Sham operated rats (group of seven) were fed 25 mg doses of [I-^{14}C]Tripalmitin in bran pellets. Absorption was expressed as the percentage of that which left the stomach. The mean percentage absorption reported was 70% ± 5% (Hamilton, Webb, and Dawson 1969).

Following the oral administration of a Glycerol-tri(1-^{14}C)-Palmitate (Tripalmitin) emulsion to pregnant female Wistar rats during late gestation, total radioactivity in the plasma increased more rapidly in 20-day pregnant rats than in either 19-day pregnant rats or virgin controls. Four hours after administration of the tracer (peak of plasma radioactivity) most of the plasma radioactivity corresponded to ^{14}C lipids in triglyceride-rich lipoproteins. Also, at 4 hours post administration, the estimated recovery of administered radioactivity in total white adipose tissue, mammary glands, and plasma lipids was greater in pregnant rats than in virgin rats (Argiles and Herrera 1989).

Trilinolein and Trioctanoin

The metabolism of Trilinolein in the rat testis was evaluated using adult male Sprague-Dawley rats (weights = 200 to 225 g). The rats were injected intratesticularly with a 1-^{14}C-Trilinolein emulsion (50 μl). Groups of two to four animals were killed at the following intervals, after which testes were excised: ¼, ½, 1, 3, 6, 12, 24, 36, and 48 hours. Results indicated that radioactive 1-^{14}C-linoleic acid was released from 1-^{14}C-Trilinolein and incorporated throughout the lipid classes. The specific activities and pattern of distribution of the radioactivity indicated that the transformation of linoleic acid between the triglyceride, diglyceride, and fatty acid pools was an equilibrium process. Furthermore, linoleic acid released from 1-^{14}C-Trilinolein was converted to higher polyunsaturated fatty acids that were incorporated throughout the lipid classes, and was catabolized. Evidence for linoleic acid catabolism was the finding of radioactivity in palmitic acid (Nakamura and Privett 1969).

The absorption of intraduodenally administered carboxyl-^{14}C-Glyceryl Trioctanoate was evaluated using 20 normal dogs (controls), 9 pancreatectomized dogs, and 4 pancreatectomized dogs with a thoracic duct fistula. In the 20 control dogs, 26.7% ± 5.2% of the administered radioactivity was recovered as expired $^{14}CO_2$ in 150 minutes. After pancreatectomy, $^{14}CO_2$ recovery rates diminished significantly. Using thin-layer and gas chromatography of lymph collected from four pancreatectomized dogs, results indicated that no 8-carbon fatty acids or glycerides were present. Labeled and unlabeled Trioctanoin were administered to the four pancreatectomized dogs. The researchers stated that the results of these experiments indicate that Trioctanoin absorption was retarded in the absence of pancreatic lipase, but that fractional amounts of the lipid were absorbed via the portal route (Schwabe et al. 1967).

The utilization and distribution of radioactive lipid emulsions were evaluated using three groups of 12 male Sprague-Dawley rats (weights = between 190 and 250 g). The medium-chain triglyceride (MCT), Trioctanoin (glycerol tri-[1-^{14}C]octanoate), and the long-chain triglyceride (LCT), Trilinolein (glycerol tri-[1-^{14}C]linoleate), were the radioactive triglycerides that were used. The composition of the typical LCT molecule includes fatty acids of 16 and 18 carbons in length with trace amounts of larger fatty acids. The fatty acids of the triglyceride fractions of emulsions prepared from MCTs are usually 8 to 10 carbons in length. Group 1 was fed [^{14}C]MCT, and group 2 was fed a 75%:25% (vol:vol) admixture of [^{14}C]MCT:unlabeled LCT lipid emulsion. Group 3 was fed [^{14}C]LCT. Radioactivity (monitored over a 24-hour period) was detected in expired CO_2 and the following body tissues: liver, brain, lungs, heart, muscle, kidneys, epididymal fat, duodenum, plasma, and urine. Study results indicated that the MCT was oxidized more rapidly and completely than the LCT. Approximately 90% of the MCT was converted to CO_2 within 24 hours, compared to 45% of LCT. Following the simultaneous administration of MCT and LCT, the metabolism of MCT was slowed, but remained more rapid than the metabolism of LCT. Additionally, removal of MCT from the blood was more rapid, and tissue radioactivity was lower. The investigators noted medium-chain fatty acids are metabolized more rapidly and completely than long-chain fatty acids because they enter the mitochondria of the liver, heart, and kidneys for oxidation without first being converted to a carnitine transport form (Johnson et al. 1990).

In Vitro Studies

Triolein

The in vitro percutaneous absorption of Triolein through full thickness Skh-1 hairless mouse skin was evaluated using one-chambered static diffusion cells. Skin samples from the mid-dorsal region were mounted on the diffusion cells with the dermal side in contact with the receptor fluid (phosphate-buffered saline [PBS]) and the epidermis open to the atmosphere. Triolein was applied as 10-μl aliquots of 40 μg/ml solutions in ethanol. Gentamicin was added to the receptor fluid to control bacterial growth in this compartment. The receptor fluid was modified during the study by adding other chemicals. The extent of percutaneous absorption, expressed as the mean and standard deviation ($n = 6$) of the percentage of the applied radioactivity recovered in the receptor fluid after 24 hours, of Triolein in PBS + gentamicin was 0.3% ± 0.2%. The percutaneous absorption of Triolein was greatest (4.7% ± 0.8%) in the presence of PBS + gentamicin + bovine serum albumin and least in the presence of PBS + gentamycin + PEG-20 oleyl ether (0.2% ± 0.1%). Thus, the chemical composition of the receptor fluid significantly affected the extent of absorption of Triolein (Moloney 1988).

The metabolism of Triolein in vitro was evaluated using isolated perfusion of a rat liver in tandem with an isolated rat hind end. This permitted the study of lipid transfer between the two. In the absence of added Triolein, a net removal of free fatty acids was demonstrated in both tissue beds when fatty acid

gradients across tissue beds were measured. Following the addition of 100 mg of Triolein (as [^{3}H]-glycerol-[^{14}C]triolein) to either reservoir in the system, an appreciable net production of free fatty acid was noted for the hind end gradient at 30 minutes. This hind-end free fatty acid efflux amounted to more than one third of the catabolism of Triolein. In the presence of Triolein, a fatty acid influx similar to the hind end–generated efflux was noted. Furthermore, after the introduction of radioactive Triolein into the peripheral (hind) end of the system, a significantly greater (compared to injection in liver reservoir) fraction of the recovered lipid ^{14}C radioactivity was detected in the liver tissue. The percentage of recovered lipid detected in peripheral tissues (i.e., muscle, subcutaneous adipose tissue, and epididymal adipose tissue) after 90 minutes of perfusion was similar regardless of the site of Triolein injection into the system. Most of the ^{14}C radioactivity was identified in subcutaneous adipose tissue (Schirmer et al. 1983).

Other Glyceryl Triesters

Hydrolysis of the following synthetic glyceryl triesters by hepatic triacylglycerol lipase in plasma from ICR mice has been demonstrated in vitro: Tricaprylin, Tricaprin, Trilaurin, Trimyristin, Tripalmitin, Tristearin, and Triolein (Masuno and Okuda 1986).

Skin Penetration Enhancement

Tricaprylin and Other Triglycerides

The skin penetration enhancement of drugs by Tricaprylin has been demonstrated in vivo using Wistar rats (Lee et al. 1993) and in vitro using hairless female mice (Lee et al. 1993; Goto et al. 1993). In the study by Goto et al. (1993), the drug permeation ratio in the presence of triglycerides increased in the following order: Tricaprylin (C8) > Triolein (C18) > Tributyrin (C4) > Triacetin (C2).

Cardiac Effects

Trilinolein

Reportedly, Trilinolein reduced infarct size and suppressed ventricular arrhythmias in vivo in male Sprague-Dawley rats (weights = 200 to 300 g) subjected to coronary ligation. Trilinolein was administered intravenously at doses ranging from 10^{-11} to 10^{-7} g/kg. Complete suppression of all ventricular arrhythmias was noted at a dose of 10^{-7} g/kg. The pretreatment of rats with 10^{-7} g/kg 15 minutes prior to the 4-hour coronary ligation resulted in significant reduction of infarct size (Chan et al. 1995).

Effect on Phagocytosis

Tricaprin

Outbred, specific pathogen free–male mice were injected intravenously with a Tricaprin suspension at intervals ranging from 30 minutes to 16 days. The animals were then killed and samples of liver and spleen were prepared for light and electron microscopy. Control mice were injected intravenously with colloidal carbon, and samples of the liver and spleen were examined microscopically at intervals ranging from 15 minutes to 24 hours after injection. Compared to controls, the injection of Tricaprin was followed by an increase in the size of Kupffer cells and the number of lysosomes within them was increased. Additionally, the liver had a heavier and more homogenous distribution of carbon within the lobule, indicating increased phagocytic activity. Microscopically and macroscopically, no differences were found between the spleens of test and control mice. No changes of toxicity were found in the liver or spleen (Stuart and Smith 1975).

Triolein

The effect of Triolein on the monocyte-macrophage system were evaluated using four groups of Wistar female rats (average body weight = 150 ± 20 g). Dosing with Triolein was according to the following schedule: single intravenous (IV) injection with 50 mg/100 g (group A); two IV doses of 25 mg/100 g, separated by 24 hours (group B); single IV dose of 16.7 mg/100 g (group C); and single IV dose of 25 mg/100 g (group D). Phagocytic activity indices were determined over a period of 7 days (at intervals of 24 hours after the last IV injection) by measuring the rate of clearance of 8 mg of colloidal carbon in 1% calf-skin gelatin per 100 g body weight. Compared to untreated controls, the overall phagocytic activity of group A increased 100% within 24 to 48 hours after dosing. In group B, the overall phagocytic activity increased 500% within 24 hours after the second dose. Results for group C indicated a fourfold increase in carbon clearance within 24 hours. This degree of phagocytic stimulation was twice as great as that induced by a single IV dose of triolein (50 mg/100 g) in group A. Results for group D indicated a greater degree of phagocytic stimulation than a dose of 50 mg/100 g (group A); however, in group D, a period of 72 hours was required for reaching peak activity (Altura and Hershey 1970). Triolein has been described as one of the most potent stimulants of macrophages (Mouton et al. 1975).

Pharmacological Effects

Trilaurin

The effect of Trilaurin in the diet on plasma apolipoprotein A-I (apo A-I) and high-density lipoprotein (HDL) cholesterol concentrations was evaluated in two experiments using Watanabe (WHHL) and New Zealand white (NZW) rabbits. In the first experiment, two WHHL rabbits (6 months old) were fed a chow diet supplemented with Trilaurin (6.5% *w/w*) for 4 days. Significant increases in plasma HDL cholesterol and apo A-I concentrations were noted after feeding (250% and 200% of the baseline value for HDL cholesterol and apo-A-I concentrations, respectively). Concentrations of both substances returned to baseline after Trilaurin was removed from the diet. In the second experiment, three WHHL rabbits and three NZW rabbits (10 months old) were fed a chow diet supplemented with Trilaurin (6.5% *w/w*) for 1 week. HDL cholesterol and apo

A-I concentrations increased 50% and 62%, respectively, in WHHL rabbits, and 43% and 31%, respectively, in NZW rabbits ($p < .01$) (Carlson and Kottke 1991).

Tricaprylin

The pharmacological activity of Tricaprylin was evaluated using dogs. Dosing with Tricaprylin resulted in loss of spontaneous movement and a slight increase in the response of the ileum. No effects were observed on the following: respiration, blood pressure, the isolated heart and uterus, electrocardiogram (ECG), auricular vessel, and duration of anesthesia. Effects on behavior and the isolated ileum were noted (Ohta et al. 1970).

Triolein

Following intravenous injection of a 10% Triolein emulsion (4- and 7-ml/kg doses) into cats after bilateral vagotomy, a rise in blood pressure in the pulmonary artery and a slight secondary fall in blood pressure were noted. The elevation in blood pressure had a high degree of tachyphylaxis. These effects were not observed when injections were repeated (Oro and Wretlind 1961).

Effect on Enzyme Activity

Trilaurin

The effect of Trilaurin and various fatty acids and derivatives on 5α-reductase activity in vitro was evaluated because of the established link between prostate cancer 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 totally lost as a result of esterification to Trilaurin (Niederpruem et al. 1995).

Effect on Glucose Production

Tricaprylin

The effect of Tricaprylin on glucose production was evaluated using the isolated perfused rat liver. Tricaprylin (1 mM) stimulated glucose production in the presence of lactate, galactose, or alanine. Tricaprylin (1 mM) also induced a twofold increase in ketogenesis (Ingebretsen and Wagle 1974).

Antioxidant Activity

Trilinolein, Triolein, and Tristearin

The antioxidant activity of Trilinolein, Triolein, and Tristearin has been demonstrated using enhanced chemiluminescence (method of measuring oxygen-derived free radicals) in a reaction mixture consisting of a human polymorphonuclear leucocyte cellular suspension. Trilinolein had the strongest antioxidant activity, followed by Triolein and then Tristearin (Chan et al. 1996).

TOXICOLOGY

To facilitate the comparison of results as a function of the molecular size of the ingredient, the length of the fatty acid carbon chain is included in parentheses after the ingredient name.

Acute Oral Toxicity

Tribehenin (C22)

An acute oral LD_{50} of 5 g/kg (mice) has been reported for Tribehenin. Details concerning the test protocol and study results were not reported (Registry of Toxic Effects of Chemical Substances 1998).

A 40% suspension of Tribehenin in corn oil did not induce toxicity in acute oral toxicity studies involving rats. Details concerning the test protocol and study results were not included (Unichema International 1992).

Tricaprylin (C8)

Acute oral LD_{50} values for Tricaprylin were 34.2 and 29.6 g/kg in male and female mice, respectively. The researchers concluded that Tricaprylin induced very low acute toxic effects in mice (Ohta et al. 1970).

In another experiment in the preceding study, acute oral LD_{50} values for Tricaprylin were 34.2 and 33.3 g/kg in male and female rats, respectively. The researchers concluded that Tricaprylin induced very low acute toxic effects in rats (Ohta et al. 1970).

Trioctanoin (C8)

The acute oral toxicity of Trioctanoin (a.k.a. Glycerol Tris(2-Ethylhexanoate)) was evaluated using ten male, Ichikawaken mice of the ddY strain (weight range = 21.8 to 25.2 g). Each animal received an oral dose of 50 ml/kg, and the LD_{50} was calculated at the end of a 1-week observation period. Suppression of spontaneous movement was observed immediately after test substance administration, and some excretion of the administered dose was observed 20 to 30 minutes later. At 1 to 2 hours post administration, the hair appeared completely wet. On the day after dosing, suppression of spontaneous movement was described as slight and gradual recovery followed. The appearance of the hair also returned to normal. None of the animals died, and it was concluded that the LD_{50} was >50 ml/kg (Sanitary Laboratory Kanagawa Prefecture 1975a).

Tristearin (C18)

The acute oral toxicity of Tristearin was evaluated using ten Sprague-Dawley rats (males and females; weights = 150 to 300 g). None of the animals died during the 14-day period after dosing. The LD_{50} was >20.0 g/kg. At necropsy, none of the animals had gross lesions (Safepharm Limited 1980).

Triisostearin (C18)

A single oral dose (2 g/kg body weight) of Triisostearin did not result in any harmful effects in rats. Details concerning

the test protocol were not provided (Unichema International 1997a).

Acute Intravenous Toxicity

Tricaprylin (C8)

The acute intravenous toxicity of Tricaprylin was evaluated using six groups of 10 mice (strain not stated; weights = 13 to 29 g). Tricaprylin (25% emulsion) was injected into the tail vein of each animal. Motor uneasiness developed immediately after injection, and was followed by spasms in the hind legs, respiratory distress, urination, lateral recumbency, as well as froth at the nose. A mean acute IV LD_{50} of 3,700 ± 194 mg/kg was reported (Wretlind 1957).

A minimum lethal intravenous dose of 4 g/kg for a Tricaprylin emulsion was reported for two groups of male and female mice respectively, and two groups of male and female rats, respectively. The researchers concluded that Tricaprylin induced very low acute toxic effects when administered intravenously to mice and rats (Ohta et al. 1970).

Triolein (C18)

Triolein was injected intravenously into two mongrel dogs (weights = 10 to 15 kg). Injection was repeated at 30, 60, 120, 180, and 240 minutes and after 24 hours. The animals were killed and lungs were prepared for gross and microscopic examination. No changes in the following parameters were noted: lung compliance, arterial gases, platelet counts, prothrombin times, activated partial thromboplastin times, serum lipase, or plasma lactate. Mild tachypnea was noted after 4 hours but not after 24 hours. Hypotension was not observed in either animal. Focal areas of hemorrhage (not extensive) were observed at gross and microscopic examination. Surfactant activity was reduced in hemorrhagic areas. No alterations in any of the parameters studied were reported for the three saline-treated control dogs (Baker, Kuenzig, and Peltier 1969).

Acute Intraperitoneal Toxicity

Tricaprylin (C8)

The minimum lethal dose for Tricaprylin in two groups of male and female mice, respectively, and in two groups of male and female rats (number of animals not stated), respectively was >27.8 g/kg. The authors concluded that Tricaprylin induced very low toxicity when administered intraperitoneally to mice and rats (Ohta et al. 1970).

Acute Subcutaneous Toxicity

Tricaprylin (C8)

The minimum lethal dose of Tricaprylin was determined to be >27.8 g/kg in two groups of male and female mice, respectively, and in two groups of male and female rats, respectively (number of animals not stated). The researchers concluded that Tricaprylin induced very low acute toxic effects when administered subcutaneously to mice and rats (Ohta et al. 1970).

Short-Term Oral Toxicity

Trilaurin (C12), Tristearin (C18), and Triolein (C18)

The short-term oral toxicity of Trilaurin, Tristearin, and Triolein was evaluated using four groups of ten weanling rats, respectively. Each glyceryl ester was administered orally at a concentration of 25% in the diet for a period of 10 weeks. Equal gains in body weight were reported for all groups tested. No lesions were found at necropsy or microscopic examinations that were attributable to administration of test diets (Procter & Gamble Company 1950).

In another study, five weanling albino rats were fed 5% Tristearin in the diet daily for 37 days. Another group of five rats was fed a control diet (no Tristearin). The animals ranged in weight from 62 to 66 g. Growth rates for the two groups were identical. At necropsy, no abnormalities were found that were related to the administration of Tristearin. No significant differences in organ weight were found between the two groups (Hodge 1954).

Tricaprylin (C8)

The short-term oral toxicity of Tricaprylin was evaluated using groups of male and female Wistar rats (7 to 10 per group). The groups were dosed for 31 days with 2, 5, or 10 ml/kg. Compared to controls dosed with distilled water, statistically significant ($.01 < p < .05$) differences in the following clinical chemistry and hematological parameters were noted: urea nitrogen (mg/dl) significantly lower in groups of female rats dosed with 5 or 10 ml/kg, GOT (glutamic oxaloacetic transaminase) activity and erythrocyte counts ($\times 10^4/mm^3$) significantly lower in males dosed with 2 ml/kg, GPT (glutamic pyruvic transaminase) activity significantly lower in females dosed with 10 ml/kg, and leukocyte counts ($\times 10^2/mm^3$) significantly higher in females dosed with 10 ml/kg. Glucose concentration (mg/dl) was significantly greater ($p < .01$) in males dosed with 2 ml/kg (Ohta et al. 1970). Results for changes in organ weights are summarized below:

Compared to distilled water controls, the following statistically significant changes in organ weight were noted: significant reduction in heart weight ($.01 < p < .05$) in males dosed with 2, 5, or 10 ml/kg; significant reduction in spleen weight ($.01 < p < .05$) in males dosed with 5 ml/kg or 10 ml/kg; significant reduction in right and left kidney weights ($p < .01$) in males dosed with 5 ml/kg or 10 ml/kg; significant reduction in left testis weight in 2 ml/kg ($.01 < p < .05$), 5 ml/kg ($p + .01$), and 10 ml/kg ($.01 < p < .05$) dose groups; and significantx reduction in right testis weight in 2 ml/kg ($.01 < p < .05$) and 10 ml/kg ($p < .01$). At microscopic examination, no lesions were found in either test or control groups (Ohta et al. 1970).

Short-Term Subcutaneous Toxicity

Tricaprylin (C8)

Tricaprylin was used as a vehicle control in a study evaluating the short-term subcutaneous toxicity of monocrotaline pyrrole. Ten male and ten female rats of the SPF CSE strain (average

weight = 1200 g) were injected with 0.25 ml Tricaprylin twice a week for 5 weeks (total of 10 injections in right flank, same site). The animals were killed in pairs (one male, one female) 24 hours after the first injection and all subsequent injections. Subcutaneous tissue at the injection site was removed and prepared for histological examination. Initially, subcutaneous injections of Tricaprylin produced a granulomatous reaction characterized by numerous oil deposits surrounded by several layers of macrophages, accompanied by mononuclear cells and a few polymorphs. Additionally, from the third injection until the end of the experiment, fibrous tissue formed around the oil globules and fibroblasts (together with other chronic inflammatory cells) were observed between strands of collagen (Hooson and Grasso 1976).

Short-Term Parenteral Toxicity

Triolein (C18)

Over a period of 1 hour, Triolein (dose = 30% of the LD_{50}, where LD_{50} equals 1.5 times the weight of the animal in kilograms) was infused into the ascending aorta of each of six spontaneously breathing dogs. Four of the six dogs were made hypoxic with a 10% oxygen–90% nitrogen air supply. An additional six dogs were ventilated with a respirator during Triolein infusion. Three control dogs received a slow saline infusion into the ascending aorta. The respiratory rate increased in spontaneously breathing dogs, and two of the four dogs made hypoxic during infusion had a respiratory arrest. Atelectasis, hemorrhage, and interstitial edema were observed in the lungs at biopsy and postmortem specimens of test animals, but not in control animals. Severe intravascular accumulation of fat was noted in sections of the brain, heart, and kidneys stained for fat. However, the accumulation of fat was small in the lungs (Shaffer et al. 1976).

Chronic Oral Toxicity

Trilaurin (C12)

Two groups of rats were fed 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. Thus, the individual glyceryl esters were fed at effective dietary concentrations of ~0.0002% (Trilaurin), ~0.0011% (Glyceryl Dilaurate), and ~0.0010% to 0.0011% (Glyceryl Laurate). Control rats were fed hydrogenated cottonseed oil at a concentration of 25% in the diet. No differences were found in growth rate and lesions between test and control rats. A slight excess of hepatic cell fatty change (compared to controls) was the only microscopic finding in both groups fed the mixture. Details concerning the test protocol and study results were not included (Unichema International 1997b).

Trierucin (C22)

The chronic oral toxicity of Trierucin (Glyceryl Trierucate) was evaluated using 18 male Wistar rats (3 weeks old; weights not stated). The rats were fed a basal diet consisting of 30 cal % Trierucin for 24 weeks. Six and 12 animals were killed by decapitation after 1 week and 24 weeks of dosing, respectively. Six animals were killed (after week 1) to determine any effects on cardiac morphology. Cardiac features were assessed using frozen sections. The remaining 12 rats were killed (after week 24) to determine any effects on renal morphology. Renal morphology was studied using sections obtained from formalin-fixed tissues. Weekly growth and organ weight (heart and kidneys) determinations were also recorded for the remaining 12 rats. Severe cardiac lipidosis was observed in all six rats killed after one week of dosing. Additionally, cardiac lesions (lipidosis and/or focal fibrosis) were observed in the remaining 12 rats that were killed after 24 weeks of dosing. It is important to note that the cardiac lipidosis observed in this group was less severe, compared to rats killed after six weeks. Cardiac fibrosis was observed in all 18 rats. Tubular dilatation, proteinaceous casts or interstitial foci of fibrosis were observed in kidneys from all rats killed after 24 weeks (Abdellatif and Vles 1973).

Tricaprylin (C8)

The chronic oral toxicity of Tricaprylin was evaluated using groups of male Wistar rats (8 to 12 per group). The groups were dosed with Tricaprylin for 26 weeks. Compared to rats dosed with distilled water, significant reductions in GOT activity and hemoglobin concentration were noted in rats dosed with 10 ml/kg. Statistically significant increases in organ weight ($.01 < p < .05$) were reported for the liver (2 ml/kg dose group) and adrenal glands (2-ml/kg and 10-ml/kg dose groups) (Ohta et al. 1970). In another chronic oral toxicity experiment, Tricaprylin caused few lesions in the kidneys, myocardium, and the aorta of Wistar rats (Ohta et al. 1970).

Ocular Irritation

Trilaurin (C12)

The ocular irritation potential of an eyeliner containing 36.3% Trilaurin was evaluated using six rabbits. The test substance was instilled three times in each animal; eyes were not rinsed. Reactions were scored according to the Draize scale (0 to 110). The eyeliner was classified as mildly irritating (Draize score = 2) (CTFA 1984a).

Tribehenin (C22)

Little or no ocular irritation was reported following the instillation of a 20% solution of Tribehenin (in liquid paraffin) into the conjunctival sac of the eyes of rabbits. Details concerning the test protocol and study results were not included (Unichema International 1992).

The ocular irritation potential of an eye enhancer (eye area cosmetic product) containing 0.32% Tribehenin was evaluated using the in vitro chorioallantoic membrane vascular assay (CAMVA). The eye enhancer (cream) was diluted and then tested at concentrations of 10%, 25%, 50%, and 75% using four

groups of 10-day-old fertilized, Dekalb chicken eggs (4 eggs/group), respectively. Undiluted eye enhancer was also tested using an additional group of 10 eggs. According to the protocol, chorioallantoic membranes of the five groups were dosed with the test substance at the end of a 10-day incubation period. The eggs were also incubated for an additional 30 minutes, after which the membranes were observed for signs of vascular hemorrhage, capillary injection, or ghost vessels. The RC_{50} (concentration that elicits a positive response in 50% of the treated eggs) was then determined. The incidence of positive responses (capillary injection and hemorrhage) per test group was as follows: 2 at 10%, 4 at 25%, 6 at 50%, and 10 at 75%. The undiluted cream did not induce positive responses. Based on the RC_{50} value of 35 (confidence limits = 18% to 67%) that was determined, the eye enhancer was not considered an ocular irritant (CTFA No date a, 1998c). A hand cream containing 0.38% Tribehenin also was not considered an ocular irritant when tested in two CAMVAs according to the same test procedure. Details concerning the study results were not included (CTFA No date a, 1998c).

Trioctanoin (C8)

In the Draize test, undiluted Trioctanoin did not induce ocular irritation when instilled (0.05 ml) into the conjunctival sac of the eyes of rabbits. Details concerning the test protocol were not included (Unichema International 1996).

Triisostearin (C18)

Triisostearin was not classified as an ocular irritant in rabbits. No reactions were found in the cornea or iris. Minor irritation reactions that were noted did not persist beyond the 24-hour assessment. Details concerning the test protocol were not provided (Unichema International 1997a).

Skin Irritation

Tribehenin (C22)

The skin irritation potential of Tribehenin (20% solution in liquid paraffin) was evaluated using six albino rabbits. The test solution was applied (0.5 ml, under surgical gauze) to abraded and intact skin sites that had been clipped free of hair. Patches were secured with adhesive tape and the entire trunk of each animal was wrapped with an impervious material (e.g., rubberized cloth), which remained in place for 24 hours. At the time of patch removal (at 24 hours) and 48 hours later, reactions were scored according to the following scales: 0 (no erythema) to 4 (severe erythema [beet redness] to slight eschar formation) and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond area of exposure). The primary irritation index (PII) was calculated after all scores had been determined. Tribehenin (20% in liquid paraffin) induced mild skin irritation when applied (under occlusive patches) to intact or abraded skin of rabbits for 24 hours (PII = 0.3) (Huntingdon Research Centre 1977).

Trilaurin (C12)

The skin irritation potential of an eyeliner containing 36.3% Trilaurin was evaluated in a single occlusive patch test using nine rabbits. The test substance (0.1 ml) was applied topically under a Whatman filter disc that was secured with Blenderm tape. The entire trunk of each animal was wrapped with a non-absorbent binder, adhesive tape, and masking tape. The test substance remained in contact with intact skin (clipped free of hair) for 24 hours. Reactions were scored at 2 and 24 hours after patch and test substance removal according to the following Draize scale: 0 (no erythema) to 4 (severe erythema [beet redness] to slight eschar formation [injuries in depth]); 0 (no edema) to 4 (severe edema [raised more than 1 mm and extending beyond area of exposure]). Neither erythema nor edema was observed in any of the rabbits at 2 or 24 hours after patch application. The test substance was classified as nonirritating (CTFA, No date b, 1984b).

Trioctanoin (C8)

The skin irritation potential of Trioctanoin was evaluated using three female Ichikawaken rabbits. The undiluted test substance was applied simultaneously to two sites on shaved skin of the back, by intracutaneous injection (0.1 ml; site at left of spine) and patch application (0.1 ml; site at right of spine), respectively. Liquid paraffin served as the control, and was applied according to the same procedure. Reactions were scored at 3, 24, 48, and 72 hours post administration according to the Draize method. Skin irritation was expressed in terms of the degree of erythema, the area of skin affected, and the area index. Trioctanoin (undiluted) did not induce skin irritation in rabbits when injected intracutaneously or applied topically (Sanitary Laboratory Kanagawa Prefecture 1975b).

Triisostearin (C18)

Undiluted Triisostearin was evaluated in a skin irritation test involving three New Zealand albino rabbits. The test substance was applied (0.5 ml) to a semiocclusive patch that was placed on intact skin of the right flank. Patches were secured with a hypoallergenic, microporous adhesive strip, and the trunk was wrapped with an elastic band (secured with adhesive tape). The dressings were removed at the end of a 4-hour contact period. At ~5 hours and at 24, 48, and 72 hours post application, reactions were scored according to the following scales: 0 (no erythema) to 4 (severe erythema [crimson red] with or without eschar [deep injuries] and lesions showing a serious cutaneous reaction such as a burn, a necrosis) and 0 (no edema) to 4 (severe edema [more than 1 mm thick and extending beyond the area of exposure] showing a serious cutaneous reaction such as a burn). The PII was calculated after all scores had been recorded. Slight erythema was noted in two rabbits at the time of patch removal and persisted to day 5 (both rabbits) and day 6 (1 rabbit) post application. A very slight loss of skin suppleness with reactional dryness was also noted. Edema was not observed. It was concluded that Triisostearin may be considered a nonirritant when

applied to the skin of rabbits (PII = 0.46) (Biogir S.A. Conseil Recherche 1989).

Skin Sensitization

Tribehenin (C22)

Tribehenin did not induce sensitization in a Magnusson-Kligman guinea pig maximization test. Details concerning the test protocol and study results were not included (Unichema International 1992).

Trioctanoin (C8)

The skin sensitization potential of Trioctanoin was evaluated using the Magnusson and Kligman (1969) guinea pig maximization test. The test concentrations used during the study were as follows: 1% (intradermal injection induction), 100% (topical application induction, occlusive patch), and 25% (topical application challenge, occlusive patch). Sensitization was induced in guinea pigs by intradermal injections of the test substance and Freund's complete adjuvant. The induction process was supplemented 6 to 7 days later by application of the test substance to the shoulder injection sites under occlusion for 48 hours. The animals were challenged with the test substance using a 24-hour occlusive patch; further challenges were made at weekly (or longer) intervals as required. A slight response was observed in two guinea pigs during the first challenge. No reactions were noted during the second challenge. Trioctanoin was classified as a non-sensitizer (Environmental Safety Laboratory 1990).

Phototoxicity and Photoallergy

Triisostearin (C18)

The phototoxicity and photoallergenicity potential of Triisostearin 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/cm^2) were applied 30 minutes 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 hours post treatment. With or without UV irradiation, Triisostearin did not induce significant cutaneous reactions. The positive control (8-methoxypsoralen) induced major reactions (Unichema International 1997a).

GENOTOXICITY

Tricaprylin (C8)

The mutagenicity of Tricaprylin in the following *Salmonella typhimurium* strains was evaluated using the Ames preincubation test procedure with and without metabolic activation: TA97, TA98, TA100, and TA1535. Tricaprylin was mutagenic only in strain TA1535 (with metabolic activation) at doses >6666 μg/plate (Zeiger et al. 1996).

The mutagenicity of Tricaprylin was evaluated in a dominant lethal study using T-stock and (C3H × C57BL)F_1 female mice. In the first experiment, 44 T-stock females were used. Forty-seven T-stock females and 37 (C3H × C57BL)F_1 females were used in the second experiment. In both experiments, a single intraperitoneal dose (0.2 ml) of Tricaprylin was administered to female mice of both strains. Over a period of six days post dosing, the females were mated with (C3H × C57BL)F_1 males. Tricaprylin did not induce dominant lethal mutations in female germ cells (Generoso, Cain, and Hughes 1985).

Tricaprylin was used as a vehicle control in a host-mediated mutagenicity assay. The induction of recombinations (mitotic gene conversion), strongly correlated with the induction of mutations, was evaluated. Male BDII rats (weights = 200 g) each received an oral dose of Tricaprylin (3 ml), after which 10^9 to 10^{10} yeast cells (*Saccharomyces cerevisiae* strain D4-RDII) were injected into the intraperitoneal cavity. Strain D4-RDII requires adenine and tryptophan for growth, and gene conversion creates cells that no longer require these two ingredients for growth. The animals were then killed by cervical dislocation and yeast cells withdrawn and cultures incubated for 8 hours. No difference in the spontaneous frequency of convertants of yeasts injected intraperitoneally was found when vehicle control cultures and yeast suspensions that were not injected into rats were compared (Siebert, Bayer, and Marquardt 1979).

Tricaprylin served as the solvent control in a study evaluating the mutagenicity of polyaromatic hydrocarbons in the following three assays: chromosome aberrations assay, micronucleus test, and sister chromatid exchanges assay. Chinese hamsters (between 8 and 20 weeks old) were used. Test procedures and study results are summarized below (Bayer 1978):

In the chromosome aberrations assay, Tricaprylin (1 ml) was injected intraperitoneally into Chinese hamsters and animals were killed 24 hours later. Bone marrow from both femurs was used for chromosome preparations. Chromosome preparations from untreated animals served as controls. The results were pooled because there were no differences between preparations from treated and untreated animals. Of the 3564 bone marrow cells, the incidence of chromosome aberrations was 1.36% (1.3% gaps and 0.06% breaks). The researchers noted that this control value corresponds to the control value achieved in another laboratory (1.33% gaps and breaks) (Bayer 1978).

In the micronucleus test, Tricaprylin (1 ml) was injected intraperitoneally into Chinese hamsters. The animals were killed 30 hours later and bone marrow smears prepared. The number of micronucleated polychromatic erythrocytes was determined. Because no differences were found between preparations from treated (12 hamsters) and untreated animals (12 hamsters), the results were pooled. In each of the 12 animals, at least 2000 erythrocytes were counted and the polychromatic to normochromatic cells ratio was 1:3.93. The control value for micronucleated polychromatic cells was 5.08% (Bayer 1978).

In a sister-chromatid exchanges (SCE) assay, one group of eight Chinese hamsters was pretreated with bromodeoxyuridine (BUdR) and fluorodeoxyuridine (FUdR), and then injected intraperitoneally with 1 ml of Tricaprylin. The eight untreated hamsters were pretreated with BudR and FUdR. Bone marrow was prepared according the procedure used in the chromosome aberrations assay. It was noted that the crucial prerequisite for the in vivo SCE test is the inhibition of thymidine kinase and the incorporation of BudR into the DNA. Because no differences were found between preparations from treated and untreated animals, the results were pooled. Based on pooled results, a control value of 3.2 ± 0.07 SCEs per cell (500 cells studied) was determined (Bayer 1978).

Trilaurin (C12), Triolein (C18), and Tristearin (C18)

The mutagenicity of Trilaurin, Triolein, and Tristearin was evaluated using *S. typhimurium* strains TA1535, TA100, TA1537, TA1538, and TA98, with and without metabolic activation, according to the procedure of Ames, McCann, and Yamasaki (1975). At a test concentration of 4 mg per plate, Trilaurin (in DMSO) and Tristearin (in DMSO) were not mutagenic, with or without metabolic activation, in any of the strains tested. The same was true for Triolein at a test concentration of 1 mg per plate. The test concentrations of 1 mg/plate and 4 mg/plate represented the greatest doses tested due to limits of solubility, which did not allow testing at concentrations great enough to cause lethality. Based on the results of this test, Trilaurin, Triolein, and Tristearin were not mutagenic (Nestmann et al. 1980).

In the micronucleus test procedure by Schmid (1976), the chromosome breaking effects (indicated by appreciable formation of micronucleated polychromatic erythrocytes) of methylmethanesulfonate, benzo(a)pyrene, and chloramphenicol in bone marrow cells were reduced in the presence of Trilaurin. Trilaurin also had an effect on the germ cell genotoxicity of these three chemicals in the dominant lethal test, performed according to the procedure of Generoso (1985). In the presence of Trilaurin, the fertility index of virgin female mice mated with male mice treated with the three genotoxins was increased, and the percentages of dead implants and females with resorptions were reduced. Methylmethanesulfonate, benzo(a)pyrene, and chloramphenicol are known to reduce the fertility index and increase the percentage of dead implants and the number of females with resorptions in the dominant lethal test that was used. It was concluded that Trilaurin was antigenotoxic in bone marrow cells as well as germ cells (Nolasco and Lim-Sylianco 1993).

Triisostearin (C18)

The mutagenicity of Triisostearin (test concentrations up to 5000 μg/plate) with and without metabolic activation was evaluated in the Ames test using the following *S. typhimurium* strains: TA1535, TA1537, TA98, and TA100. Triisostearin was not mutagenic and did not induce toxicity in any of the strains tested (Unichema International 1997a).

Trioctanoin (C8)

The mutagenicity of Trioctanoin was evaluated using the spot test (gene mutation test). The basis of the spot test is the detection of mutant clones of pigment cells arising in mouse embryos, heterozygous for a number of coat color genes, after somatic mutation induced in utero. After fertilization had occurred (time zero) female mice were dosed intraperitoneally (dose = 2.0 ml; vehicle not stated) with the test substance for 17 days. The day of gestation was stated as day 10.25. Trioctanoin was classified as mutagenic in this test (Styles and Penman 1985).

Trioctanoin was not mutagenic when tested at concentrations up to 5000 μg/plate in a bacterial mutagenicity assay using *S. typhimurium* strains. Additionally, no clastogenic activity was observed in an in vitro cytogenetic test assay. In both experiments, details concerning the test protocol were not provided (Unichema International 1996).

Trioctanoin served as a vehicle control in a micronucleus test using 15 male Sch:ICR Swiss mice (8 to 9 weeks old). After intraperitoneal dosing with Trioctanoin (0.5 ml/dose), the three groups of five mice were killed at 30, 42, and 54 hours post dosing, respectively. Slides of bone marrow cells (from femur) were prepared, and the percentage of polychromatic erythrocytes (PCEs) that contained micronuclei determined. One thousand PCEs were scored per mouse. The percentage of PCEs containing micronuclei varied from 0.04 to 0.22 for control mice in two separate experiments. There was no untreated control group for comparative purposes (Lockard et al. 1982).

Trioctanoin also served as the vehicle control in an in vivo SCE assay using eight male Sch:ICR mice (10 to 14 weeks old). Twenty-two hours after intraperitoneal (IP) dosing with Trioctanoin (0.5 ml per mouse), the mice were killed by cervical dislocation. Seven of the eight animals that survived were used. Slides of bone marrow cells (from femur) were prepared, and a total of 175 cells was examined. The numbers of SCEs were counted in 25 metaphase cells from each mouse; each metaphase had 36 to 42 chromosomes. Another control group of five mice, dosed with water (0.2 ml/mouse), was also used in the study. A mean of 5.3 SCEs/cell was reported for mice dosed with Trioctanoin. The five mice dosed with water had a mean of 4.8 ± 0.4 SCEs/cell (total of 125 cells examined) (Lockard et al. 1982).

The intrarectal administration of Trioctanoin (50 mM in saline) into male Sprague-Dawley rats increased the incorporation of tritiated deoxythymidine (^{3}[H]dThd) into colonic DNA. Compared to the control group, there was a $299\% \pm 82\%$ increase in ^{3}[H]dThd incorporation. The researchers noted that many of the chemicals that increase colonic ^{3}[H]dThd incorporation also are known to enhance colonic tumorigenesis (Bull et al. 1983).

Triolein (C18)

In an in vitro differential DNA repair assay using *Escherichia coli*, Triolein reduced nitrosamine-induced DNA damage in the 1 to 10 μg/ml dose range, and in an in vitro liquid preincubation

assay, prevention of the genotoxic activity of nitrosamines by Triolein was also demonstrated (Knasmüller et al. 1993).

CARCINOGENICITY

Tricaprylin (C8)

Tricaprylin served as the vehicle control in a study evaluating the tumorigenicity of manufactured gas plant residue. The vehicle control group and an untreated control group both consisted of 30 female A/J mice (6 weeks old). Both groups of mice were fed NIH-07 pellet diet. Each vehicle control mouse was injected intraperitoneally with Tricaprylin (0.25 ml; single injection). The mice were killed by cervical dislocation at 260 days post injection. The lungs and stomach were removed from each animal and examined microscopically for tumors. Lung tumors were observed in 37% of vehicle controls and in 23% of untreated control mice. Pulmonary adenomas predominated. When the two groups were compared, values for the mean number of tumors per mouse were not significantly different. Gastric tumors involving the squamous portion were not observed in either group (Weyland et al. 1995).

The carcinogenicity of Tricaprylin also was evaluated using three groups of 60 male F344/N rats (average weights $\approx$ 145 g). The three groups received 2.5, 5, and 10 ml of Tricaprylin/kg body weight by gavage 5 days per week for 2 years. Sixty untreated rats (average weight = 146 g) served as controls. Groups of rats were also dosed with corn oil and safflower oil according to the same procedure to evaluate the carcinogenicity of these two oils. Untreated control groups were also used. Groups of 50 rats (instead of 60) were used for the corn oil experiment. After a period of 15 months, 10 rats from each group were selected for interim hematologic evaluations. Rats found in a moribund state, selected for the 15-month interim evaluations or surviving to the end of the 2-year study, were killed by CO_2 asphyxiation. Necropsy and histopathologic evaluation were performed on all animals. The numbers of rats that survived to study termination are listed as follows: 2.5 ml/kg group (30 rats), 5 ml/kg group (31 rats), and 10 ml/kg group (23 rats), and untreated-control group (31 rats). Compared to untreated controls, statistically significant differences in hematocrit (%), hemoglobin (g/dl), and erythrocytes ($10^6/\mu$l) were noted in the 10 ml/kg dose group (15-month interim evaluation). Results relating to incidences of neoplasia are summarized below (NTP 1994).

In addition to untreated controls, 50 saline control rats were used to determine whether 10 ml of gavage fluid/kg could affect the exocrine pancreas. The incidences of exocrine pancreatic hyperplasia (5/50) and adenoma (1/50) were essentially identical to the incidences of hyperplasia and exocrine pancreatic adenoma in the corn oil, safflower oil, and Tricaprylin untreated control groups. The incidence of skin neoplasms was greater in untreated controls (skin tumor incidence = 7 of 50 rats) than in saline controls (skin tumor incidence = 1 of 50 rats). Skin neoplasms included papillomas, trichoepitheliomas, keratoacanthomas, squamous cell carcinomas, and basal cell carcinomas. This finding was not considered biologically significant because no statistically significant differences were found between saline controls and corn oil or safflower oil untreated control groups (NTP 1994).

Results for Tricaprylin are as follows: Compared to untreated controls, a statistically significant dose-related increase in the incidence of pancreatic acinar cell hyperplasia and adenoma was reported for groups dosed with Tricaprylin. Tricaprylin did not induce any acinar cell carcinomas. Additionally, a dose-related decrease (not statistically significant) in the incidence of pancreatic islet cell hyperplasia and adenoma or carcinoma combined was noted in rats dosed with Tricaprylin. The incidence of squamous cell papilloma in the squamous portion of the stomach of rats of the highest dose group (10 ml/kg) was significantly greater when compared to the tumor incidence in untreated controls. Squamous cell papilloma was accompanied by focal to diffuse cell hyperplasia of the nonglandular stomach. The incidence of mononuclear cell leukemia in the 10 ml/kg dose group (9/53, 17% incidence) was much less than that noted for the untreated control group (23/50, 46% incidence). Additionally, compared to untreated controls, both the incidence and severity of nephropathy were diminished in the highest dose group (10 ml/kg) (NTP 1994).

The researchers noted that the results of this study demonstrated that Tricaprylin and safflower oil do not offer significant advantages over corn oil as a gavage vehicle in long-term rodent studies. This is based on results indicating that each of the three caused hyperplasia and adenoma of the exocrine pancreas, decreased incidences of mononuclear cell leukemia, and reduced incidences and severity of nephropathy in male F344/N rats (NTP 1994).

Tricaprylin served as the vehicle control in a study evaluating the neoplastic potential of monocrotaline pyrrole. Two control groups of SPF CFE rats (5 males, 5 females/group; average weight = 100 g) were used. In one of the groups, Tricaprylin (0.2 ml) was injected subcutaneously twice weekly for 30 weeks (60 injections). Dosing was followed by a 36-week nontreatment period. In the second group, injections were made twice weekly for a total of 75 weeks (150 injections). Animals with tumors were killed when their health deteriorated or when the neoplasm became ulcerated. Of the 20 rats treated, tumors were observed in 2 animals (at 50 and 61 weeks, respectively). Both tumors were sarcomas arising from the connective tissue at the injection site. According to the investigators, the occurrence of tumors in control rats was unexpected (Hooson and Grasso 1976).

Tricaprylin also served as a vehicle control in a study evaluating the carcinogenicity of the pesticide, maleic hydrazide. Tricaprylin was injected subcutaneously into 61 newborn mice (of 16 litters) in volumes of 0.1, 0.1, 0.2, and 0.2 ml, on days 1, 7, 14, and 21 after birth, respectively. The results were reported based on the number of survivors at the time that the first tumor was observed (23 males, 22 females injected with Tricaprylin). There were 47 male and 47 female survivors in the

untreated control group. Sixteen and 14 tumors were reported for the 23 male and 22 female survivors injected with Tricaprylin, respectively. In both males and females, most of the tumors were found in the lymphoid tissues. Tumors of the lung and liver were observed in male mice, but were not observed in females. Of the Tricaprylin-treated mice that survived (23 males, 22 females) the percentages of males and females with tumors were 60.9% and 59.1%, respectively. In untreated controls (47 male and 47 female survivors), the percentages of males and females with tumors were 51.1% and 42.6%, respectively (Cabral and Ponomarkov 1982).

In a study evaluating the carcinogenicity of di- and trifunctional α-chloro ethers and 1,4-Dichlorobutene-2 in ICR/Ha female Swiss mice (4 to 6 weeks old) , Tricaprylin (vehicle), and untreated controls were used. Tricaprylin was injected either subcutaneously or intraperitoneally weekly for 502 to 569 days (depending on level of survival). With the exception of the cranial region, all mice were necropsied either at the end of the experiment or at the time of interim death. Tissues were subjected to histopathological evaluation. In the subcutaneous injection experiment (left flank; 0.05 ml weekly), the vehicle control group consisted of 50 mice and the untreated control group consisted of 85 mice. No tumors were observed in untreated control mice or mice injected subcutaneously with Tricaprylin. In the intraperitoneal injection experiment (lower abdomen; 0.05 ml once weekly), the vehicle-control group consisted of 30 female mice and the untreated control group consisted of 85 female mice. No tumors were observed in untreated controls or mice injected intraperitoneally with Tricaprylin (Van Duuren, Goldschmidt, and Seidman 1975).

In addition to the preceding study, Tricaprylin has been used as a negative/solvent control in a number of carcinogenicity/cocarcinogenicity or tumorigenicity studies (Fugi and Epstein 1979; Prahalad et al. 1997; Nesnow et al. 1994). An untreated-control group was not used in either of these studies.

Trioctanoin (C8)

Trioctanoin was used as the vehicle control in a study evaluating the carcinogenic activity of polycyclic hydrocarbons. The control group consisted of 10 male hamsters (weights = 55 to 75 g). Trioctanoin (0.4 ml) was injected subcutaneously (single injection) into the nape of the neck of each animal. No tumors were reported over a period of 17 weeks (Wodinsky, Helinski, and Kensler 1964).

Trioctanoin also served as the vehicle control in another carcinogenicity study using Syrian golden hamsters. The focus of this study was the induction of respiratory tract tumors in Syrian golden hamsters by a single dose of 4-(methylnitrosamino)-1-(3-pyridyl)-1-(3-pyridyl)-1-butanone (NNK) and the effect of smoke inhalation. Respiratory tract tumors were not observed in two groups of hamsters (10 males, 10 females/group) injected subcutaneously with Trioctanoin (single injection at 8 weeks) and subjected to sham smoking in the 69 week study (Hecht et al. 1983).

In another study, differences in the incidence of mammary tumors between the offspring of pregnant COBS SD rats injected intraperitoneally with Trioctanoin (1 ml/kg on days 16 and 17 of gestation) and untreated control offspring were determined. The percentage of Trioctanoin-treated female offspring with mammary tumors was 43% (9 of 21 females), and the percentage of untreated female offspring with mammary tumors was 29% (10 of 35 females). In this study, Trioctanoin served as the vehicle control in a study evaluating the enhanced development of mammary tumors in rats following transplacental and neonatal exposure to ethylnitrosourea (Mandybur, Ormsby, and Buncher 1978).

No tumors were observed in the offspring of vehicle-control groups of pregnant Sendai virus-free Syrian Golden hamsters that received a single subcutaneous injection of Trioctanoin (40 males, 42 females, day 15 of gestation) or three subcutaneous injections of Trioctanoin (43 males, 40 females, last 3 days of gestation). This study was concerned with the transplacental carcinogenicity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (Correa et al. 1990).

The intraperitoneal administration of Trioctanoin to two strains of pregnant rabbits (IIIVO/J and WH/J) did not induce tumors in any of the offspring. Eighteen does of the WH/J strain and 10 does of the IIIVO/J strain were dosed over a 10-day period. In this study, the transplacental carcinogenic potential of *N*-Ethyl-*N*-nitrosourea (ENU) was evaluated, and Trioctanoin served as the vehicle control. Doses of ENU (10 mg/kg/day) were injected over a 10-day period, and equal volumes of Trioctanoin were administered to controls (Fox et al. 1980).

Triolein (C18)

Triolein served as a negative control in a carcinogenicity study involving rats. Ten control rats were injected subcutaneously with Triolein (0.2 to 0.5 cc, in groin). No tumors were observed at the injection site over a period of 540 days (Burrows, Hieger, and Kennaway 1936).

Cocarcinogenicity

Triolein (C18)

The cocarcinogenicity of Triolein was evaluated using groups of 33 castrated male Marsh mice and groups of 28 intact male BALB/c mice. Groups of Marsh mice were injected subcutaneously with 6β-hydroxyperoxy-4-cholesten-3-one (in Triolein or sesame oil) and with sesame oil (control). Groups of BALB/c mice were injected with 6β-hydroxyperoxy-4- cholesten-3-one in either Triolein, sesame oil, or 2% Balb serum, or with either Triolein or sesame oil (controls) alone. Comparisons between groups were made up to age 19 months. In Marsh mice, 6β-hydroxyperoxy-4-cholesten-3-one (5 mg) in sesame oil and Triolein produced 9% and 18% sarcomas, respectively. In Balb/c mice, 6β-hydroxyperoxy-4-cholesten-3-one (10 mg) alone did not produce local sarcomas, but caused 7% local hemorrhagic cysts when tested in sesame oil. Tumors were not observed in any of the groups (both strains) injected with Triolein or

sesame oil alone. In another comparison, 6β-hydroxyperoxy-4-cholesten-3-one did not increase the incidence of lung adenomas in Marsh mice over that observed in Triolein and sesame oil control groups. However, in Balb/c mice, the incidence of 6β-hydroxyperoxy-4-cholesten-3-one (in saline)-induced lung adenomas (39%) was significantly greater when compared to Triolein and sesame oil controls (Bryson and Bischoff 1964).

The researchers in the preceding study added that, to date, 6β-hydroxyperoxy-4-cholesten-3-one in sesame oil, cottonseed oil, and/or Triolein has produced sarcomas in Marsh and C57 mice and in Evans rats, but not in Swiss and Balb mice. Additionally, 6β-hydroxyperoxy-4-cholesten-3-one, administered as an isotonic aqueous suspension, did not produce neoplasms in Marsh, Balb, or Evans strains. The investigators also stated that, when effective, Triolein (a major constituent of the oils tested) apparently acts as the local cocarcinogenic factor (Bryson and Bischoff 1964).

Tumor Inhibition

Trilaurin (C12)

The effect of Trilaurin on the promotion stage of carcinogenesis was evaluated using groups of ten Swiss Webster mice. In the test group, the back of each mouse was shaved and dimethylbenzanthracene (DMBA) (250 μg/0.25 ml) was applied to the shaved area 3 days later. Croton oil (0.03% in acetone) was applied to the same site 3 days after DMBA application, and Trilaurin was brushed on three minutes later. Applications of each chemical were made three times per week for 20 weeks, after which the animals were killed by cervical dislocation. Four additional groups were treated with DMBA (alone), croton oil (alone), DMBA + croton oil, and DMBA + Trilaurin, respectively, for the same duration. Cutaneous neoplasms and neoplasms of the internal organs were recorded, and the incidence of neoplasms determined. After 20 weeks of exposure, no neoplasms were found in the groups treated with DMBA (alone) and croton oil (alone), respectively, and all mice in the group treated with DMBA + croton oil had neoplasms. Trilaurin completely inhibited the formation of neoplasms (0% incidence) initiated by DMBA and promoted by croton oil. No neoplasms were observed in the group treated with DMBA + Trilaurin (Nolasco et al. 1994).

Tricaprylin (C8)

Inbred Nb rats with implants of Nb2 lymphoma (liver implantation) were treated orally with two 150-mg doses of Tricaprylin. Extensive damage to tumor cells was evident microscopically 4 to11 hours after implantation; hepatocytes were unaffected. On day 17, nuclei were pyknotic and angular, and cells were not in close contact (Burton 1991).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Tricaprylin (C8)

Two groups of 20 female mice received oral doses of 2 ml/kg and 10 ml/kg Tricaprylin, respectively, during gestation. Of the 220 live fetuses from the 2-ml/kg dose group, the following six were malformed: cleft palate (1 fetus), club foot (3 fetuses), and assimilation of the ribs (2 fetuses). Of the 219 live fetuses from the 10-ml/kg group, the following 8 were malformed: cleft palate (3 fetuses), club foot (4 fetuses), and assimilation of the cervical vertebrae (1 fetus). Curled tail (1 fetus), cleft palate (1 fetus), and club foot (1 fetus) were the only malformations reported for 3 of 220 live control fetuses. The investigators concluded that Tricaprylin was not teratogenic in mice (Ohta et al. 1970).

In another experiment from the above study, eight female mice were dosed orally with Tricaprylin during gestation. No malformations were reported for any of the 61 live fetuses (Ohta et al. 1970).

Tricaprylin was effective in producing fusion of the endometrial epithelium (symplasma formation) and decidualization of the stroma in pseudopregnant New Zealand white rabbits. (With this in mind, the investigators noted that many of the oils used as vehicles for fat-soluble materials, such as the steroidal sex hormones, have significant estrogenic activity.) On day 0, Tricaprylin (0.1 ml) was injected into isolated segments of the uterus in which pseudopregnancy had been induced by IV injection of human chorionic gonadotropin (HCG). The animals were killed as groups of three on days 1, 2, 3, 4, and 6. Saline, simple ligation of the uterus or uterine trauma served as control treatments in other uterine segments in the same animals. Trauma and ligation with saline, but not ligation alone, induced formation of symplasma. Decidualization was observed after trauma but not after ligation or saline injection alone. Compared to control treatments, Tricaprylin was much more effective in inducing symplasma formation. Symplasma, most typically observed in the rabbit, has been specifically described as a fusion of originally columnar cells into large, multinucleated cells with intensely acidophilic cytoplasm. According to the researchers, it is usually found at the implantation site and covering areas of decidua at the margin of the placenta, as well as in areas of decidualization induced by trauma or other artificial means (Davies and Davenport 1979).

Tricaprylin was used as a vehicle control in a study evaluating the developmental toxicity of dichloroacetonitrile. Tricaprylin (dose not stated) was administered orally to pregnant female Long-Evans hooded rats (65 to 80 days old) on days 6 to 18 of gestation. Another control group was dosed with water according to the same procedure. Pregnant females were killed on day 20 of gestation. No statistically significant differences were found in reproductive parameters between Tricaprylin and water control groups (Smith et al. 1989).

Trioctanoin (C8)

The developmental toxicity of Trioctanoin was evaluated using time-mated, female specific-pathogen-free CD-1 mice (6 to 8 weeks old). Nonpregnant mice were dosed orally for 8 consecutive days in a dose-finding study; the LD_{10} was used in the reproductive phase. In this phase of the study, time-mated mice received oral doses of 4750 mg/kg/day (dose

volume = 5 ml/kg, corn oil vehicle) on gestation days 6 to 13 and were allowed to deliver litters. Litter size, birth weight, and neonatal growth and survival to postnatal day 3 were recorded as indices of potential developmental toxicity. The proportion of pregnant survivors that delivered a viable litter (at least one liveborn pup) was compared with the concurrent vehicle control (corn oil) using a one-tail Fisher's exact test. For mice that delivered a viable litter, the following were analyzed by pairwise multiple comparisons of control and treated groups using the two-tail Mann-Whitney *U* test: the number of liveborn pups per litter, percent neonatal survival to postnatal day 3, average pup weight at birth, and average pup weight gain by postnatal day 3. Study results indicated no significant differences in any of the parameters evaluated between pregnant mice dosed with Trioctanoin and corn oil–treated controls (Hardin et al. 1987).

Trioctanoin was used as a vehicle control in a study evaluating the teratogenicity of 1-ethyl-1-nitrosourea. The following strains of pregnant mice (mated at 10 weeks of age) were tested: AKR/J, SWR/J, DBA/2J, C57Bl/6J, and C57L/J. In test groups, 1-ethyl-1-nitrosourea was injected intraperitoneally (0.5 mmole/kg body weight) on days 8 and 12 of gestation. Control groups received an equivalent volume of Trioctanoin. Various kinds of eye abnormalities were observed in 6.2% of 291 control fetuses of the five strains studied; other malformations were also observed. However, no untreated-control group or historical control data were used for comparative purposes (Diwan 1974).

Trioctanoin was used as the vehicle control in a sperm abnormality test. Ten male control mice ($B6C3F_1$/Hap hybrid strain; 10- to 12-week-old) received an intraperitoneal injection of Trioctanoin (0.25 ml per injection) daily for 5 days. After day 35, the animals were killed, caudae epididymides removed, and slides of sperm preparations made. The percentage of abnormal sperm in 500 sperm per animal was determined to be 4.5% ± 1.7%. No untreated controls or historical control data were used for comparative purposes (Lockard et al. 1982).

CLINICAL ASSESSMENT OF SAFETY

Metabolism

Tricaprin (C10)

Following the oral administration of Tricaprin to three human subjects, a considerable amount of sebacic acid (C10) was isolated from the urine along with smaller quantities of suberic acid (C8) and adipic acid (C6) (Verkade and vander Lee 1934).

Trioctanoin (C8)

[^{13}C]-Trioctanoin was administered orally to five normal term neonates and five growing preterm infants. ^{13}C enrichment in carbon dioxide was analyzed using isotope ratio mass spectrometry; oxidation rates over 6 hours were calculated. The peak for ^{13}C appearance was between 120 and 240 minutes post administration in preterm infants and between 90 and 180 minutes post administration in full-term infants. Oxidation rates for [^{13}C]-Trioctanoin were 46.2% ± 3.6% in preterm infants and 53.5% ± 13.8% in normal neonates. The difference between these two values was not statistically significant. Study results indicated that Trioctanoin was utilized sufficiently, even in the neonatal period, during which energy intake is restricted by immaturity of digestive or excretory function (Hoshi et al. 1992).

Triolein (C18)

Eight adult subjects (ages 21 to 51) were fed 10 μCi [^{14}C]-Triolein in 5 g olive oil together with a standard breakfast. The collection and assay of expired air began 1 hour after dosing and continued until lunch time. The maximum rate of excretion of Glyceryl-Trioleate-1-^{14}C as $^{14}CO_2$ in expired air occurred 5 to 6 hours after the beginning of the experiment (Blomstrand and Kager 1973).

In another study, five adult subjects (ages 31 to 63) were fed a breakfast containing 20 μCi [^{14}C]-Triolein. The quantity of expired $^{14}CO_2$ was estimated from measurements of specific activity of $^{14}CO_2$ in duplicate samples of breath over a period of days, the last of which occurred at 28 days post ingestion. At day 1, 15% to 33% of the ingested dose was expired, and 25% to 40% of the dose was expired at 10 days post-ingestion. From day 10 on, $^{14}CO_2$ was expired at a slow, but constant rate (Pedersen and Marqversen 1981).

The fate of orally administered [1-^{13}C]- and [8-^{13}C]-Triolein was evaluated using four healthy human subjects (two males, two females). In the first experiment, 100 mg of [1-^{13}C]-Triolein was administered orally (postprandial). One week later in a second experiment, the four subjects received 100 mg of [8-^{13}C]-Triolein. The fate of both radioactive compounds was traced in serum lipids. A trend of an increase in absolute concentration of triglyceride (TG) oleic acid was noted. ^{13}C enrichment in palmitic, stearic, linoleic, and oleic acids of these fractions was determined using gas chromatography/isotope ratio mass spectrometry. At time points 1, 2, 4, 7, and 9 hours after dosing, a range of 2% to 24% of [1-^{13}C]-Triolein was recovered in the serum TG fraction, compared to 10% to 60% of the [8-^{13}C]-Triolein dose. Thus, after administration of [8-^{13}C]-Triolein , the TG oleic acid in serum was significantly more highly enriched (significantly higher enrichment peak) in ^{13}C than after [1-^{13}C]-Triolein administration. This difference could have been due to faster elimination of [1-^{13}C]-Triolein from the serum. ^{13}C enrichment in other fatty acids of the TG fraction as well as phospholipid and cholesterol ester fractions were in the range of natural ^{13}C abundance (Metges, Kempe, and Wolfram 1994).

Eight patients with chronic pancreatitis were fed a breakfast containing [^{14}C]-Triolein (10 μCi). These patients, regarded as having normal lipid assimilation (<7 g of fat per day excreted), excreted in the feces ≤10.4% of the dose of ^{14}C ingested (Pedersen and Halgreen 1985).

Tripalmitin (C16)

The metabolic fate of a triglyceride oral load labeled with [1,1,1-$^{13}C_3$]-Tripalmitin was investigated by noting the appearance of labeled palmitate in the circulating nonesterified

fatty acids (NEFA) and TG. Six healthy adult subjects (five females, one male; 21 to 29 years old) were used in this evaluation. The average body mass index (BMI) for these subjects was 21 kg/m^2. Sunflower oil (30 g) enriched with 300 mg of [1,1,1-$^{13}C_3$]-Tripalmitin was ingested by each subject, after which blood samples were collected. Blood was collected at 10, 20, and 30 minutes, and then every 30 minutes up to 480 minutes. [1-^{13}C]-palmitate appeared in the plasma TG at 90 minutes, and the mole percent excess (MPE) of [1-^{13}C]-palmitate in TG increased and reached a plateau after 240 minutes. At 240 minutes, the MPE of [1-^{13}C]-palmitate was significantly greater in NEFA than in TG. At the conclusion of the study, the MPE of [1-^{13}C]-palmitate in TG remained significantly greater than baseline values ($p < .0001$) (Binnert et al. 1995).

In the same study, four additional adult subjects (three males, one female; 22 to 30 years old), the reesterification of NEFA was determined during [1-^{13}C]-palmitate infusion. The average BMI for these subjects was 21 kg/m^3. Albumin-bound [1-^{13}C]-palmitate was infused intravenously for 150 minutes, and blood samples were collected at 120 and 150 minutes. Hepatic reesterification of intravenously infused [1-^{13}C]-palmitate was estimated from the appearance of labeled palmitate in TG. A constant ^{13}C-palmitate enrichment of 1.6 ± 0.2 MPE was noted in NEFA after 120 minutes of [1-^{13}C]-palmitate infusion. However, [^{13}C]-palmitate enrichment increased from 0.23 ± 0.07 to 0.37 ± 0.07 MPE ($p < .001$) in plasma TG between 120 and 150 minutes. The estimated contribution from NEFA to palmitate of total TG (estimated reesterification) increased from $13.9\% \pm 3.6\%$ to $22.6\% \pm 2.6\%$ over the same period (Binnert et al. 1995).

The metabolic fate of an oral long-chain TG load was determined using 10 healthy female subjects (mean age $= 23 \pm 2$ years BMI $= 20.3 \pm 1.6$). The women were studied during a 6-hour period after ingestion of 30 g of olive oil made radioactive with [1,1,1-$^{13}C_3$]-Triolein. Total lipid oxidation was determined using indirect calorimetry. After 90 minutes, radioactivity was greater in chylomicron triglycerides (CM-TG) than in NEFA of very-low-density lipoprotein (VLDL). CM-TG were radioactive first, followed by NEFA and then VLDL. Thus, in this study, a long-chain TG mainly followed the classical lymph pathway. A plateau of enrichment was noted for CM-TG and NEFA at 180 minutes, demonstrating the entry of exogenous lipids into the NEFA pool. For VLDL-TG, a plateau of enrichment was noted after 300 minutes. The extent of enrichment for VLDL-TG ($0.38\% \pm 0.04\%$) was similar to that noted for NEFA ($0.36\% \pm 0.03\%$). The investigators stated that these similar results were suggestive of a precursor-product relationship. The percentage of the TG load that was oxidized was $19\% \pm 2\%$. Exogenous TG accounted for 70% of the total lipid oxidation over the period of 300 to 360 minutes. The investigators concluded that after ingestion of a lipid load, a cycle of fatty acids TG from CM to NEFA and from NEFA to VLDL takes place. Additionally, this lipid load has a sparing effect on endogenous lipid stores (Binnert et al. 1996).

Ocular Irritation

Tribehenin (C22)

The ocular irritation potential of an eye enhancer (eye area cosmetic product) containing 0.32% Tribehenin was evaluated using a group of 20 subjects (males and females). The test substance (undiluted cream, 10 to 30 μl) was instilled into one eye of each subject. Eye examinations were performed by a board-certified ophthalmologist before and after instillation of the test substance. During the subjective evaluation, few subjects reported transient burning/stinging sensation. However, itching, dryness, pain, and foreign body sensation were minimal throughout the study. During the objective evaluation, increased lacrimation was noted in one subject within 120 minutes post instillation, whereas, none of the remaining subjects had increased lacrimation at 5 minutes post instillation. Eyelid inflammation was not observed during the study. Mild to moderate irritation of the upper and/or lower palpebral conjunctivae was noted in all subjects at 30 seconds post instillation. However, at the time of the final evaluation (120 minutes post instillation), the subjects either had no irritation or mild irritation. Mild bulbar conjunctival irritation was noted in the majority of the subjects within the first few minutes after instillation. These reactions subsided during the remainder of the study (CTFA No date a, 1998c).

The in-use safety of two eye enhancers (eye area cosmetic products) containing 0.32% Tribehenin was evaluated using 40 female subjects (between 18 and 65 years old) who were contact lens wearers and regular users of eye shadow products. The subjects were instructed to use the two products (20 subjects per cream) for four consecutive weeks. Pre- and post-test eye examinations were performed by a board-certified ophthalmologist to support the claims of "ophthalmologist-tested" and "safe for contact lens wearers." Clinically relevant alterations in visual acuity were not observed in any of the subjects during the course of the study. Eye examinations performed by the ophthalmologist did not reveal any signs of ocular irritation either before or after product use. Additionally, none of the subjects reported any problems that were related to product use. It was concluded that both products were safe for their intended use (CTFA No date a, 1998c)

In another in-use study conducted according to the preceding test procedure, the safety of another eye enhancer containing 0.32% Tribehenin was evaluated using 31 female subjects (contact lens wearers). Eye examinations performed by an ophthalmologist did not reveal any signs of ocular irritation after product use. Additionally, clinically relevant alterations in visual acuity were not observed in any of the subjects tested. It was concluded that the eye enhancer was safe for its intended use (CTFA No date a, 1998c).

Tristearin (C18)

The ocular irritation potential of an eye defining pencil containing 1.68% Tristearin was evaluated in an in-use study using a group of 31 female subjects who were contact lens wearers. The

test procedure is stated in the preceding section. Ocular irritation was not observed in either of the subjects prior to product use or after four consecutive weeks of daily use. It was concluded that the eye defining pencil was safe for its intended use (CTFA No date a, 1998c).

Skin Irritation

Trilaurin (C12)

The skin irritation potential of an eyeliner containing 36.3% Trilaurin was evaluated in a single-insult occlusive patch test using 17 subjects (ages not stated). A control group of 17 subjects was also used. Reactions were scored according to the following scale: 0 (no evidence of any effect) to 4 (severe; deep red erythema with vesiculation or weeping with or without edema). No skin irritation was observed in any of the subjects (CTFA 1984c).

Trioctanoin (C8)

The primary skin irritation potential of Trioctanoin was evaluated using a panel of 25 men and women. Results were negative at 24 and 72 hours. Details concerning the test protocol were not included (Unichema International 1996).

Skin Irritation and Sensitization

Trilaurin (C12)

The skin sensitization potential of an eyebrow pencil containing 40% Trilaurin was evaluated using 91 subjects (88 males, 3 females). The subjects ranged in age from 18 to >65 years old. A total of nine induction applications (24-hour occlusive patches, covered with test material) were made to the same test site on each subject. Alternate test sites were used for the challenge phase. The eyebrow pencil induced mostly mild skin irritation during induction in one subject and there was no evidence of delayed contact hypersensitivity in any of the 91 subjects (Hill Top Research, Inc. 1988).

Tristearin (C18)

The skin irritation and sensitization potential of an eye defining pencil containing 1.68% Tristearin was evaluated in a 6-week study using 160 subjects (mainly females). Seven subjects withdrew from the study for reasons unrelated to administration of the test substance, reducing the test population to 153 subjects. The repeated-insult patch test (RIPT) protocol used was a modification of the Draize-Shelanski RIPT procedure. The undiluted test substance was applied liberally (under occlusive patches) to the scapular back three times per week for a total of nine applications. After a 2-week nontreatment period, two consecutive occlusive challenge patches containing the test substance were applied to a different site on the scapular back. Reactions were not observed in any of the subjects during the induction or challenge phase. It was concluded that the eye defining pencil did not induce irritant contact dermatitis or allergic contact dermatitis (CTFA No date a, 1998c).

Tribehenin (C22)

The skin irritation and sensitization potential of an eye enhancer (eye area cosmetic product) containing 0.32% Tribehenin was evaluated in a 6-week study using 211 subjects. One hundred ninety-eight subjects completed the study because 13 withdrew for reasons unrelated to the conduct of the study. The RIPT protocol was a modification of the procedure by Draize. Occlusive patches (occlusive plastic chambers) moistened with approximately 0.02 g of the cream were applied to the test site (upper arm or back) and secured with an occlusive bandage. During the 3-week induction period, patches were applied (same site) three times per week for 48 to 72 hours. The challenge phase was initiated 2 weeks after the end of induction. Challenge patches were applied to new test sites for 72 hours. Reactions were scored at 96 hours post application according to the following scale: 1 (erythema) to 4 (erythema, induration, and bullae). G (minimal glazing, such as "peau d'orange"), O (negative), and + (equivocal reaction) designations were also used. An equivocal reaction was observed in three subjects during the induction phase. Challenge reactions were not observed in any of the subjects tested. It was concluded that the eye enhancer did not induce clinically significant irritant contact dermatitis or allergic contact dermatitis (CTFA No date a, 1998c).

Both a hand cream and a lip cream containing 0.38% Tribehenin were evaluated in human RIPTs according to a procedure similar to that stated in the preceding paragraph. The hand cream and lip cream were tested in one and two RIPTs, respectively. The modifications of the test procedure previously mentioned were as follows: In each test, enrollment was sufficient to ensure that 200 men and/or women completed the study. The application period for induction and challenge patches (occlusive) was 24 hours; the quantity of test substance per patch application was not stated. Induction reactions were scored at 48 and 72 hours post application and challenge reactions were scored at 48 and 96 hours. The nontreatment period between induction and challenge phases ranged from 10 to 15 days. It was concluded that the hand cream and the lip cream were neither skin irritants nor sensitizers. Details concerning the study results were not included (CTFA No date a, 1998c).

Skin Sensitization

Trioctanoin (C8)

Reportedly, Trioctanoin did not induce sensitization in a contact allergy test involving human subjects. Details concerning the test protocol were not provided (Unichema International 1996).

Comedogenicity

The comedogenicity of a lip enhancer (cream) containing 0.38% Tribehenin was evaluated using 18 subjects (18 to 45 years old). One hundred microliters of the cream were dosed onto the surface of each occlusive patch that was taped to the upper back. Test sites were situated at the right and left of the spinal column. The subjects were instructed to return to the clinic every

Monday, Wednesday, and Friday for a total of 4 consecutive weeks (28 days) of patch removal, scoring of irritation reactions, and application of fresh patches. Reactions were scored using the North American Contact Dermatitis grading scale: 0 (no reaction) to +3 (a bullous reaction or an ulcer). At the time of the final visit, reactions were scored and follicular biopsies (cyanoacrylate follicular biopsy technique) taken at test and control sites. Specimens were evaluated according to the following scale using a stereomicroscope: 0 (no microcomedones, 0%) to 3 (severe, 75% to 100% larger globoid microcomedones). Data from the global assessments of test and control sites were compared statistically for biological significance ($p \leq .05$). A recorded mean value of 1 or greater that is significantly different from the negative control was considered positive for comedogenicity. Study results are summarized below:

None of the subjects had clinically significant skin irritation during the study. However, occasionally, macular erythema (score = +0.5) was observed in one subject. Statistical comparisons of microcomedone formation between test and control sites yielded a p value of >05. Thus, it was concluded that there was no difference between test and control sites and that the lip enhancer was not comedogenic (CTFA No date a, 1998c).

Case Reports

Triarachidin (C20), Trilinolein (C18), Triolein, (C18), and Tripalmitin (C16)

Thirteen eczema patients (median age = 68) with contact allergy to olive oil were patch-tested with the following glyceryl triesters, constituents of olive oil: Triolein (~30% in petrolatum [pet]), Tripalmitin (~30% in pet), Trilinolein (~5% in pet), and Triarachidin (~30% in pet). Patch tests were applied to normal skin of the back using Finn chambers secured with Scanpor tape. The chambers were removed after 48 hours, and reactions were recorded according to International Contact Dermatitis Research Group recommendations. All patch tests with the glyceryl triesters were negative (Malmkvist, Pettersson, and Svensson 1990).

In another case report, a woman (71 years old) and a man (60 years old) with dermatitis were patch-tested with Triolein (30% in vaseline). The results were negative (van Joost, Smitt, and van Ketel 1981).

SUMMARY

The safety of the following glyceryl triesters in cosmetics is reviewed in this report: Trilaurin, Triarachidin, Tribehenin, Tricaprin, Tricaprylin, Trierucin, Triheptanoin, Triheptylundecanoin, Triisononanoin, Triisopalmitin, Triisostearin, Trilinolein, Trimyristin, Trioctanoin, Triolein, Tripalmitin, Tripalmitolein, Triricinolein, Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, Glyceryl Triacetyl Ricinoleate, and Glyceryl Stearate Diacetate.

The ingredients mentioned above are used mostly as skin-conditioning agents—occlusive and/or viscosity-increasing agents—nonaqueous. Frequency of use data submitted to FDA in 1998 indicate that 12 of the 23 ingredients in this safety assessment (Trilaurin, Tricaprylin, Tribehenin, Triisononanoin, Triisostearin, Trilinolein, Trimyristin, Trioctanoin, Tripalmitin, Tristearin, Glyceryl Triacetyl Hydroxystearate, and Glyceryl Triacetyl Ricinoleate) are being used in cosmetics. Collectively, these data indicate use in a total of 443 cosmetic products. Concentration of use data received from the cosmetics industry in 1999 indicated use of Glyceryl Triesters in cosmetic products at concentrations up to 46.3%.

Metabolism data indicate that most triglycerides (or glyceryl triesters) are split into monoglycerides, free fatty acids, and glycerol in the small intestine and absorbed by the intestinal mucosa.

In mice and guinea pigs, little skin penetration was observed, althrough Tricaprylin did enhance the skin penetration of drugs in vivo (Wistar rats) and in vitro (hairless mice). The skin penetration enhancement of drugs in the presence of Triolein has also been reported.

Acute oral LD_{50} values range from 5 g/kg in mice (Tribehenin, C8 aliphatic acid chains) to >20 g/kg in rats (Tristearin, C18). In other acute oral toxicity studies, Trioctanoin (C8) was not toxic following oral administration to male mice at a dose of 50 ml/kg, and Triisostearin did not induce toxicity in rats at a dose of 2 g/kg. In an acute intravenous toxicity study, Tricaprylin (C8) induced very minimal acute effects following administration to rats and mice, although, in another acute study, spasms in the hindlegs and respiratory distress were observed in mice injected intravenously with a 25% Tricaprylin emulsion. In acute parenteral toxicity studies, Tricaprylin induced very minimal toxicity in groups of mice and rats dosed intraperitoneally/subcutaneously.

The short-term oral administration of Trilaurin (C12), Tristearin (C18), or Triolein (C18) to weanling rats did not result in gross or microscopic lesions; however, in another short-term study, significant differences in hematological and clinical chemistry parameters as well as organ weights were noted after administration of Tricaprylin (C8) to male and female Wistar rats.

No significant differences were found in growth rate or the incidence of lesions between groups of rats fed a mixture containing 0.0002% Trilaurin (C12) for 2 years and controls. In another chronic study, cardiac lipidosis and/or focal fibrosis was observed in rats fed a basal diet consisting of 30 cal % Trierucin (C22) for 24 weeks. Renal tubular dilatation, proteinaceous casts, or fibrosis were also reported.

When the chronic oral toxicity of Tricaprylin (C8) was evaluated using groups of male rats, significant reductions in hematological/clinical chemistry parameters and significant increases in organ weight were noted after 26 weeks of dosing. Few lesions in the kidneys, myocardium, and aorta were noted when Tricaprylin was tested in another chronic oral toxicity study.

An eyeliner containing 36.3% Trilaurin (C12) and a 20% solution of Tribehenin (C22) in liquid paraffin were, at most, mildly irritating to the eyes of rabbits. Trioctanoin (C8) and

Triisostearin (C18) did not induce ocular irritation in rabbits. An eye enhancer cream containing 0.32% Tribehenin and a hand cream containing 0.38% Tribehenin were classified as nonirritants in an in vitro chorioallantoic membrane vascular assay for determining the ocular irritation potential of chemicals.

Triisostearin (C18) and a 20% solution of Tribehenin (C22) in liquid paraffin were, at most, mildly irritating when applied to the skin of rabbits. However, Trioctanoin (C8) and an eyeliner containing 36.3% Trilaurin (C12) did not induce cutaneous irritation in rabbits. Neither Tribehenin (C22) nor Trioctanoin (C8) induced sensitization in the Magnusson-Kligman guinea pig maximization test. Triisostearin (C18) did not induce significant cutaneous reactions in a study evaluating the phototoxicity and photoallergenicity potential of this ingredient in guinea pigs.

Most of the mutagenicity data in this report are on the ingredient, Tricaprylin (C8). In the Ames test, Tricaprylin was mutagenic in one of four *S. typhimurium* strains tested. Negative test results were reported in the following assays: dominant lethal test, host-mediated mitotic gene conversion assay, chromosomal aberrations assay, micronucleus test, SCE assay, spot test for gene mutations, and cytogenetic assay for clastogenic activity.

In the Ames test, Trilaurin (C12), Trioctanoin (C8), Triolein (C18), Tristearin (C18), and Triisostearin (C18) were not mutagenic in *S. typhimurium* strains. However, Trioctanoin was mutagenic in the spot test for gene mutations. In other tests, no clastogenic activity was noted when Trioctanoin was tested in a cytogenetics assay and results were negative in a sister chromatid exchanges mutagenicity assay.

Following intraperitoneal injection of Tricaprylin (C8) into 30 female mice in a tumorigenicity study, lung tumors were observed in 37% of the animals. In the untreated-control group of 30 mice, the lung tumor incidence was 23%. The results of an oral carcinogenicity study by the National Toxicology Program (NTP) indicated that Tricaprylin (C8) caused a statistically significant dose-related increase in the incidence of pancreatic acinar cell hyperplasia and adenoma in rats. Tricaprylin did not induce acinar cell carcinomas. Additionally, the incidence of squamous cell papilloma in the squamous portion of the stomach of rats in the highest dose group (10 ml/kg Tricaprylin) was significantly greater when compared to controls.

Trilaurin (C12) completely inhibited the formation of neoplasms initiated by DMBA and promoted by croton oil. Additionally, extensive damage to tumor cells (lymphoma implants in the liver) was noted in rats after oral dosing with Tricaprylin (C8).

Tricaprylin (C8) was not teratogenic in mice or rats when administered orally. In another study on reproductive effects, Tricaprylin was effective in producing fusion of the endometrial epithelium (symplasma formation) and decidualization of the stroma in pseudopregnant New Zealand white rabbits.

The oral administration of Trioctanoin (C8) to mice did not result in any significant differences in indices of potential developmental toxicity (i.e., litter size, birth weight, and neonatal growth and survival to postnatal day 3) between test and control groups. Test results for 291 fetuses from various strains of mice injected intraperitoneally with Trioctanoin (vehicle control) in a teratogenicity study indicated various kinds of eye abnormalities in 6.2% of the fetuses.

An eye enhancer cream containing 0.32% Tribehenin induced reactions ranging from mild to moderate ocular irritation in a group of 20 subjects, which resolved to either mild irritation or no irritation reactions at 2 hours post exposure. In a clinical in-use safety test of two eye enhancer creams containing 0.32% Tribehenin, neither ocular irritation nor clinically relevant alterations in visual acuity were observed after 4 consecutive weeks of daily product use. Similar results were reported after testing of another eye enhancer cream containing 0.32% Tribehenin and an eye defining pencil containing 1.68% Tristearin in separate studies according to the same procedure. All of the subjects tested in these studies were contact lens wearers.

An eyeliner containing 36.3% Trilaurin (C12) did not induce skin irritation reactions in test subjects. Trioctanoin (C8) itself did not induce skin irritation. A lip enhancer cream containing 0.38% Tribehenin was not comedogenic and did not induce clinically significant skin irritation in any of the subjects evaluated in a 28-day test. RIPT results (occlusive patches) for the following products were negative: eye enhancer cream containing 0.32% Tribehenin (198 subjects), hand cream containing 0.38% Tribehenin (at least 200 subjects), lip cream containing 0.38% Tribehenin (at least 200 subjects), and an eye defining pencil containing 1.68% Tristearin. None of these products induced clinically significant irritant or allergic contact dermatitis.

In a skin sensitization test involving 91 subjects, there was no evidence of delayed contact hypersensitivity after repeated applications (occlusive patches) of an eyebrow pencil containing 40% Trilaurin (C12). Also, reportedly, Trioctanoin (C8) did not induce sensitization in a contact allergy test.

DISCUSSION

The Panel noted that, as part of an effort to evaluate vehicles used in carcinogenicity studies, the NTP conducted a 2-year carcinogenicity study in rats given Tricaprylin by gavage. This treatment was associated with a statistically significant dose-related increase in pancreatic acinar cell hyperplasia and adenoma, but there were no acinar carcinomas, the incidence of mononuclear leukemia was less, and nephropathy findings were reduced, compared to corn oil controls. The Panel agreed that, overall, the study concluded that Tricaprylin did not offer significant advantages over corn oil as vehicles in carcinogenicity studies. Trilaurin was also found to inhibit the formation of neoplasms initiated by DMBA and promoted by croton oil.

The available short- and long-term toxicity test results (NTP oral carcinogenicity study on Tricaprylin included) summarized above, do not warrant any restrictions on the use of any of the

Glyceryl Triesters included in this safety assessment in rinse-off or leave-on cosmetic products. The Expert Panel recognizes that some of the Glyceryl Triesters included in this review are not in use, but would be considered safe if used at concentrations similar to those of Glyceryl Triesters that are being used in cosmetic products.

Although minimal percutaneous absorption of Triolein has been demonstrated in vivo using guinea pigs (but not hairless mice) and in vitro using full-thickness skin from hairless mice, the Expert Panel recognizes that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals, and recommends that care should be exercised in using these and other Glyceryl Triesters in cosmetic products.

CONCLUSION

On the basis of the animal and clinical data included in this report, the CIR Expert Panel concludes that the following ingredients are safe as used in cosmetics: Trilaurin, Triarachidin, Tribehenin, Tricaprin, Tricaprylin, Trierucin, Triheptanoin, Triheptylundecanoin, Triisononanoin, Triisopalmitin, Triisostearin, Trilinolein, Trimyristin, Trioctanoin, Triolein, Tripalmitin, Tripalmitolein, Triricinolein, Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, Glyceryl Triacetyl Ricinoleate, and Glyceryl Stearate Diacetate.

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FINAL REPORT OF THE SAFETY ASSESSMENT FOR CAPRYLIC/CAPRIC TRIGLYCERIDE

Caprylic/Capric Triglyceride, an oily mixed ester preparation predominantly composed of caprylic and capric fatty acids derived from coconut oil, has been used extensively in cosmetics, foods, and pharmaceuticals. When absorbed from the digestive tract, it is hydrolyzed, and the fatty acids are catabolized to C_2 fragments which may be further metabolized either to CO_2 or to form long-chain fatty acids.

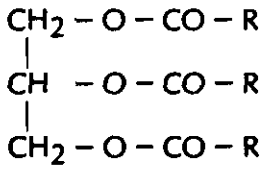
It has a very low toxicity to man and animals as shown by tests involving oral ingestion, intraperitoneal and intramuscular injection, skin and eye irritation tests, skin sensitization, percutaneous toxicity and finally, by two generation feeding studies.

The data reviewed support the conclusion that Caprylic/Capric Triglyceride is safe when incorporated in amounts similar to those presently marketed in cosmetic products.

CHEMICAL AND PHYSICAL PROPERTIES

STRUCTURE

Caprylic/Capric Triglyceride is a medium-chain triglyceride with the following structural formula (CTFA, 1978)[1]:



R represents the alkyl moieties primarily of C_8, caprylic (octanoic) and C_{10}, capric (decanoic) acids.

This mixed ester is manufactured by hydrolyzing coconut oil, removing the free glycerine, and separating the medium chain length fatty acids by fractional distillation. The acids are then blended in the proper ratio and re-esterified with glycerine. The resulting oil is soluble in ethanol to about 20% by weight (CTFA, 1978, Babayan, 1968, 1974).

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

PROPERTIES

The data in Table 1 characterizes this ingredient as it is currently manufactured:

TABLE 1. Chemical and Physical Properties (CTFA, 1978)[1]

Test	Range (% W/W or other basis)	Methodology
Specific gravity at 25°/25°C	0.92 – 0.96	USP
Refractive index at 20°C	1.4480 – 1.4510	USP
Saponification value	300 – 360	AOCS cd 3-25
Hydroxyl value	5.0 maximum	PAP
Acid value	0.1 maximum	AOCS cd-3a-63
Iodine value	1.0 maximum	AOCS cd 1-25
Moisture	0.15% maximum	Fischer

REACTIVITY

These triglycerides can undergo hydrolysis by enzymatic or chemical means to produce free fatty acids, partial glycerides, and glycerol. The free fatty acids may, in turn, undergo enzymatic beta-oxidation. Beta-oxidation of caprylic acid forms beta-ketocaprylic acid and can be further oxidized to yield acetic acid and C_6-acid. However, it is possible that the beta-ketocaprylic may also be oxidized to form methyl-n-phenylketone by decarboxylation. In the case of capric acid, methyl-n-heptylketone may also be formed (Hilditch, 1940).

ANALYTICAL METHODS

Older analytical methods for this ingredient involve the use of its infrared spectrum and the distillation range of its hydrolyzed fatty acids as a means of identification. Today, this ingredient may be analyzed by gas-liquid chromatography (CTFA, 1974; Guillot et *al.*, 1977).

IMPURITIES

The only known impurities are approximately 300 ppm free fatty acids and as much as 0.2% glycerol. The relatively low iodine number 5, which is determined in an arbitrary but standard method, indicates very little unsaturated material present (CTFA, 1978)[1].

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

TABLE 2. Product Formulation Data (FDA, 1976)

Ingredient	Cosmetic Product Type	Concentration (%)	Number of Product Formulations
Caprylic/Capric Triglyceride	Bath oils, tablets, and salts	> 1 to 5	1
		> 0.1 to 1	1
	Other bath preparations	> 1 to 5	1
	Eye shadow	> 25 to 50	2
		> 10 to 25	2
		> 5 to 10	89
		> 1 to 5	2
		> 0.1 to 1	39
	Other eye makeup preparations	> 25 to 50	2
		> 10 to 25	1
		> 5 to 10	1
	Colognes and toilet water	> 0.1 to 1	4
	Perfumes	> 25 to 50	1
		> 5 to 10	38
	Other fragrance preparations	> 5 to 10	28
	Hair conditioners	> 1 to 5	1
	Hair sprays (aerosol fixatives)	> 1 to 5	1
	Shampoos (noncoloring)	> 0.1 to 1	1
	Tonics, dressings, and other hair grooming aids	> 1 to 5	1

TABLE 2. (Continued). Product Formulation Data (FDA, 1976)

Ingredient	Cosmetic Product Type	Concentration (5)	Number of Product Formulations
Caprylic/Capric Triglyceride	Blushers (all types)	> 50	3
		> 25 to 50	8
		> 10 to 25	5
		> 5 to 10	8
	Foundations	> 25 to 50	1
		> 5 to 10	10
		> 1 to 5	11
		> 0.1 to 1	1
	Lipstick	> 10 to 25	7
		> 5 to 10	140
		> 1 to 5	20
	Makeup bases	> 10 to 25	3
		> 5 to 10	1
	Rouges	> 5 to 10	8
	Makeup fixatives	> 25 to 50	1
	Nail creams and lotions	> 25 to 50	1
		> 5 to 10	1
	Deodorants (underarm)	> 0.1 to 1	2
	Aftershave lotions	> 1 to 5	2
	Shaving cream (aerosol, brushless and lather)	> 1 to 5	2
	Other shaving preparation products	> 1 to 5	1

TABLE 2. (Continued). Product Formulation Data (FD ., 1976)

Ingredient	Cosmetic Product Type	Concentration (%)	Number of Product Formulations
Caprylic/Capric Triglyceride	Cleansing (cold creams,	> 10 to 25	1
	cleansing lotions, liquids	> 5 to 10	1
	and pads)	> 1 to 5	1
		> 0.1 to 1	1
	Face, body and hands	> 10 to 25	3
	(excluding shaving prepara-	> 5 to 10	8
	tions)	> 1 to 5	1
		> 0.1 to 1	2
	Moisturizing	> 5 to 10	1
		> 1 to 5	58
	Night	> 5 to 10	1
		> 1 to 5	1
	Wrinkle smoothing (removers)	> 0.1 to 1	1
	Other skin care preparations	> 25 to 50	1
		> 1 to 5	2
	Suntan gels, creams and	> 10 to 25	2
	liquids	> 5 to 10	1
		> 1 to 5	8
		> 0.1 to 1	1
	Other suntan preparations	> 10 to 25	1
		> 5 to 10	1
		> 0.1 to 1	1

USE

PURPOSE AND EXTENT OF USE IN COSMETICS

The desirability of this ingredient is based on its stability, solubility, lack of odor, color, and its blandness. It provides lubricity, promotes pigment dispersion and modifies the viscosity or hardness of finished formulation.

Caprylic/Capric Triglyceride is present in over 500 varieties of cosmetic formulations in concentrations from >0.1 – >50% as shown in Table 2 (FDA, 1976). The ingredient functions as a vehicle for pigment dispersions, as noted above. It is compatible with oleophilic ingredients and can be emulsified in water.

It presence in bath oils, hair sprays, and lipsticks provides contact with, and opportunity for absorption through, most body surfaces including skin, mucous membrane, and respiratory tract. The use of Caprylic/Capric Triglyceride in lipsticks provides an opportunity for frequent daily contact for a duration of perhaps 16 to 18 hours. When used in other products such as hair sprays, frequency of application may be once or twice a day with the ingredient remaining in contact for a few days.

NON-COSMETIC USES

Letters issued by the Food and Drug Administration have attested to the safety of Caprylic/Capric Triglyceride when used as a food additive. Its status as a Generally Recognized As Safe (GRAS) food additive is under review as are all GRAS materials (FDA, 1962, 1963, 1972).

In addition, it has also been marketed for consumption since 1962 as a nutritional supplement and blood lipid lowering agent. It has also been suggested for use in enteric drugs and rectal suppositories and as a vehicle for topically applied pharmaceuticals (Mead, 1977[1]; Kalser, 1971; Franz, 1976; Regdon, 1977; Dowrick, 1977).

BIOLOGICAL PROPERTIES

GENERAL EFFECTS, ABSORPTION, AND METABOLISM

There are no published data available concerning absorption and metabolism of Caprylic/Capric Triglyceride when topically applied to the skin. It is not known if the oil is absorbed through the skin. If absorbed, the liver would likely be the organ primarily involved in its metabolism.

Most of the data available deal with the absorption and metabolic behavior of ingested Caprylic/Capric Triglyceride (Greenberger and Skillman, 1969). The substance is rapidly absorbed from the intestine and predominantly catabolized in the liver to C_2 fragments. The C_2 fragments are further converted to CO_2 or used to synthesize longer chain fatty acids. Very little of the ingredient, if any, is said to be stored in adipose tissues. The development of cholesterolemia and atheromatous lesions in rabbits by dietary cholesterol

differs when Caprylic/Capric Triglyceride is fed as the vehicle as compared to when corn oil is offered as the vehicle. Medium-chain triglycerides are absorbed readily when fed to cirrhotic patients with poor fat absorption. Caprylic and Capric triglycerides greatly reduce the fecal fat content of patients with liver cirrhosis and steatorrhea. Long-chain fatty acids appear to be collected into the thoracic duct lymph as chylomicrons of triglycerides, whereas medium-chain fatty acids may be absorbed directly into the portal system as albumin-bound free fatty acids. Puromycin, which inhibits the absorption of oleic acid triglycerides has no effect on the absorption of ^{14}C labeled trioctanoin (caprylic triglyceride) in rats. Medium-chain triglycerides stimulate pancreatic enzymes in rats less effectively than long-chain triglycerides (Kalser, 1971; Kritchevsky and Tepper, 1965; Linscheer *et al.*, 1966; Feres *et al.*, 1967; Kayden and Midick, 1969; Leveille *et al.*, 1967).

ANIMAL TOXICOLOGY

General Studies

Acute Toxicity

Oral: Single doses of several preparations of Caprylic/Capric Triglyceride have been administered orally to mice or rats in a number of different laboratories. The results are summarized in Table 3.

TABLE 3. Acute Oral Toxicity of Caprylic/ Capric Triglyceride

Dose/kg	Species (no./group, sex)	Mortality (%)	LD50/kg	Reference
25.0 ml	Mouse (10F)	0	> 25 ml	(Consultox, 1977)'
12.5 ml	Mouse (10F)	0		
20.0 ml	Mouse (10F)	20	> 25 ml	(Consultox, 1977)'
25.0 ml	Mouse (10F)	10		
4.5 ml	Rat (10M)*	0		
9.0 ml	Rat (10M)*	0	> 36 ml	(Rheinischen, 1971)'
18.0 ml	Rat (10M)*	0		
36.0 ml	Rat (10M)*	0		
5.0 g	Rat (5M, 5F)	0	> 5 g	(Henkel, 1977)'
5.0g	Rat (5M, 5F)	0	> 5 g	(Henkel, A1835)'
5.0g	Rat (5M, 5F)	0	> 5 g	(PVO, 1976a)'
5.0 g**	Rat (5M, 5F)	0	> 5 g	(PVO, 1976b)'

* Fasted rats.

**Approximately 50% Caprylic/Capric Triglyceride in coconut oil.

In one test on mice, lethargy and ataxia occurred within ten minutes after the administration of 25 ml/kg and dyspnea was noted in some animals within one hour. All animals appeared asymptomatic at the end of the first day and no deaths were reported. In the second mouse test, ataxia, lethargy, dyspnea, and diuresis occurred within 15 minutes, and in several animals complete loss of activity was observed within two hours. Following the two highest doses, three deaths occurred in 24 to 48 hours. All symptoms disappeared in the survivors by the end of the third day. No necropsy observations were reported from either test. From the results of these tests it may be concluded that the acute oral LD50 in female mice is higher than 25 ml/kg (Conxultox, 1977)[1].

In the test on fasted male rats, no mortality resulted from any dose up to 36 ml/kg. At the two highest dose levels of 18 and 36 ml/kg, the rats consumed less food and excreted softer feces in the first two days. Otherwise, no notable symptoms were observed. At necropsy on the eleventh day, there were no striking findings. From the results of this study, it may be concluded that the acute oral LD50 of this ingredient in male rats is greater than 36 ml/kg (Rheinischen, 1971)[1].

Table 3 shows that 5 g/kg of four other samples of Caprylic/Capric Triglyceride produced no mortality in male or female rats. These animals, all observed for 14 days, showed no changes in appearance or behavior and presented no abnormalities at necropsy (Henkel, 1977; Henkel A1835; PVO 1976a, 1976b)[1].

Intraperitoneal: Six groups of five male rats each were injected intraperitoneally with single doses of Caprylic/Capric Triglyceride ranging from 1 to 24 ml/kg. There were no deaths. After doses of 8 ml/kg and higher, the rats showed a lack of appetite and decreased mobility during the first two days. Subsequently, the animals became normal in these respects. Necropsy after 14 days revealed some unabsorbed test material in the stomach area and "slight vascular complications." No histological observations were described. Though no LD50 could be calculated, this test shows that the intraperitoneal LD50 of this product in the rat is greater than 24 ml/kg (Rheinischen, 1971)[1].

Inhalation: Male rats and guinea pigs in groups of ten each were exposed for six hours in a 40-liter chamber containing an aerosol of Caprylic/Capric Triglyceride at a nominal concentration of 28.1 μl/l of air. The fraction of the aerosol with particles small enough to be inhaled into the lung, *i.e.*, with a diameter of 5 μm or less, represented 1.97 μl/1 of the test substance. Three controls of each species were sham exposed.

Observation during the exposure and for 14 days thereafter revealed no symptoms, abnormal behavior, or effects on body weight. One hour after the exposure, three animals and one control of each species were sacrificed for pathological examination, and the remaining test animals were sacrificed at 14 days. No gross or microscopic defects attributable to the substance were

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

reported. Examination of the respiratory tract for adverse effects, including the detection of accumulated oil droplets, gave negative results (INBIFO, 1977)[1].

Intramuscular: Four rabbits received a single injection of 0.5 ml Caprylic /Capric Triglyceride in both thigh muscles. Two were sacrificed after 5 days and two after 14 days. Four other rabbits were treated in the same way with olive oil and sacrificed on the same schedule. Local tolerance to both test substances was good, with no effect on muscle function. Microscopic examination showed somewhat more mesenchymal reaction to this ingredient than to the olive oil. The latter was possibly absorbed more slowly, but pulmonary fatty embolism was more pronounced with the olive oil after both five- and 14-day sacrifice periods. However, the differences between the findings resulting from the injection of the experimental material and those of olive oil were so minor that the two materials were judged equally acceptable in regard to absorption and local tolerance (Hamburg Univ., 1963)[1].

Skin Irritation: The results of primary skin irritation tests of nine different lots or preparations of Caprylic/Capric Triglyceride are shown in Table 4. Tests of three lots performed by an official French method (Journal Official de la Republique Francaise) showed irritation indices of 0.21, 0.21, and 0.46, from which it was concluded that the material was nonirritating (Guillot *et al.*, 1977). One test on the hair-covered backs of rabbits showed the material to be nonirritating under this condition, though no irritation index was given (Henkel, Inc. 1977; Henkel, Inc. A 1838; PVO Int'l. Inc., 1976a; PVO Int'l Inc. 1976b; Warf Inst., 1975)[1]. All other tests shown in Table 4 were done by the Draize method with irritation indices above zero in only two cases:0.25 (Henkel A 1838)[1] and 0.05 (PVO, 1976b)[1]. These scores reflected "mild irritation potential" and "no irritation," respectively.

Skin Sensitization: Two samples of Caprylic/Capric Triglyceride were tested for skin sensitization potential in six male albino guinea pigs. A 4% solution in ethanol was applied to closely clipped areas on the backs and flanks of the test animals every other day for priming purposes until ten such applications had been made. Twenty-four hours after each priming treatment, erythema and edema readings were zero in all cases. Challenge applications made two weeks after the last priming dose also resulted in zero readings, thus showing no evidence of a sensitization potential for these materials in the guinea pig under the conditions of the test (Consultox, 1972)[1].

Eye Irritation: The design and results of eye irritation tests of seven different preparations of Caprylic/Capric Triglyceride are shown in Table 5. All applications of test materials were made in one eye of each rabbit, with the other eye, as a control, left untreated. According to the time schedules shown in the table, observations were made of the cornea for opacity and area involved, of the iris, and of the conjunctiva for redness, chemosis and discharge. The severity of ocular lesions was graded by the Draize method to

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

TABLE 4. Primary Skin Irritation - Rabbits

No. and Sex of Rabbits	Concentration	Method	PII[1]	Conclusion	Reference
Unspecified	Undiluted 15%[2]	Occlusive patches "Neodermotest"[4]	0.21 0.08	Non-irrit. "	Guillot *et al.*, 1977
Unspecified	Undiluted 15%[2]	"	0.21 0.00	"	Guillot *et al.*, 1977
Unspecified	Undiluted 15%[2]	"	0.46 0.04	"	Guillot *et al.*, 1977
3M	Undiluted	Occluded soaked pad 2.5 cm^2 on hair-covered back for 24, 48 and 72 hrs.	—	"	(Rheinischen, 1971)[1]
3M, 3F	Full strength	Draize *et al.*, 0.5 ml, abraded and non-abraded skin, occluded patch; observed at 24 and 72 hours	0.00	"	(Henkel, 1977)[1]
6 (sex unspec.)	Full strength	Draize *et al.*, same as above.	0.25	Mild irrit. potential	(Henkel A1838)[1]
3M, 3F	Full strength	"	0.00	Non-irrit.	(PVO, 1976a)[1]
3M, 3F	Full strength[3]	"	0.05	Non-irrit.	(PVO, 1976b)[1]
6 (sex unspec.)	Full strength	Draize *et al.*,	0.92	Mild irrit.	(Warf, 1975)[1]

[1]PII - Primary irritation index.

[2]Also contains 3% polyoxyethylene sorbitan stearate (emulsifier), 0.2% preservative (not specified) and water to 100%.

[3]Approximately 50% Caprylic/Capric Triglyceride in coconut oil.

[4]J. official de la Republique, 1971[1].

arrive at the scores tabulated; the maximum score by the grading system used is 110. Only one of the six tests involving the single application of the test substance resulted in a very mild irritation: it yielded a score of 0.7 on the first day, 0.3 on the second and third days, and 0 thereafter. In this study only the conjunctiva was affected (PVO, 1976a)[1].

In one test the material was administered by pipette daily for six days "into the tear duct" of the left eye and the eye was held closed for five minutes.

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

TABLE 5. Acute Eye Irritation

No. of Rabbits	Method, Dose and Concentration	Times of Observation Days / Hours	Score	Conclusion	Reference
3	*0.05 ml*	*10*	...	*No tear duct infection or change in cornea*	FDA, 1972
6	0.1 ml single dose full strength	1 2 3	0 0 0	No. irrit.	Henkel, 1977[2]
6	0.1 ml single dose full strength	24 48 96 108	0 8 0 0	No irrit.	Henkel, A1838[2]
6	0.1 ml single dose	1 2 3 4	0.7 0.3 0.3 0	Very mild, transient, conjuctival, redness and discharge	PVO, 1976a[1]
6	0.1 ml single dose full strength of approx. 50% Caprylic/Capric Triglyceride in *coconut oil*	1 2 3	0 0 0	Non-irrit.	PVO, 1976b[1]
6	0.1 ml *single dose,* undiluted	24 48 72	0 *0* 0	Non-irrit.	Warf, 1975[2]

Observation after ten days revealed no effect; however, this report did not indicate whether there was evidence of irritation at any earlier time (Rheinischen, 1971)[1].

The above studies indicate that Caprylic/Capric Triglyceride is at most only a very mild, transient irritant to the eye of the rabbit.

Subchronic Toxicity

Oral: Two groups of ten male white rats weighing 120 to 150 g were given undiluted Caprylic/Capric Triglyceride by throat probe daily for 30 days. Each rat of one group received 1.0 ml daily, equivalent to an average dose of 7.6 ml/kg, while each rat of the other group received 3 ml daily, equivalent to an average dose of 21.3 ml/kg. Weight gains of these two groups and of a 10-rat control group did not differ significantly. The group receiving the lower dose showed no abnormal appearance or behavior and no urinary changes throughout the test. Although no histopathology studies were reported, there were no

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

gross pathologic findings at necropsy. The group receiving 3 ml per day exhibited a decrease in appetite, fatty feces and a shaggy coat in the first five to seven days, but thereafter, these effects disappeared. Also, there were no abnormal urinary findings in this group and no notable macroscopic abnormalities at necropsy (Rheinischen, 1971)[1].

Groups of 20 male white rats received 1 and 5% Caprylic/Capric Triglyceride in their diet for three months. Urine analysis and blood counts were done in the middle and at the end of the feeding period, and serum GOT and GPT transaminases and free and esterified fatty acids were measured when the animals were sacrificed. In none of these respects did the experimentals differ significantly from the controls. No effects of the test diets were reported for behavior, food intake, weight gain, organ:body weight ratios, or on the histological picture. Specific data on the organs selected for histological evaluation were not available (Rheinischen, 1971)[1].

Intramuscular: Five rabbits received, intramuscularly in both thighs, 0.5 ml of Caprylic/Capric triglyceride twice a week for 90 days. Blood samples taken before treatment started and before its termination showed no effects on total lipids or cholesterol levels, nor on hemoglobin, red and white cell counts and the differential blood picture, as compared with the findings in control animals. From histological examination of the thigh muscles, it was concluded that the test substance was absorbed without any reaction except for slight changes due to the injection itself and the depot of the injected material. There were no indications of pathological effects in the large parenchymatous organs and no fatty degeneration or pulmonary fatty embolism (Univ. of Hamburg, 1963)[1].

Dermal: Caprylic/Capric Triglyceride has been tested for toxicity and skin irritation in two formulations. A perfumed skin softener formulation containing 4% Caprylic/Capric Triglyceride was applied to the shaved skin of 15 female rats at a dose of 2 ml/kg five days per week for 13 weeks. This treatment had no effect on body weight, appearance or behavior. All blood-cell and serum chemistry parameters measured one week before termination of the study were within normal limits and comparable to those seen in an equal group at controls. At necropsy, organ weights and gross finding revealed no effects of the test substance, and no histopathological changes were observed. There were no localized effects on the skin. An additional study with a tanning butter formulation containing 22% Caprylic/Capric Triglyceride was applied to the clipped backs of three male and three female New Zealand strain albino rabbits at a dose of 2 g/kg five times per week for four weeks. At weekly intervals the backs of three of these animals and of three controls were abraded through the stratum corneum, leaving the dermis intact. The backs of the other three test rabbits and of six controls were not abraded. Throughout the test, no effects attributable to the treatment were noted on body weight, physical appearance

and behavior. Blood samples taken 23 days after initiation of the test showed no effects on hematocrit, hemoglobin concentration, cell counts, urea nitrogen, alkaline phosphatase or glutamic pyruvic transaminase activities, or glucose concentration. At the end of the test, no systemic, gross or histopathologic changes referable to the test material were observed. On the treated area of the skin there was slight to moderate erythema and slight peeling and cracking regardless of whether the skin was abraded or left intact (CTFA, 1976; CTFA, 1974)[1].

The oral tests and the two skin tests described above indicate the lack of systemic effects. Observations for local effects on the skin were only incidental and are not considered pertinent in the latter test because of the relative resistance of the rat skin to irritation.

Chronic Toxicity

Groups of 15 male and 15 female rats were fed a diet containing 19.6% of a medium-chain triglyceride composed of about 75% caprylic acid and 25% capric acid for 47 weeks. This diet supported normal growth and development, though growth rate was slightly less than that of rats fed conventional dietary fats. At autopsy, the carcass protein, ash levels and organ weights of test rats were similar to those of control rats but there was less carcass fat and smaller epididymal fat pads in the test group. Histological study revealed no abnormalities in intestine and liver (Harkins and Sarett, 1968)[1].

An earlier study showed that male rats fed medium-chain triglycerides at a level of 20% in their diet for a year weighed significantly less than rats fed a lard diet and had higher caloric requirements to maintain weight. Fertility and organ weight relationships remained normal (Kaunitz *et. al.*, 1958).

The above studies showed nutritional effects of long-term consumption of this ingredient in the diet of rats, but no effects were interpreted as adverse or toxic.

No conclusive studies on the mutagenic, or carcinogenic effects of Caprylic/Capric Triglycerides have been reported. Tricaprylin, however, has been widely used as a vehicle for the bioassay of suspected carcinogens (Lawely, 1976), because it does not induce tumors within the life span for experimental animals (Miller and Miller, 1960).

Special Studies

In a reproduction study, young adult male and female rats were fed a balanced diet containing 19.6% of a triglyceride of 75% caprylic and 25% capric acid for three weeks before mating. Litter size and birth weight of the test animals were similar to those of rats on conventional or low fat diets, but mortality during lactation was somewhat higher, and there was less weight gain due to a smaller volume of milk secreted. After weaning, the F_1 generation was fed as the F_0 generation had been and showed a weight gain comparable to that of control rats on an oleo oil diet (Harkins and Sorett, 1968).

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

CLINICAL ASSESSMENT OF SAFETY

In France, 100 patients of a dermatology clinic who "constituted all of the dermatological allergies" (presumably patients having a wide spectrum of allergic dermatologic diagnoses) were tested with patches (1 cm^2) of tissue paper saturated with Caprylic/Capric Triglyceride for 48 hours. No positive reactions occurred (Degos, 1968)[1].

In another study, forty subjects were patch tested to undiluted Caprylic /Capric Triglyceride (patch test technique not described). Three readings were made (times not stated). "No skin irritation" was noted (Ippen, 1970)[1].

Caprylic/Capric Triglyceride (10, 20, and 50% solutions) dissolved in paraffin liquid DAB 6 was dropped into one eye each of two test persons at four- to six-day intervals. An additional five male subjects were tested with the undiluted material. No "incompatibility reactions" were perceived (Henkel, 1971)[1].

One hundred and twenty-eight adult males and females were tested with Caprylic/Capric Triglyceride using a modification of the Draize repeated insult patch test. All subjects had little or no irritation and none was sensitized. One subject had barely perceptible erythema at the first reading immediately following the removal of the first patch which had been applied for 48 hours (Hilltop, 1975a)[1].

Twelve women (age and race not stated) were tested with 0.4 ml of Caprylic/Capric Triglyceride on each patch. Patches were applied daily to the same site for 21 consecutive days. They were removed 23 hours after application and read at 24 hours. One subject had a score of 1.0 on a scale of 0 to 3 on day 16. The investigators reported that all other scores were negative and were given a 0 score. This ingredient was considered essentially nonirritating in the amount used (Hilltop, 1975b)[1].

When four human volunteers who had fasted overnight were fed 1 g/kg body weight of a medium-chain length triglyceride (71% caprylic, 25% capric, 3% lauric), their serum free fatty acids showed a high proportion of octanoic acid and a low proportion of long-chain acids for four hours (Tamir *et al.*, 1968).

Of ten human volunteers who ingested 100 ml of synthetic fat (a triglyceride of 74% lauric, 17% capric, 5% caprylic, 3% myristic, and a trace of caproic) eight had no chylomicrons in their sera, and none developed diarrhea or had fat in their feces; all had increased free fatty acids in their sera (Metais *et al.*, 1966).

SUMMARY

Caprylic/Capric Triglyceride, an oily mixed ester predominantly composed of caprylic and capric fatty acids derived from coconut oil, has been used extensively in cosmetics, foods, and pharmaceuticals. When absorbed from the digestive tract, it is hydrolyzed, and the fatty acids are catabolized to

[1]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

C_2 fragments which may be further metabolized either to CO_2 or to form long-chain fatty acids.

It has a very low toxicity to man and animals as shown by tests involving oral ingestion, intraperitoneal and intramuscular injection, skin and eye irritation tests, skin sensitization, percutaneous toxicity and finally, by two generation feeding studies.

The safety assessment of this ingredient rests on the information at hand and on the considerable usage at various concentrations in a variety of cosmetic and other consumer products. Additional biological assessment might reasonably be recommended to include studies on photosensitization.

CONCLUSIONS

It is the opinion of the Expert Panel, based on the evidence at hand which it believes to be relevant and accumulated in a reasonable manner, that the cosmetic product, Caprylic/Capric Triglyceride, is safe when incorporated in amounts similar to those presently marketed.

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CAPRYLIC/CAPRIC TRIGLYCERIDE

A safety assessment of Caprylic/Capric Triglyceride was published in 1980 with the conclusion "safe when incorporated in amounts similar to those presently marketed" (Elder 1980). New studies, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The CIR Expert Panel noted that recent safety test data are presented in a safety assessment of Trilaurin and 22 other triglycerides completed in 1999, with the conclusion that those triglycerides are safe as used in cosmetic formulations (CIR 1999).

In 1976, Caprylic/Capric Triglyceride was used in 550 cosmetic products, with the largest single use in lipsticks in the concentration range of >1% to 25%. In 2001, uses in 763 products were reported to FDA (2001) and the largest single use was in eyeliner products at a maximum concentration of 35% (CTFA 2001). Table 2 presents the available use information.

TABLE 2
Caprylic/Capric Triglyceride use

Product category	1976 use (Elder 1980)	2001 use (FDA 2001)	1976 concentrations (Elder 1980)	2001 concentrations (CTFA 2001)
Baby lotions, oils, powders, etc.	—	2	—	0.8%
Bath oils, tablets, and salts	2	—	>0.1%–5%	25%–78%
Other bath preparations	1	—	>1%–5%	7%–10%
Eyebrow pencil	—	9	—	4%–19%
Eyeliner	—	131	—	0.5%–35%
Eye shadow	134	33	>0.1%–50%	0.03%–49%
Eye lotion	—	4	—	2%–10%
Eye makeup remover	—	2	—	6%–10%
Mascara	—	—	—	0.008%
Other eye makeup preparations	4	28	>5%–50%	6%–18%
Colognes and toilet waters	4	1	>0.1%–1%	7%
Perfumes	39	7	>5%–50%	9%–84%
Other fragrance preparations	28	22	>5%–10%	7%–33%
Hair conditioners	1	4	>1%–5%	1%–5%
Hair sprays (aerosol fixatives)	1	—	>1%–5%	0.00005%–0.02%
Hair straighteners	—	1	—	—
Shampoos (noncoloring)	1	1	>0.1%–1%	0.02%–0.5%
Hair tonics, dressings, etc.	1	4	>1%–5%	0.0001%–18%
Other hair preparations (noncoloring)	—	—	—	—[a]
Hair rinses (coloring)	—	1	—	—
Blushers (all types)	24	18	>5%–>50%	5%–33%
Face powders	—	11	—	0.01%–22%
Foundations	23	18	>0.1%–50%	1%–21%
Lipstick	167	75	>1%–25%	0.1%–54%
Makeup bases	4	13	>5%–25%	8%–13%
Rouges	8	2	>5%–10%	4%–7%
Makeup fixatives	1	4	>25%–50%	—
Other makeup preparations	—	26	—	12%–17%
Cuticle softeners	—	2	—	5%
Nail creams and lotions	2	—	>5%–50%	—
Nail polish and enamel	—	—	—	12%
Nail polish and enamel removers	—	2	—	2%–5%
Other manicuring preparations	—	1	—	0.2%–15%
Dentifrices	—	—	—	0.002%
Bath soaps and detergents	—	—	—	0.3%
Deodorants (underarm)	2	1	>0.1%–1%	0.00001%–5%
Other personal cleanliness products	—	—	—	0.3%–1%
Aftershave lotion	2	4	>1%–5%	2%–5%
Shaving cream	2	—	>1%–5%	—

(Continued on next page)

TABLE 2
Caprylic/Capric Triglyceride use *(Continued)*

Product category	1976 use (Elder 1980)	2001 use (FDA 2001)	1976 concentrations (Elder 1980)	2001 concentrations (CTFA 2001)
Other shaving preparation products	1	1	>1%–5%	2%
Skin cleansing preparations	4	33	>0.1%–25%	2%–9%
Face and neck skin care preparations[b]	—	36	—	1%–48%
Body and hand skin care preparations[b]	14	68	>0.1%–25%	0.06%–45%[c]
Foot powders and sprays	—	—	—	18%
Moisturizing preparations[d]	59	95	>1%–10%	0.002%–10%
Wrinkle smoothing (removers)[d]	1	—	>0.1%–1%	—
Night creams, lotions, etc.	2	31	>1%–10%	2%–12%
Paste masks (mud packs)	—	14	—	2%–6%
Skin fresheners	—	—	—	6%
Other skin care preparations	3	38	>1%–50%	9%–51%
Suntan gels, creams, and liquids	12	4	>0.1%–25%	2%–11%
Indoor tanning preparations	—	12	—	0.6%–5%
Other suntan preparations	3	4	>0.1%–25%	4%–19%
Totals/ranges	550	763	>0.1%–50%	0.00001%–84%

[a]Reported to be in use, but no concentration of use was provided.
[b]Originally, Face and Neck and Body and Hand were combined as one category, but now they are separated.
[c]43% in a spray product.
[d]Wrinkle smoothing (removers) are now part of the Moisturizing category.

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CARBOMER 934, 910, 934P, 940, 941, AND 962

A safety assessment of Carbomers 934, 910, 934P, 940, 941, and 962 was published in 1982 with the conclusion "are safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1982). New studies, along with the updated information in Tables 3 to 6 regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The CIR Expert Panel acknowledged the potential aerosol use of Carbomers 934 and 940. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is $\leq 80\ \mu$, and the diameter of anhydrous hair spray particles is 60 to 80 μ. Typically less than 1% are below 10 μ, which is the upper limit for respirable particles (Bower 1999). Based on the particle size, Carbomers 934 and 940 would not be respirable in formulation.

The Panel acknowledged the industry practice of removing benzene from Carbomers. Resulting levels should be below those shown to have no risk to human health. For example, the Environmental Protection Agency (EPA) has established for drinking water that the 10^{-6} risk level for cancer is between 1 and 10 μg/L (EPA 2002).

The current terminology in the *International Cosmetic Ingredient Dictionary and Handbook* is Carbomers, the number extensions appear only as technical names (Pepe, Wenninger, and McEwen 2002). Carbomers 910 and 962 were not used in either 1976 or 2001.

TABLE 3
Carbomer 934 use

Product category	1976 use (Elder 1982)	2001 use (FDA 2001)	1976 concentration (Elder 1982)	2001 carbomers concentration[a] (CTFA 2001)
Baby shampoos	—	9	—	—
Baby lotions, oils, powders, etc.	6	—	≤1%	0.2%–0.8%
Other baby products	—	1	—	0.3%
Other bath preparations	7	—	>0.1%–25%	0.1%–1%
Eyebrow pencil	—	1	—	—
Eyeliner	5	4	>0.1%–1%	0.2%
Eye shadow	20	—	>0.1%–1%	0.4%–0.7%
Eye lotion	—	1	—	0.4%–2%
Mascara	1	1	≤0.1%	0.7%–1%
Other eye makeup preparations	—	18	—	0.7%–1%
Perfumes	9	9	>0.1%–1%	0.3%–0.8%
Sachets	11	9	≤1%	0.8%
Other fragrance preparations	5	10	>0.1%–1%	0.7%–1%
Hair conditioners	3	3	>0.1%–1%	0.8%–0.9%
Hair sprays (aerosol fixatives)	—	1	—	—
Permanent waves	1	—	>0.1%–1%	—
Shampoos (non-coloring)	1	5	≤0.1%	0.3%–1.5%
Hair tonics, dressings, etc.	8	12	>0.1%–5%	0.7%–1.5%
Wave sets	1	—	>0.1%–1%	—
Other hair preparations	4	1	>0.1%–5%	0.7%

(Continued on next page)

CAPRYLIC/CAPRIC TRIGLYCERIDE	1	01A - Baby Shampoos
CAPRYLIC/CAPRIC TRIGLYCERIDE	25	01B - Baby Lotions, Oils, Powders, and Creams
CAPRYLIC/CAPRIC TRIGLYCERIDE	11	01C - Other Baby Products
CAPRYLIC/CAPRIC TRIGLYCERIDE	20	02A - Bath Oils, Tablets, and Salts
CAPRYLIC/CAPRIC TRIGLYCERIDE	1	02B - Bubble Baths
CAPRYLIC/CAPRIC TRIGLYCERIDE	2	02D - Other Bath Preparations
CAPRYLIC/CAPRIC TRIGLYCERIDE	20	03A - Eyebrow Pencil
CAPRYLIC/CAPRIC TRIGLYCERIDE	202	03B - Eyeliner
CAPRYLIC/CAPRIC TRIGLYCERIDE	598	03C - Eye Shadow
CAPRYLIC/CAPRIC TRIGLYCERIDE	122	03D - Eye Lotion
CAPRYLIC/CAPRIC TRIGLYCERIDE	3	03E - Eye Makeup Remover
CAPRYLIC/CAPRIC TRIGLYCERIDE	20	03F - Mascara
CAPRYLIC/CAPRIC TRIGLYCERIDE	98	03G - Other Eye Makeup Preparations
CAPRYLIC/CAPRIC TRIGLYCERIDE	1	04A - Cologne and Toilet waters
CAPRYLIC/CAPRIC TRIGLYCERIDE	40	04B - Perfumes
CAPRYLIC/CAPRIC TRIGLYCERIDE	5	04C - Powders (dusting and talcum, excluding aftershave talc)
CAPRYLIC/CAPRIC TRIGLYCERIDE	74	04E - Other Fragrance Preparation
CAPRYLIC/CAPRIC TRIGLYCERIDE	57	05A - Hair Conditioner
CAPRYLIC/CAPRIC TRIGLYCERIDE	7	05B - Hair Spray (aerosol fixatives)
CAPRYLIC/CAPRIC TRIGLYCERIDE	2	05C - Hair Straighteners
CAPRYLIC/CAPRIC TRIGLYCERIDE	18	05F - Shampoos (non-coloring)
CAPRYLIC/CAPRIC TRIGLYCERIDE	38	05G - Tonics, Dressings, and Other Hair Grooming Aids
CAPRYLIC/CAPRIC TRIGLYCERIDE	1	05H - Wave Sets
CAPRYLIC/CAPRIC TRIGLYCERIDE	37	05I - Other Hair Preparations
CAPRYLIC/CAPRIC TRIGLYCERIDE	22	06B - Hair Tints
CAPRYLIC/CAPRIC TRIGLYCERIDE	118	07A - Blushers (all types)
CAPRYLIC/CAPRIC TRIGLYCERIDE	72	07B - Face Powders
CAPRYLIC/CAPRIC TRIGLYCERIDE	94	07C - Foundations
CAPRYLIC/CAPRIC TRIGLYCERIDE	3	07D - Leg and Body Paints
CAPRYLIC/CAPRIC TRIGLYCERIDE	583	07E - Lipstick
CAPRYLIC/CAPRIC TRIGLYCERIDE	18	07F - Makeup Bases
CAPRYLIC/CAPRIC TRIGLYCERIDE	35	07G - Rouges
CAPRYLIC/CAPRIC TRIGLYCERIDE	2	07H - Makeup Fixatives
CAPRYLIC/CAPRIC TRIGLYCERIDE	149	07I - Other Makeup Preparations
CAPRYLIC/CAPRIC TRIGLYCERIDE	3	08A - Basecoats and Undercoats
CAPRYLIC/CAPRIC TRIGLYCERIDE	4	08B - Cuticle Softeners
CAPRYLIC/CAPRIC TRIGLYCERIDE	1	08C - Nail Creams and Lotions
CAPRYLIC/CAPRIC TRIGLYCERIDE	2	08E - Nail Polish and Enamel
CAPRYLIC/CAPRIC TRIGLYCERIDE	1	08F - Nail Polish and Enamel Removers
CAPRYLIC/CAPRIC TRIGLYCERIDE	6	08G - Other Manicuring Preparations
CAPRYLIC/CAPRIC TRIGLYCERIDE	2	09B - Mouthwashes and Breath Fresheners
CAPRYLIC/CAPRIC TRIGLYCERIDE	24	10A - Bath Soaps and Detergents
CAPRYLIC/CAPRIC TRIGLYCERIDE	6	10B - Deodorants (underarm)
CAPRYLIC/CAPRIC TRIGLYCERIDE	66	10E - Other Personal Cleanliness Products
CAPRYLIC/CAPRIC TRIGLYCERIDE	46	11A - Aftershave Lotion
CAPRYLIC/CAPRIC TRIGLYCERIDE	4	11D - Preshave Lotions (all types)
CAPRYLIC/CAPRIC TRIGLYCERIDE	31	11E - Shaving Cream
CAPRYLIC/CAPRIC TRIGLYCERIDE	11	11G - Other Shaving Preparation Products
CAPRYLIC/CAPRIC TRIGLYCERIDE	214	12A - Cleansing
CAPRYLIC/CAPRIC TRIGLYCERIDE	592	12C - Face and Neck (exc shave)
CAPRYLIC/CAPRIC TRIGLYCERIDE	760	12D - Body and Hand (exc shave)
CAPRYLIC/CAPRIC TRIGLYCERIDE	4	12E - Foot Powders and Sprays
CAPRYLIC/CAPRIC TRIGLYCERIDE	1137	12F - Moisturizing
CAPRYLIC/CAPRIC TRIGLYCERIDE	179	12G - Night
CAPRYLIC/CAPRIC TRIGLYCERIDE	117	12H - Paste Masks (mud packs)
CAPRYLIC/CAPRIC TRIGLYCERIDE	15	12I - Skin Fresheners
CAPRYLIC/CAPRIC TRIGLYCERIDE	201	12J - Other Skin Care Preps
CAPRYLIC/CAPRIC TRIGLYCERIDE	25	13A - Suntan Gels, Creams, and Liquids
CAPRYLIC/CAPRIC TRIGLYCERIDE	49	13B - Indoor Tanning Preparations
CAPRYLIC/CAPRIC TRIGLYCERIDE	4	13C - Other Suntan Preparations
TRIBEHENIN	1	01B - Baby Lotions, Oils, Powders, and Creams
TRIBEHENIN	3	03A - Eyebrow Pencil

TRIBEHENIN	5	03B - Eyeliner
TRIBEHENIN	15	03C - Eye Shadow
TRIBEHENIN	14	03D - Eye Lotion
TRIBEHENIN	1	03E - Eye Makeup Remover
TRIBEHENIN	33	03F - Mascara
TRIBEHENIN	24	03G - Other Eye Makeup Preparations
TRIBEHENIN	2	04B - Perfumes
TRIBEHENIN	6	04E - Other Fragrance Preparation
TRIBEHENIN	1	05B - Hair Spray (aerosol fixatives)
TRIBEHENIN	1	05C - Hair Straighteners
TRIBEHENIN	16	05G - Tonics, Dressings, and Other Hair Grooming Aids
TRIBEHENIN	10	05I - Other Hair Preparations
TRIBEHENIN	17	07A - Blushers (all types)
TRIBEHENIN	2	07B - Face Powders
TRIBEHENIN	86	07C - Foundations
TRIBEHENIN	249	07E - Lipstick
TRIBEHENIN	12	07F - Makeup Bases
TRIBEHENIN	2	07G - Rouges
TRIBEHENIN	2	07H - Makeup Fixatives
TRIBEHENIN	59	07I - Other Makeup Preparations
TRIBEHENIN	1	08B - Cuticle Softeners
TRIBEHENIN	1	08C - Nail Creams and Lotions
TRIBEHENIN	2	08G - Other Manicuring Preparations
TRIBEHENIN	2	10A - Bath Soaps and Detergents
TRIBEHENIN	4	10E - Other Personal Cleanliness Products
TRIBEHENIN	1	11G - Other Shaving Preparation Products
TRIBEHENIN	16	12A - Cleansing
TRIBEHENIN	31	12C - Face and Neck (exc shave)
TRIBEHENIN	22	12D - Body and Hand (exc shave)
TRIBEHENIN	44	12F - Moisturizing
TRIBEHENIN	11	12G - Night
TRIBEHENIN	3	12H - Paste Masks (mud packs)
TRIBEHENIN	1	12I - Skin Fresheners
TRIBEHENIN	18	12J - Other Skin Care Preps
TRIBEHENIN	1	13A - Suntan Gels, Creams, and Liquids
TRIBEHENIN	1	13B - Indoor Tanning Preparations
TRIBEHENIN	3	13C - Other Suntan Preparations

Tricaprin as-

CAPRIC TRIGLYCERIDE	4	03C - Eye Shadow
CAPRIC TRIGLYCERIDE	1	03D - Eye Lotion
CAPRIC TRIGLYCERIDE	1	05I - Other Hair Preparations
CAPRIC TRIGLYCERIDE	3	07E - Lipstick
CAPRIC TRIGLYCERIDE	9	11A - Aftershave Lotion
CAPRIC TRIGLYCERIDE	4	12A - Cleansing
CAPRIC TRIGLYCERIDE	5	12C - Face and Neck (exc shave)
CAPRIC TRIGLYCERIDE	11	12D - Body and Hand (exc shave)
CAPRIC TRIGLYCERIDE	1	12E - Foot Powders and Sprays
CAPRIC TRIGLYCERIDE	5	12F - Moisturizing
CAPRIC TRIGLYCERIDE	6	12J - Other Skin Care Preps
CAPRIC TRIGLYCERIDE	1	13A - Suntan Gels, Creams, and Liquids

TRICAPRYLIN	1	01B - Baby Lotions, Oils, Powders, and Creams
TRICAPRYLIN	105	03C - Eye Shadow
TRICAPRYLIN	3	03D - Eye Lotion
TRICAPRYLIN	3	03G - Other Eye Makeup Preparations
TRICAPRYLIN	12	04C - Powders (dusting and talcum, excluding aftershave talc)
TRICAPRYLIN	1	04E - Other Fragrance Preparation
TRICAPRYLIN	3	05A - Hair Conditioner
TRICAPRYLIN	1	05I - Other Hair Preparations
TRICAPRYLIN	12	07A - Blushers (all types)
TRICAPRYLIN	27	07B - Face Powders

TRICAPRYLIN	37	07E - Lipstick
TRICAPRYLIN	3	07I - Other Makeup Preparations
TRICAPRYLIN	3	11A - Aftershave Lotion
TRICAPRYLIN	1	11E - Shaving Cream
TRICAPRYLIN	2	12A - Cleansing
TRICAPRYLIN	10	12C - Face and Neck (exc shave)
TRICAPRYLIN	13	12D - Body and Hand (exc shave)
TRICAPRYLIN	17	12F - Moisturizing
TRICAPRYLIN	6	12G - Night
TRICAPRYLIN	2	12J - Other Skin Care Preps

Tricaprylin, as

CAPRYLIC TRIGLYCERIDE	1	03C - Eye Shadow
CAPRYLIC TRIGLYCERIDE	2	03G - Other Eye Makeup Preparations
CAPRYLIC TRIGLYCERIDE	2	05G - Tonics, Dressings, and Other Hair Grooming Aids
CAPRYLIC TRIGLYCERIDE	11	07E - Lipstick
CAPRYLIC TRIGLYCERIDE	1	11E - Shaving Cream
CAPRYLIC TRIGLYCERIDE	6	12C - Face and Neck (exc shave)
CAPRYLIC TRIGLYCERIDE	4	12D - Body and Hand (exc shave)
CAPRYLIC TRIGLYCERIDE	13	12F - Moisturizing
CAPRYLIC TRIGLYCERIDE	5	12G - Night
CAPRYLIC TRIGLYCERIDE	1	12J - Other Skin Care Preps
CAPRYLIC TRIGLYCERIDE	2	13A - Suntan Gels, Creams, and Liquids

TRIETHYLHEXANOIN	1	01C - Other Baby Products
TRIETHYLHEXANOIN	11	03A - Eyebrow Pencil
TRIETHYLHEXANOIN	39	03B - Eyeliner
TRIETHYLHEXANOIN	51	03C - Eye Shadow
TRIETHYLHEXANOIN	10	03D - Eye Lotion
TRIETHYLHEXANOIN	1	03E - Eye Makeup Remover
TRIETHYLHEXANOIN	2	03F - Mascara
TRIETHYLHEXANOIN	17	03G - Other Eye Makeup Preparations
TRIETHYLHEXANOIN	2	04C - Powders (dusting and talcum, excluding aftershave talc)
TRIETHYLHEXANOIN	1	05G - Tonics, Dressings, and Other Hair Grooming Aids
TRIETHYLHEXANOIN	9	07A - Blushers (all types)
TRIETHYLHEXANOIN	24	07B - Face Powders
TRIETHYLHEXANOIN	50	07C - Foundations
TRIETHYLHEXANOIN	1	07D - Leg and Body Paints
TRIETHYLHEXANOIN	116	07E - Lipstick
TRIETHYLHEXANOIN	17	07F - Makeup Bases
TRIETHYLHEXANOIN	31	07G - Rouges
TRIETHYLHEXANOIN	3	07H - Makeup Fixatives
TRIETHYLHEXANOIN	32	07I - Other Makeup Preparations
TRIETHYLHEXANOIN	1	08F - Nail Polish and Enamel Removers
TRIETHYLHEXANOIN	1	10B - Deodorants (underarm)
TRIETHYLHEXANOIN	1	10E - Other Personal Cleanliness Products
TRIETHYLHEXANOIN	14	12A - Cleansing
TRIETHYLHEXANOIN	79	12C - Face and Neck (exc shave)
TRIETHYLHEXANOIN	10	12D - Body and Hand (exc shave)
TRIETHYLHEXANOIN	44	12F - Moisturizing
TRIETHYLHEXANOIN	5	12G - Night
TRIETHYLHEXANOIN	10	12H - Paste Masks (mud packs)
TRIETHYLHEXANOIN	2	12I - Skin Fresheners
TRIETHYLHEXANOIN	13	12J - Other Skin Care Preps
TRIETHYLHEXANOIN	1	13A - Suntan Gels, Creams, and Liquids
TRIETHYLHEXANOIN	2	13B - Indoor Tanning Preparations

TRIHEPTANOIN	1	07C - Foundations
TRIHEPTANOIN	2	07E - Lipstick
TRIHEPTANOIN	1	10E - Other Personal Cleanliness Products
TRIHEPTANOIN	2	12A - Cleansing
TRIHEPTANOIN	4	12C - Face and Neck (exc shave)

TRIHEPTANOIN	2	12D - Body and Hand (exc shave)
TRIHEPTANOIN	12	12F - Moisturizing
TRIHEPTANOIN	1	12G - Night
TRIHEPTANOIN	1	12H - Paste Masks (mud packs)
TRIHYDROXYSTEARIN	1	03A - Eyebrow Pencil
TRIHYDROXYSTEARIN	5	03B - Eyeliner
TRIHYDROXYSTEARIN	22	03C - Eye Shadow
TRIHYDROXYSTEARIN	3	03D - Eye Lotion
TRIHYDROXYSTEARIN	1	03E - Eye Makeup Remover
TRIHYDROXYSTEARIN	30	03F - Mascara
TRIHYDROXYSTEARIN	18	03G - Other Eye Makeup Preparations
TRIHYDROXYSTEARIN	19	05F - Shampoos (non-coloring)
TRIHYDROXYSTEARIN	3	05G - Tonics, Dressings, and Other Hair Grooming Aids
TRIHYDROXYSTEARIN	2	05I - Other Hair Preparations
TRIHYDROXYSTEARIN	4	07A - Blushers (all types)
TRIHYDROXYSTEARIN	2	07B - Face Powders
TRIHYDROXYSTEARIN	35	07C - Foundations
TRIHYDROXYSTEARIN	64	07E - Lipstick
TRIHYDROXYSTEARIN	6	07F - Makeup Bases
TRIHYDROXYSTEARIN	2	07G - Rouges
TRIHYDROXYSTEARIN	22	07I - Other Makeup Preparations
TRIHYDROXYSTEARIN	1	08B - Cuticle Softeners
TRIHYDROXYSTEARIN	9	10A - Bath Soaps and Detergents
TRIHYDROXYSTEARIN	1	10E - Other Personal Cleanliness Products
TRIHYDROXYSTEARIN	5	12A - Cleansing
TRIHYDROXYSTEARIN	5	12C - Face and Neck (exc shave)
TRIHYDROXYSTEARIN	3	12D - Body and Hand (exc shave)
TRIHYDROXYSTEARIN	5	12F - Moisturizing
TRIHYDROXYSTEARIN	1	12G - Night
TRIHYDROXYSTEARIN	2	12J - Other Skin Care Preps
TRIHYDROXYSTEARIN	1	13A - Suntan Gels, Creams, and Liquids
TRIHYDROXYSTEARIN	1	13B - Indoor Tanning Preparations
TRIISONONANOIN	1	07E - Lipstick
TRIISONONANOIN	4	10E - Other Personal Cleanliness Products
TRIISONONANOIN	3	12C - Face and Neck (exc shave)
TRIISONONANOIN	1	12D - Body and Hand (exc shave)
TRIISONONANOIN	4	12F - Moisturizing
TRIISONONANOIN	2	12J - Other Skin Care Preps
TRIISOSTEARIN	1	03B - Eyeliner
TRIISOSTEARIN	17	03C - Eye Shadow
TRIISOSTEARIN	7	03D - Eye Lotion
TRIISOSTEARIN	1	03E - Eye Makeup Remover
TRIISOSTEARIN	1	03G - Other Eye Makeup Preparations
TRIISOSTEARIN	13	07A - Blushers (all types)
TRIISOSTEARIN	12	07B - Face Powders
TRIISOSTEARIN	3	07C - Foundations
TRIISOSTEARIN	161	07E - Lipstick
TRIISOSTEARIN	43	07G - Rouges
TRIISOSTEARIN	13	07I - Other Makeup Preparations
TRIISOSTEARIN	7	12C - Face and Neck (exc shave)
TRIISOSTEARIN	3	12D - Body and Hand (exc shave)
TRIISOSTEARIN	2	12F - Moisturizing
TRIISOSTEARIN	3	12G - Night
TRIISOSTEARIN	4	12J - Other Skin Care Preps
TRILAURIN	3	03A - Eyebrow Pencil
TRILAURIN	101	03B - Eyeliner
TRILAURIN	2	03C - Eye Shadow
TRILAURIN	1	03D - Eye Lotion
TRILAURIN	1	04E - Other Fragrance Preparation

TRILAURIN	2	07C - Foundations
TRILAURIN	1	07E - Lipstick
TRILAURIN	1	07I - Other Makeup Preparations
TRILAURIN	5	10B - Deodorants (underarm)
TRILAURIN	1	10E - Other Personal Cleanliness Products
TRILAURIN	1	12A - Cleansing
TRILAURIN	2	12C - Face and Neck (exc shave)
TRILAURIN	1	12D - Body and Hand (exc shave)
TRILAURIN	3	12F - Moisturizing
TRILINOLEIN	5	07I - Other Makeup Preparations
TRILINOLEIN	3	10A - Bath Soaps and Detergents
TRILINOLEIN	12	10E - Other Personal Cleanliness Products
TRILINOLEIN	1	12C - Face and Neck (exc shave)
TRILINOLEIN	3	12F - Moisturizing
TRILINOLEIN	1	12G - Night
TRILINOLEIN	2	12J - Other Skin Care Preps
TRIMYRISTIN	1	03A - Eyebrow Pencil
TRIMYRISTIN	2	03C - Eye Shadow
TRIMYRISTIN	2	07A - Blushers (all types)
TRIMYRISTIN	10	07B - Face Powders
TRIMYRISTIN	12	07C - Foundations
TRIOLEIN	1	03D - Eye Lotion
TRIOLEIN	2	03G - Other Eye Makeup Preparations
TRIOLEIN	3	07C - Foundations
TRIOLEIN	68	07E - Lipstick
TRIOLEIN	13	07I - Other Makeup Preparations
TRIOLEIN	3	10A - Bath Soaps and Detergents
TRIOLEIN	12	10E - Other Personal Cleanliness Products
TRIOLEIN	1	12D - Body and Hand (exc shave)
TRIOLEIN	2	12F - Moisturizing
TRIOLEIN	1	12G - Night
TRIOLEIN	1	12J - Other Skin Care Preps
TRIPALMITIN	1	03A - Eyebrow Pencil
TRIPALMITIN	5	03B - Eyeliner
TRIPALMITIN	2	03G - Other Eye Makeup Preparations
TRIPALMITIN	1	10E - Other Personal Cleanliness Products
TRIPALMITIN	1	12A - Cleansing
TRIPALMITIN	1	12F - Moisturizing
TRIPALMITIN	1	12J - Other Skin Care Preps
TRISTEARIN	7	03B - Eyeliner
TRISTEARIN	2	03G - Other Eye Makeup Preparations
TRISTEARIN	2	04E - Other Fragrance Preparation
TRISTEARIN	7	07C - Foundations
TRISTEARIN	3	07E - Lipstick
TRISTEARIN	1	07F - Makeup Bases
TRISTEARIN	1	07H - Makeup Fixatives
TRISTEARIN	1	07I - Other Makeup Preparations
TRISTEARIN	8	10A - Bath Soaps and Detergents
TRISTEARIN	1	10E - Other Personal Cleanliness Products
TRISTEARIN	3	12A - Cleansing
TRISTEARIN	8	12C - Face and Neck (exc shave)
TRISTEARIN	6	12D - Body and Hand (exc shave)
TRISTEARIN	11	12F - Moisturizing
TRISTEARIN	1	12G - Night
TRISTEARIN	1	12H - Paste Masks (mud packs)
TRISTEARIN	2	12J - Other Skin Care Preps
TRISTEARIN	1	13B - Indoor Tanning Preparations

Triundecanoin, as-

GLYCERYL TRIUNDECANOATE	1	12A - Cleansing
GLYCERYL TRIUNDECANOATE	1	12D - Body and Hand (exc shave)
GLYCERYL TRIUNDECANOATE	1	12F - Moisturizing
GLYCERYL TRIUNDECANOATE	1	12G - Night
GLYCERYL TRIACETYL HYDROXYSTEARATE	20	07E - Lipstick
GLYCERYL TRIACETYL RICINOLEATE	3	03C - Eye Shadow
GLYCERYL TRIACETYL RICINOLEATE	4	07C - Foundations
GLYCERYL TRIACETYL RICINOLEATE	7	07E - Lipstick
GLYCERYL TRIACETYL RICINOLEATE	2	07G - Rouges
GLYCERYL TRIACETYL RICINOLEATE	1	13B - Indoor Tanning Preparations

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Bart Heldreth, PhD, Chemist
Date: July 9, 2014
Subject: Request for Endorsement of a Re-Review Strategy for Trihydroxystearin as Used in Cosmetics

The Panel is being asked to answer two primary questions:

1. **Two previous reports described herein are comprised of ingredients that all share a common structural motif, namely they are all triglycerides. Should these two reports be reviewed together as one re-review?**
2. **There is a potential to re-review these two prior reports as one re-review, *and* add 1 new, previously un-reviewed ingredient that shares the same structural motif. Should CIR prepare a draft re-review report, combining these two reports *and this* proposed add-on?**

In 2000, the International Journal of Toxicology published the Panel's safety assessment of the cosmetic, triglyceride ingredient Trihydroxystearin (International Journal of Toxicology, 19(Suppl. 1):89-94, 2000).

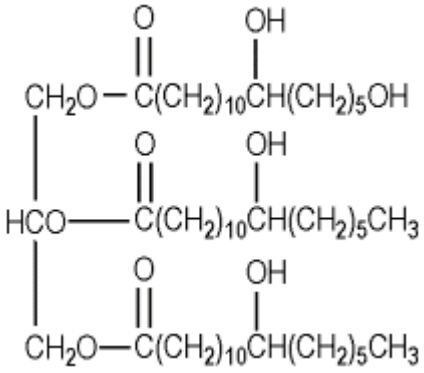

Figure 1. Trihydroxystearin

At that time the Panel's conclusion was:

> Based on the available animal and clinical data in this report, which includes study summaries from CIR Safety Assessments of Hydroxystearic Acid and Glyceryl Stearate and Glyceryl Stearate/SE, the Expert Panel concludes that Trihydroxystearin is safe as used in cosmetic formulations.

And of note in the discussion:

> The CIR Expert Panel agrees that data on sensitization potential are important in assessing the safety of an ingredient. In this case, there are data on a related ingredient. When tested at concentrations up to 20.0% in human RIPTs involving a large number of subjects, Glyceryl Stearate was neither an irritant nor a sensitizer. Thus, in the absence of sensitization data on Trihydroxystearin, it was concluded that this ingredient is not likely a sensitizer based on data on a chemically similar ingredient. All of the available data suggest that Trihydroxystearin and its component chemical species are safe as used in cosmetic formulations.

A copy of the published report is provided herein (file name Trihydroxystearin_2000).

According to data from FDA's VCRP received this year, the reported number of uses for this ingredient is 196.

Additionally, in 2001, the International Journal of Toxicology published the Panel's safety assessment of the cosmetic ingredients Trilaurin, Triarachidin, Tribehenin, Tricaprin, Tricaprylin, Trierucin, Triheptanoin, Triheptylundecanoin, Triisononanoin, Triisopalmitin, Triisostearin, Trilinolein, Trilinolenin, Trimyristin, Trioctanoin (now Triethylhexanoin), Triolein, Tripalmitin, Tripalmitolein, Triricinolein (which is also a hydroxy substituted triglyceride), Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, Glyceryl Triacetyl Ricinoleate, and Glyceryl Stearate Diacetate (International Journal of Toxicology, 20 (Suppl. 4):61-94, 2001), making is a ***2016*** re-review priority.

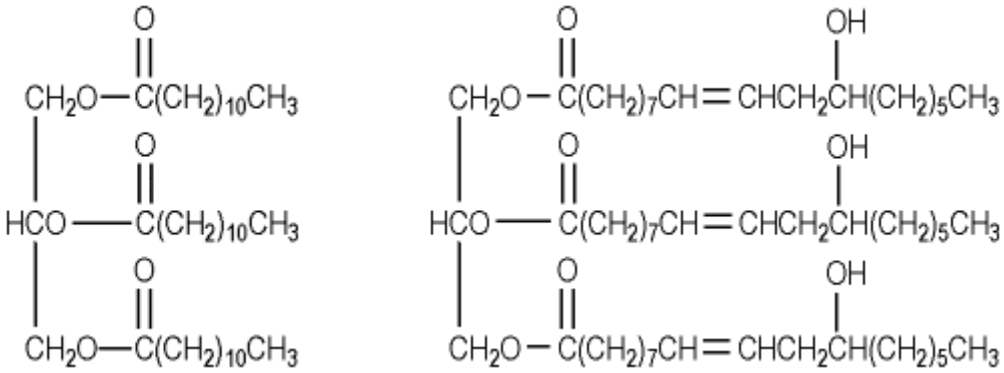

Figure 2. Trilaurin and Triricinolein

At that time the Panel's conclusion was:

> On the basis of the animal and clinical data included in this report, the CIR Expert Panel concludes that the following ingredients are safe as used in cosmetics: Trilaurin, Triarachidin, Tribehenin, Tricaprin, Tricaprylin, Trierucin, Triheptanoin, Triheptylundecanoin, Triisononanoin, Triisopalmitin, Triisostearin, Trilinolein, Trimyristin, Trioctanoin, Triolein, Tripalmitin, Tripalmitolein, Triricinolein, Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, Glyceryl Triacetyl Ricinoleate, and Glyceryl Stearate Diacetate.

And of note in the discussion:

> Although minimal percutaneous absorption of Triolein has been demonstrated in vivo using guinea pigs (but not hairless mice) and in vitro using full-thickness skin from hairless mice, the Expert Panel recognizes that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals, and recommends that care should be exercised in using these and other Glyceryl Triesters in cosmetic products.

A copy of the published report is provided herein (file name Triglycerides_2001).

These two previous reports are comprised of ingredients that all share a common structural motif, namely they are all triglycerides.

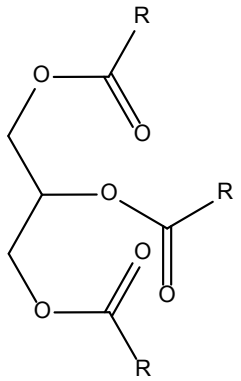

Figure 3. RCO- represents a fatty acid residue

Accordingly, there is a potential to re-review these two prior reports as one re-review, and add a new, previously unreviewed ingredient that shares the same structural motif. Namely, that potential add-on is: Isomerized Safflower Glycerides (which despite the vague name, has as its technical names "…triglyceride" and "… 1,2,3-glyceride").

The Panel should decide whether a draft re-review report should be prepared, which combines these two previous reports and proposed add-on. If a decision to request a draft re-review document is made, then any input the Panel would be willing to provide on what information would be required to facilitate their decision to re-open, would be greatly appreciated. Additionally, a request for survey of all of these ingredients to the Council would be very helpful.

Concentration of Use by FDA Product Category – Glyceryl Triesters*

Trihydroxystearin
Trilaurin
Triarachidin
Tribehenin
Tricaprin
Tricaprylin
Trierucin
Triheptanoin
Triheptylundecanoin
Triisononanoin
Triisopalmitin
Triisostearin
Trilinolein
Trilinolenin
Trimyristin
Triethylhexanoin
Triolein
Tripalmitin
Tripalmitolein
Triricinolein
Tristearin
Triundecanoin
Glyceryl Triacetyl Hydroxystearate
Glyceryl Triacetyl Ricinoleate
Glyceryl Stearate Diacetate
Isomerized Safflower Glycerides

Ingredient	Product Category	Maximum Concentration of Use
Trihydroxystearin	Eye liners	0.3-14.7%
Trihydroxystearin	Eye shadows	1-4.5%
Trihydroxystearin	Mascara	1-2.5%
Trihydroxystearin	Other eye makeup preparations	1-2.9%
Trihydroxystearin	Shampoos (noncoloring)	0.25%
Trihydroxystearin	Tonics, dressings and other hair grooming aids	1.5-4%
Trihydroxystearin	Blushers	0.5%
Trihydroxystearin	Face powders	1-2%
Trihydroxystearin	Foundations	0.3-2.8%
Trihydroxystearin	Lipstick	0.5-8%
Trihydroxystearin	Makeup bases	0.01%
Trihydroxystearin	Makeup fixatives	0.3-0.5%
Trihydroxystearin	Other makeup preparations	0.35-2.1%
Trihydroxystearin	Bath soaps and detergents	0.5%
Trihydroxystearin	Other personal cleanliness products	6.6%
Trihydroxystearin	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	3%
Trihydroxystearin	Body and hand products Not spray	1.7-4%
Trihydroxystearin	Moisturizing products Not spray	0.8%
Trilaurin	Eyebrow pencils	20%
Trilaurin	Eyeliners	36.3%
Trilaurin	Eye shadows	0.2-10%
Trilaurin	Lipstick	46.3%
Trilaurin	Face and neck products Not spray	0.00005%
Tribehenin	Eyebrow pencils	5.5%
Tribehenin	Eyeliners	3.6%
Tribehenin	Eye shadows	1.5-6.5%

Tribehenin	Eye lotions	0.04-3.7%
Tribehenin	Mascara	0.74-15%
Tribehenin	Other eye makeup preparations	3.7%
Tribehenin	Other fragrance preparations Not spray	0.6%
Tribehenin	Hair conditioners	0.1-0.11%
Tribehenin	Tonics, dressings and other hair grooming aids	0.015-8%
Tribehenin	Blushers	1-6.5%
Tribehenin	Face powders	0.015-5.4%
Tribehenin	Foundations	0.5-8%
Tribehenin	Leg and body paints	1.3%
Tribehenin	Lipstick	0.01-5.6%
Tribehenin	Makeup bases	0.5-3%
Tribehenin	Rouges	2%
Tribehenin	Makeup fixatives	3.2%
Tribehenin	Other makeup preparations	0.2-2.7%
Tribehenin	Bath soaps and detergents	7%
Tribehenin	Deodorants Not spray	50.6%
Tribehenin	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.002-2.5%
Tribehenin	Face and neck products Not spray	0.4-4.8%
Tribehenin	Body and hand products Not spray	0.002-2%
Tribehenin	Moisturizing products Not spray	0.002-8%
Tribehenin	Night products Not spray	0.4%
Tribehenin	Paste masks and mud packs	4%
Tribehenin	Skin fresheners	0.002%
Tribehenin	Suntan products Not spray	0.5-3%
Tribehenin	Other suntan preparations	1%
Tricaprin	Other hair coloring preparations	0.75%
Tricaprin	Face and neck products Not spray	0.75%
Tricaprin	Body and hand products Not spray	0.75%
Tricaprylin	Eye shadows	2-8%
Tricaprylin	Eye lotions	2-5%
Tricaprylin	Other eye makeup preparations	4%
Tricaprylin	Hair conditioners	0.25%
Tricaprylin	Tonics, dressings and other hair grooming aids	7%
Tricaprylin	Hair dyes and colors	12.7%
Tricaprylin	Blushers	1.5-11%

Tricaprylin	Face powders	1.5-2.3%
Tricaprylin	Foundations	0.43%
Tricaprylin	Lipstick	0.035-5%
Tricaprylin	Other makeup preparations	11%
Tricaprylin	Aftershave lotions	6.9%
Tricaprylin	Face and neck products Not spray	 0.0002-7.5%
Tricaprylin	Body and hand products Not spray Spray	 0.01-7% 4.1%
Tricaprylin	Moisturizing products Not spray	 5.2-7%
Triheptanoin	Eye lotions	4.5%
Triheptanoin	Lipstick	5.3%
Triheptanoin	Face and neck products Not spray	 4%
Triheptanoin	Body and hand products Not spray	 4-5%
Triisononanoin	Lipstick	25.3%
Triisononanoin	Body and hand products Not spray	 1-10%
Triisostearin	Eyebrow pencils	2-8.8%
Triisostearin	Eye shadows	3.3-35%
Triisostearin	Eye lotions	3%
Triisostearin	Eye makeup removers	5%
Triisostearin	Mascara	6%
Triisostearin	Other eye makeup preparations	6.4%
Triisostearin	Perfumes	30%
Triisostearin	Other fragrance preparations Not spray	 2.5%
Triisostearin	Hair conditioners	6%
Triisostearin	Rinses (noncoloring)	1%
Triisostearin	Tonics, dressings and other hair grooming aids	6%
Triisostearin	Hair tints	3%
Triisostearin	Hair bleaches	0.05%
Triisostearin	Blushers	7-10%
Triisostearin	Face powders	3-10.4%
Triisostearin	Foundations	0.3-17%
Triisostearin	Lipstick	8.3-45%
Triisostearin	Makeup bases	2%
Triisostearin	Rouges	7.2%
Triisostearin	Nail creams and lotions	45%
Triisostearin	Other manicuring preparations	45%
Triisostearin	Deodorants Not spray	 0.8%
Triisostearin	Skin cleansing (cold creams, cleansing lotions,	0.05-30%

	liquids and pads)	
Triisostearin	Face and neck products Not spray	 2.9-10%
Triisostearin	Body and hand products Not spray	 2.5-11%
Triisostearin	Moisturizing products Not spray	 7%
Trilinolein	Bubble baths	0.00048%
Trilinolein	Shampoos (noncoloring)	0.00048%
Trilinolein	Lipstick	0.0048%
Trilinolein	Bath soaps and detergents	0.00048%
Trilinolein	Face and neck products Not spray	 0.017%
Trilinolein	Body and hand cream Not spray	 0.0048%
Trilinolein	Other skin care preparations	0.0048%
Trimyristin	Eyeliners	7.2-8%
Trimyristin	Eye shadows	0.2%
Trimyristin	Blushers	0.56%
Trimyristin	Face powders	0.12%
Trimyristin	Foundations	0.3%
Trimyristin	Skin cleansing (cold creams, cleansing lotions liquids and pads)	2%
Trimyristin	Face and neck products Not spray	 0.5%
Triethylhexanoin	Bath oils, tablets and salts	52.8%
Triethylhexanoin	Eyebrow pencils	10.4-16%
Triethylhexanoin	Eyeliners	13-34%
Triethylhexanoin	Eye shadows	0.002-41%
Triethylhexanoin	Eye lotions	1-10%
Triethylhexanoin	Eye makeup removers	27.3-52%
Triethylhexanoin	Mascara	2%
Triethylhexanoin	Other eye makeup preparations	2-13.2%
Triethylhexanoin	Perfumes	6-36%
Triethylhexanoin	Hair conditioners	0.3%
Triethylhexanoin	Hair sprays Aerosol Pump spray	 0.035-0.15% 1-1.5%
Triethylhexanoin	Permanent waves	0.1%
Triethylhexanoin	Rinses (noncoloring)	0.5%
Triethylhexanoin	Shampoos (noncoloring)	0.2%
Triethylhexanoin	Tonics, dressings and other hair grooming aids Not spray	5% 30%
Triethylhexanoin	Hair tints	10%
Triethylhexanoin	Blushers	1.8-23%
Triethylhexanoin	Face powders	0.83-14.7%

Triethylhexanoin	Foundations	0.2-36.1%
Triethylhexanoin	Lipstick	8-63%
Triethylhexanoin	Makeup bases	11%
Triethylhexanoin	Rouges	48%
Triethylhexanoin	Makeup fixatives	21%
Triethylhexanoin	Other makeup preparations	0.002-42.8%
Triethylhexanoin	Nail polish and enamel	45%
Triethylhexanoin	Nail polish and enamel removers	8-20%
Triethylhexanoin	Other manicuring preparations	46%
Triethylhexanoin	Deodorants Not spray	 0.8-9%
Triethylhexanoin	Aftershave lotions	2%
Triethylhexanoin	Shaving cream	2%
Triethylhexanoin	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	9-61.1%
Triethylhexanoin	Face and neck products Not spray Spray	 2.3-100% 1%
Triethylhexanoin	Body and hand products Not spray Spray	 0.6-57.9% 3%
Triethylhexanoin	Moisturizing products Not spray	 3.2-36%
Triethylhexanoin	Night products Not spray	 4%
Triethylhexanoin	Paste masks and mud packs	0.5%
Triethylhexanoin	Other skin care preparations	5-48.7%
Triethylhexanoin	Suntan products Not spray	 4%
Triolein	Bubble baths	0.00053%
Triolein	Eye shadows	0.14%
Triolein	Eye lotions	0.005-0.025%
Triolein	Shampoos (noncoloring)	0.00053%
Triolein	Lipstick	0.0008-0.0053%
Triolein	Bath soaps and detergents	0.00053-0.0053%
Triolein	Face and neck products Not spray	 0.0053-0.025%
Triolein	Body and hand products Not spray	 0.0053-0.025%
Triolein	Paste masks and mud packs	0.025%
Triolein	Other skin care preparations	0.0053-0.013%
Tripalmitin	Eyebrow pencils	19.3%
Tripalmitin	Eyeliners	0.94-3.5%
Tripalmitin	Eye shadows	0.2%
Tripalmitin	Other hair coloring preparations	1%
Tripalmitin	Lipstick	15.6%

Tripalmitin	Body and hand products Not spray	0.7%
Tristearin	Eyeliners	1.7-24%
Tristearin	Eye shadows	0.004-9.7%
Tristearin	Other eye makeup preparations	1.6%
Tristearin	Rouges	15%
Triundecanoin	Bath soaps and detergents	1.5%
Glyceryl Triacetyl Hydroxystearate	Lipstick	1-19.6%
Glyceryl Triacetyl Ricinoleate	Eye shadows	49.2%
Glyceryl Triacetyl Ricinoleate	Eye lotions	27.1%
Glyceryl Triacetyl Ricinoleate	Face powders	6.3%
Glyceryl Triacetyl Ricinoleate	Lipstick	1-8%

*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 2015-2016

Table prepared February 12, 2016