
Amended Safety Assessment of Triglycerides as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: November 10, 2017
Panel Meeting Date: December 4-5, 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume *MMF*
Senior Director
Date: November 10, 2017
Subject: Amended Safety Assessment of Triglycerides as Used in Cosmetics

Enclosed is the draft Final Amended Report on Triglycerides as Used in Cosmetics. At the September 2017 meeting, the Panel issued a Tentative Amended Report with a conclusion stating that the 51 triglycerides named in this report are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Prior to the meeting, CIR received information that Tripelargonin had been added to the *wINCI Dictionary*. The results of a literature search found ADME data, as well as acute and short-term toxicity information, for this ingredient. These data have been added to the report and are indicated by yellow highlighting.

No new unpublished data have been received since the Tentative Amended Report was issued. Council comments on that report were received and have been addressed. Panel edits from the September 2017 meeting were also addressed.

The following are included in this report package:

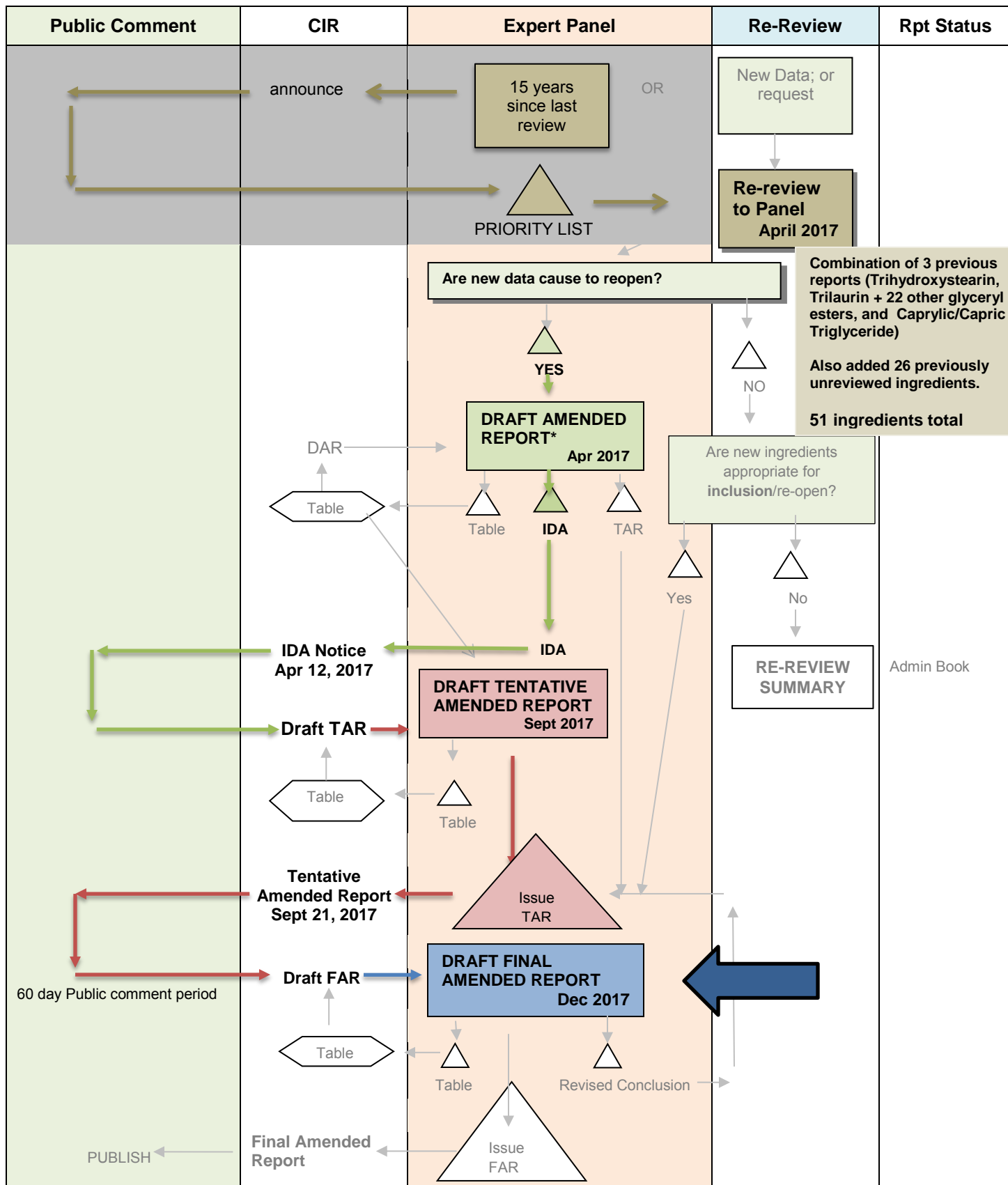
trygly122017flow: report flowchart
trygly122017hist: report history
trygly122017prof: data profile
trygly122017strat: search strategy
trygly122017min: transcripts from deliberations at the April and September 2017 meetings
trygly122017min_orig: minutes from the original deliberations of Trihydroxystearin and Trilaurin and glyceryl triesters
trygly122017rep: draft Final Amended Report
trygly122017prev_1: Final Report on the Safety Assessment of Trihydroxystearin (2000)
trygly122017prev_2: Final Report on the Safety Assessment of Trilaurin and other glyceryl triesters (2001)
trygly122017prev_3: Final Report on the Safety Assessment of Caprylic/Capric Triglyceride (1980)
trygly122017prev_4: Caprylic/Capric Triglyceride re-review summary (2003)
trygly122017FDA: 2017 VCRP data
trygly122017pcpc: PCPC comments on the Tentative Amended Report

The Panel should be prepared to finalize the Discussion and issue a Final Amended Report.

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Triglycerides

MEETING Dec 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. The Panel finalized the list of add-on ingredients. An IDA was issued with the following data needs:

1. sensitization data for Tribehenin at the reported maximum concentration of use;
2. sensitization data for Caprylic/Capric Triglyceride at the reported maximum concentration of use;
3. sensitization data for Triethylhexanoin at the reported maximum concentration of use;
4. irritation and sensitization testing of C10-40 Isoalkyl Acid Triglyceride at the expected maximum concentration of use;
5. clarification of the skin bleaching potential of Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride, including a dose-response for this action; and clarification of the structure of the eicosandioic acid residue of Glyceryl Tribehenate/Isostearate/Eicosandioate.

The following were received in response to the IDA:

1. TKL Research. (2000) Human repeated insult patch test: Moisturizer with 6% Tribehenin
2. Consumer Product Testing Co. (2000) Repeated insult patch test protocol of a material containing 20% Tribehenin;
3. Anonymous. (2015) Clinical evaluation report: Human patch test (facial oil containing 95.51% Caprylic/Capric Triglyceride);
4. Product Investigations, Inc. (2015) Determination of the sensitizing propensities of facial oil (containing 95.51% Caprylic/Capric Triglyceride) on human skin; and
5. KGL. Inc. (2015) Photocontact allergenicity potential of a facial oil containing 95.51% Caprylic/Capric Triglyceride.

Also received were concentration of use data for the additional (add-on) triglycerides, and concentration of use information that was an update to that which was reported in the re-review document that the Panel reviewed in April. The most significant change that was reported in the update is that the maximum concentration of use of Tribehenin in deodorants is 5.1%, not 50.6%. Therefore, the maximum concentration of use reported for Tribehenin is 15% in mascara.

Sept 2017: draft Tentative Amended Report

The Panel issued a TAR with a conclusion of safe as used.

Although irritation and sensitization data were submitted only for 2 of 4 ingredients, the Panel stated that the WoE was strong to support safety of all ingredients.

An update on the concentration of use of Tribehenin was received from industry; the max conc of use in deodorants is 5.1%, not 50.6%.

Also at the meeting the Panel agreed to delete Glyceryl Tribehenate/Isostearate/Eicosandioate (because it wasn't truly a triglyceride), and to add Tripelargonin (which was recently added to the INCI database).

Dec 2017: draft Final Amended Report

Data on Tripelargonin were added to the report.

[illegible]

[illegible]

Triglycerides - - Dec 2017 – Monice Fiume
(X- new data; O- data were included in the original report)

	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	Animal Tox – Rptd Dose, Parenteral	DART	Genotoxicity	Carcinogenicity	Dermal Irritation	Dermal Sensitization	Phototoxicity	Case Reports	Ocular Irritation	Mucous Membrane Irr
Caprylic/Capric/Linoleic Triglyceride																					
Cod Liver/Mink/Tallow Triglyceride																					
Glyceryl Tri-Hydrogenated Rosinate																					
Glyceryl Tripalmitate/Palm Kernelate/Olivate/ Macadamiate/Rapeseedate																					
Hydrogenated C12-18 Triglycerides	X																				
Jobba Oil/Caprylic/Capric Triglyceride Esters																					
Lauric/Palmitic/Oleic Triglyceride																					
Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride																					
Ricinoleic/Caproic/Caprylic/Capric Triglyceride																					

Note: ingredients that were previously reviewed are indicated in blue

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		---			---							
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- pentoic/Oleic/Palmitic Triglyceride	---	√	√	√		---	√	---		---			---							
Glyceryl Tri- Hydrogenated Rosinate	---	√		√		---	√	---		---			---							
Glyceryl Tripalmitate/Palm Kernelate/Olivate/ Macadamiate/Rapeseedate	---	√		√		---	√	---		---			---							
Hydrogenated C12-18 Triglycerides	---	√	√			---	√	---		---			---							
Joboba Oil/Caprylic/ Capric Triglyceride Esters	---	√	√	√		---	√	---		---			---							
Lauric/Palmitic/Oleic Triglyceride	---	√	√			---	√	preR		---			---							

Ingredient	CAS #	InfoB	SciFin	PubMed		FDA	EU	ECHA		SIDS	ECETOC		NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Oleic/Linoleic Triglyceride	---	√	√	√		---	√	preR		---			---							
Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride	---	√	√	√		---	√	---		---			---							
Palmitic/Stearic Triglyceride	---	√	√	√		---	√	---		---			---							
Ricinoleic/Capric/Caprylic/Capric Triglyceride	---	√	√	√		---	√	---		---			---							
Tripelargonin	126-53-4	√	√	√			√	preR												
Generic Terms																				
short chain triglycerides				√																
medium-chain triglycerides				√		X														
long-chain triglycerides				√																
triglycerides, general																				

Search Strategy

10/20/17 – Tripelargonin searched Pubmed - 6 hits/3 useful; SciFinder – 386 hits/3 useful

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 Oliviate 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

developmental 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
developmental 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>

SciFinder (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/fcnavigation.cfm?rpt=eafuslisting&displayall=true> (EAFUS);

<http://www.fda.gov/food/ingredientpackaginglabeling/gras/default.htm> (GRAS);

<http://www.fda.gov/food/ingredientpackaginglabeling/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/HPVISlogin>

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

TRIGLYCERIDES RE-REVIEW TRANSCRIPTS

FULL PANEL – SEPT 12, 2017

Now, we're moving on to the next one, ingredient which is Dr. Marks for triglycerides.

DR. MARKS: So at the April meeting this year, the panel in a re-review of the triglyceride ingredients felt it appropriate to open the previous reports. There are three of them with 25 triglyceride ingredients, and then also to add 27 more ingredients to make it as one consolidated report.

We had information that we wanted so an insufficient data announcement was produced. We did arrive, or receive information about some of these ingredients. Since then, it was also the proposal that one ingredient be deleted, that's the glyceryl tribehenate/isostearate/eicosandioate, and our team felt that that was appropriate, that it was chemically not similar and so should be deleted. And there was also a proposal that we add another triglyceride, the tripelargonin, and our team felt that was appropriate.

So after considering the information we had, we felt that 51 of these ingredients were safe, one was insufficient, that was the C10-40 isoalkyl acid triglyceride, and we still wanted irritation and sensitization data along with concentration of use in the lipstick. So that's a motion.

DR. BERGFELD: That's a motion. So 51 safe, one insufficient, and specifically the C10-40.

DR. MARKS: Correct.

DR. BERGFELD: Okay.

DR. MARKS: And then, needs for that was irritation and sensitization data and concentration of use in the lipstick.

DR. BERGFELD: Is there a second?

DR. BELSITO: I'm sorry, but my computer is totally frozen. I'm trying to deal with it right now.

DR. BERGFELD: Okay.

DR. BELSITO: We -- there was one that we were dropping because it's not a triglyceride, right?

DR. BERGFELD: Right.

DR. MARKS: Yeah.

DR. BELSITO: (Inaudible). And then we were adding --

DR. SNYDER: (inaudible)

DR. BELSITO: Right.

DR. MARKS: That's what I --

DR. BELSITO: And we went with the "safe as used."

DR. MARKS: For everyone. Yeah, we had that discussion also, but still felt as in the insufficient data announcement that we had not received the irritation sensitization data for the C10-40. So we still wanted to see that, particularly since it's used in a lipstick.

DR. BELSITO: Have you ever seen sensitization or irritation from a triglyceride?

DR. MARKS: Now, that -- we could certainly go on clinical experience.

DR. BELSITO: I mean, I think that --

DR. MARKS: I know you were not concerned about sensitization in the previous meeting with any of these.

DR. BELSITO: The weight of evidence of all of these would suggest that they're not sensitizers or irritants.

DR. BERGFELD: Ron Hill?

DR. HILL: Yeah, I think -- I don't know if I was the only one that raised this the last time or I was, is that we have seen sensitization to isoalkyl groups on long-chain alcohols or acids. And in the absence of data in this particular case, you're right. But we have seen a few instances that are select instances.

I don't know even know why it occurs. It doesn't really make good sense to me that it does occur, but we have seen that. And because it's used in a lipstick and it might be used at 80 percent in a lipstick, I feel like we're missing that piece of information and somebody could and should supply it.

DR. BERGFELD: Other comments? Paul?

DR. SNYDER: No.

DR. BERGFELD: Curt?

DR. KLAASSEN: No comments.

DR. BERGFELD: Dan?

DR. LIEBLER: None.

DR. BERGFELD: Ron Shank?

DR. SHANK: I think it's insufficient for the C10-40. We need irritation sensitization, concentration of use.

DR. BERGFELD: Tom?

DR. SLAGA: I have no comments.

DR. BERGFELD: No comment.

DR. SNYDER: Did we get irritation data on C10?

DR. SHANK: I didn't see it.

DR. LIEBLER: I think, you know, I don't think we need it. Honestly, I don't. And this is going to be one of the largest molecules we have. If there are branched alkyl esters that we have seen sensitization on, I don't recall them and maybe Ron Hill can remind me about specifics. If not, I'm not sure that that's real. And this is a family of compounds that has, you know, no irritation sensitization, so.

In, you know, for one of the larger molecules in the bunch, I find it a stretch to think that we really have any realistic prospect of encountering that with data. So I don't think that's a data need. That's my two cents.

DR. BERGFELD: David's asking to speak, so. Please come to the table.

MR. STEINBERG: I disagree. There is one group of triglycerides that can cause sensitization and that's triglycerides made from unsaturated fatty acids because they all contain antioxidants. And we had that problem with a lipstick when I was with you in Hershey one time. And it was the antioxidant was causing sensitization, so the triglycerides which are unsaturated can cause that because of the need for the antioxidant.

DR. BERGFELD: Thank you. All right.

DR. LIEBLER: Just to be clear, this particular ingredient is not unsaturated.

DR. BERGFELD: Okay.

DR. SHANK: It's not unsaturated?

DR. LIEBLER: It's not unsaturated. At least from the name. You know, it doesn't say alkenyl anything, or -- so.

DR. BERGFELD: So any other comments? We had a motion, we did not have a second.

DR. HILL: So ethyl hexanoic acid and there was an iso -- it was a longer chain, nine or 10 chain, where we saw that sensitization effect and I can't come up with a mechanism. I have to be quite honest. So it could be artifactual, but I just feel like somebody has this data and probably could supply it and just hasn't.

DR. BERGFELD: Jim Marks?

DR. MARKS: So after a very nice discussion, I withdraw my motion and will restate the motion that we issue a tentative report with all 51 ingredients with a conclusion of safe.

DR. BELSITO: Second.

DR. BERGFELD: Second. Any further discussion?

MR. GREMILLION: It sounds like, again, there's, you know, there's some uncertainty about, you know, one of these ingredients and, you know, from this discussion, it seems clear to me that asking for some more data, you know, makes the most sense.

DR. BERGFELD: Thank you. Any other comments? I'm going to call the --

DR. BELSITO: Just that I think since you're new to the panel, you're always going to find that there will be discussions on someone's part about uncertainty about certain areas so that -- but, in terms of -- I can tell you that, in terms of sensitization and irritation, these triglycerides are not sensitizers or irritants.

I've been doing this for 40 years, and I have absolutely no concern about these materials. And I think the weight of evidence of -- when you look at the data that we do have, overwhelmingly supports that.

DR. BERGFELD: Thank you. I'm going to call the question in.

All those in favor of a safe conclusion. Thank you very much. Unanimous.

DR. HILL: (Inaudible)

DR. BERGFELD: I didn't see your hand go up, so you were --

DR. HILL: I didn't put it up.

DR. BERGFELD: Are you abstaining, or?

DR. HILL: No. I'm going against for that one ingredient.

DR. BERGFELD: Okay. One against. Okay. Thank you.

(The motion passed 7 to 1; Dr. Hill votes against.)

Belsito Team – Sept 11, 2017

DR. BELSITO: ... So then, I guess, we're on triglycerides. So at the April meeting we agreed that we could consolidate the 25 reports that we previously reviewed with 26 key ingredients. A question came up though about whether Glyceryl Tribehenate/Isostearate/ Eicosandioate is actually a triglyceride and we were told now that it is not. So I guess that's gone out of the report. Am I on the right one? I'm doing this from memory.

SPEAKER: Yes, yep.

DR. BELSITO: And that Tripelargonin --

SPEAKER: (Inaudible), yes.

DR. BELSITO: Yeah, is a --

SPEAKER: (Inaudible 0:01:41.)

DR. BELSITO: -- triglyceride and could be added on.

DR. LIEBLER: Perfectly fine with me.

DR. BELSITO: So that's where we are. So I guess the first question I had from Monice with these is that, did you, based upon that, assume that we would add Tripelargonin, and did you search the literature for any data on those?

MS. FIUME: I actually realized it as I was preparing the report, and I don't think I got to do a total search of it. And I will do that for you. I will do a quick search tonight, and make sure that there's no issues with it. But I have not had a -- did not get the chance to do a complete search for that ingredient yet.

DR. BELSITO: Okay. And --

MS. FIUME: I believe I did a quick search, though.

DR. BELSITO: Yeah. And I don't think I saw it added to the new materials, so that needs to be added to the report. So having said that, do we agree that we can delete one and add the other? We're all okay with that. So then at the last meeting, we had asked for -- we had come out with an insufficient for a maximum -- for sensitization for tribehenin at maximum concentration of use. And we've gotten that.

We've asked for sensitization for caprylic capric triglycerides at maximum concentration and we've gotten that. We have not gotten our other requests which were for triethylhexanoin at 100% for irritation and sensitization for the C10-40 isoalkyl acid triglyceride, and for clarification of the skin bleaching. So the question is, do we really still need all of those? I mean, for the triethylhexanoin, and for the isoalkyl acid triglyceride, can we almost do, like, a weight of evidence and say, based upon the others we don't --

SPEAKER: Yes.

DR. BELSITO: -- see a sensitization concern with these?

DR. LIEBLER: Right. I completely agree.

DR. BELSITO: And then for the skin bleaching, simply say, that's not a cosmetic end point and, you know, manufact -- I mean, we can either go insufficient and say we want a dose response, or we can say, it's sufficient, but manufacturers need to be aware that, you know, producing a cosmetic product that might lighten the skin is not cosmetic and would not be

appropriate or some language to that effect. But I in the end thought that, I mean, I don't even think we need to say irritating, because I never quite believed any of the irritation data for these triglycerides. But if you want to add that to the conclusion, I don't have a problem. But I don't see a sensitization potential for triethylhexanoin and isoalkyl acid triglyceride based upon everything else we have here, which shows no sensitization, including up to 95.6% for the caprylic capric triglycerides.

DR. LIEBLER: And we've reviewed a lot of ethylhexanoin containing chemicals.

DR. BELSITO: Right.

DR. LIEBLER: And there's no sensitization there.

SPEAKER: No, I never had (inaudible).

DR. LIEBLER: So I don't think there's any reason to be concerned about that. I agree with you about the others. The weight of evidence, I think, is very strong. This is a group of ingredients, a family of ingredients, that all have a very good safety profile. There are no red flags.

DR. BELSITO: Okay. So then what do we do with the (inaudible)? Because I think we were saying, safe as used.

DR. LIEBLER: Yes.

DR. BELSITO: And they were the ones that came up with these data needs. So how are we going to deal with skin bleaching? Are we going to say, insufficient, or are we going to say, that's not a cosmetic effect and manufacturers should be aware that this could occur and formulate to avoid bleaching? Like we say, formulate to avoid sensitization.

DR. LIEBLER: Remind me, Monice, was skin bleaching listed as a use?

DR. BELSITO: No. It was reported as --

MS. FIUME: Cosmetic function.

DR. LIEBLER: A cosmetic function? In other words, there wasn't data --

DR. BELSITO: Right.

DR. LIEBLER: -- suggesting? So if there were data suggesting bleaching, then that's a red flag and we need to investigate. But if it was simply reported as a cosmetic use, then, you know, I don't think we'd go after it.

MS. FIUME: So there's language on PDF page 48 that I've built into the discussion. Is that adequate? It's the - -

DR. LIEBLER: Which paragraph?

MS. FIUME: The third full paragraph.

DR. LIEBLER: Oh, okay, one reported possible function is skin bleaching agent. In the United States skin bleaching agent is not considered a cosmetic function. Therefore use in that manner is not being assessed in this report.

DR. BELSITO: Perfect, done. Okay. So safe as used. I don't think we need an irritation caveat.

DR. LIEBLER: And I think there's strong enough weight of evidence that if, you know, if somebody on Jim's team wants to argue these -- you know, we have a lot to say about this.

DR. BELSITO: Right. The only other thing, Monice, on page 48, you repeat a paragraph.

MS. FIUME: Oh, I do?

DR. BELSITO: Yeah. If you go, let's see, I don't know what paragraph. It's sort of towards the, I guess, bottom of the page, middle of the page. The one that starts with, although minimal percutaneous absorption of (inaudible) and then the paragraph below is basically the same thing, but a little bit more expanded.

MS. FIUME: Okay. Sorry about that.

DR. BELSITO: Because of the existing information, that should be from. So I think the paragraph above you can just delete, because it's all in the paragraph below. Do you see where I am?

MS. FIUME: Yeah, I'll look.

DR. BELSITO: Okay.

MS. FIUME: (Inaudible 0:08:16.)

DR. BELSITO: So yes. I said, safe as used. And not even the formulated to be irritating.

Marks Team – Sept 11, 2017

DR. MARKS: ... Next is triglycerides. And this is a draft tentative amended report. You recall that we had in the April meeting decided to consolidate three previous reports on 25 of triglycerides and to include 27 new ones. And that memo from Monice we have first, in the second paragraph there was a question whether or not the Glyceryl Tribehenate/Isostearate/Eicosandioate, boy. Whether that ingredient is chemically so much different that that should be deleted.

DR. SHANK: Yes.

DR. MARKS: Okay. And then -- well, you're...

DR. HILL: I think I probably brought it to the floor in the first place. But I'm still not sure I came to the right conclusion. I mean, it is chemically different, you could delete it on that basis.

DR. MARKS: Okay.

DR. HILL: But then it's just a stray cat.

DR. MARKS: Okay. And then the council -- I'm going to go to ingredients which ones we include and delete. So we're going to delete that ingredient, our team proposes and agrees with. And then if you look towards the bottom of the memo there was a short paragraph beginning finally, the council informed us, that an ingredient that seems appropriate for inclusion is the tripelargonin -- is that how you say it? And so, team add it?

DR. SHANK: Yes.

DR. MARKS: Okay. And let's go back up Curt in addition this is now, I'm back up in the middle of the memo. Clarification of structure of the eicosanoic acid, the following information requested from the meeting sensitization data, sensitization data, sensitizations irritation, sensitization and clarifying the skin, bleaching. And actually, when you read the minutes Don wasn't concerned about bleaching, Don Belsito wasn't concerned about bleaching or sensitization, but we did receive data, sensitization data. That was for the tribehenin we got 20 percent was okay, for the caprylic capric triglyceride 95.6 percent was okay. We didn't get anything for the other ingredients. So team what do you think at this point, 49 safe, 3 insufficient? What do -- for the tripelargonin -- am I saying that right, how do you say that Ron?

DR. HILL: It's tripelargonate, isn't it?

DR. MARKS: No, there's no ate it's an "n".

DR. HILL: Okay. Wait a minute.

DR. MARKS: That's the one we're adding. Do we need have needs for that particular one? So really --

DR. HILL: Tripelargonin.

DR. SHANK: I thought they were all safe as used.

DR. MARKS: Okay.

DR. SHANK: Except one. The C1040 isoalkyl acid triglyceride we don't have irritation and sensitization data.

DR. MARKS: Um-hum.

DR. SHANK: It's not used, no, it's used in one formulation of lipstick with no reported concentration. So I put that insufficient.

DR. BERGFELD: Which one was that again, please?

DR. SHANK: That was C1040 isoalkyl acid triglyceride.

DR. MARKS: And that was in the needs before.

DR. SHANK: Um-hum. I think so.

DR. MARKS: Yes, it was. So irritation sensitization and concentration of use.

DR. SHANK: Yes.

DR. HILL: Okay, so it's a high concentration in lipstick alright. And that will be the concern.

DR. MARKS: So that would bring us up to 51 are safe and one is insufficient. Tom, does Ron Hill sets.

DR. HILL: Yes.

DR. MARKS: And the bleaching we'll handle in the discussion?

DR. SLAGA: Yes.

MS. FIUME: There is already (inaudible) into this.

DR. MARKS: Um-hum.

DR. SLAGA: Um-hum.

MS. FIUME: Okay.

DR. MARKS: Okay. So tomorrow I'll move a tentative report that 51 of these ingredients are safe, one we have an insufficient. The 51 includes deleting the glyceryl tribehenate/isostearate/eicosandioate and includes the tripelargonin, okay.

SPEAKER: Good.

DR. MARKS: And then the insufficient is the C10 the 40 isoalkyl acid triglycerides for irritation, sensitization and concentration of use, okay. Any other comments? If not, we'll move on to the next.

DR. HILL: Did we succeed in finding the distribution of fatty acids in cod liver oil while we're moving on?

MS. FIUME: It's in the table.

DR. HILL: It is now in there, yeah. Okay, I see it, yes thank you. I've seen it before I just -- where was it.

DR. MARKS: Next, Ron Hill can we move on?

DR. HILL: Yes.

FULL PANEL – APRIL 11, 2017

DR. BERGFELD: And so, the next ingredient then is Dr. Belsito, the triglycerides.

DR. BELSITO: Okay. So, this report includes a combination of 25 previously reviewed ingredients. And 29 ingredients, in which the safety has not yet been assessed. At the September 2014 meeting, we agreed to include trilaurin and additional glycerol tri esters and two add-on ingredients to the re-review of trihydroxystearin, which is up for re-review. And then the question was raised as to whether to include 27 additional ingredients and those were added to the Safety Assessment. And so we are now looking at this re-opened and added to Safety Assessment.

The first question, as always, is as to whether the add-ons were okay. And Dan at least felt that they were okay. The next question was that there were three materials that had VCRP reported uses that do not even appear in the dictionary, as cosmetic ingredients. And we felt that those should be excluded from the report. That there could be a mention at some place that they were reported to the VCRP as being used. However, they are not listed as cosmetic ingredients, and we are not reviewing them with this group of triglycerides. And, having said that, and even noting that there was 100 percent leave-on and a 63 percent lipstick use, we felt that we could go safe as used when formulated to be non-irritating. There was some irritating data. I really don't think these are irritating. But to cover any question that we weren't aware of that. We should put that in.

DR. BERGFELD: Comment by the Marks team.

DR. MARKS: Yeah. We had a little as expected, since there are a lot of ingredients. We had a little bit of a different take. We thought that this amended report should go out as an insufficient data announcement. And I'll say the things that we didn't feel comfortable about. One, we wanted to clarify the skin bleaching use for the DDOPT, which is Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride. So, there was a mention of skin bleaching. And we felt uncomfortable that that could be included in a cosmetic and may have a hypopigmentation or depigmentation. The other thing that I thought we needed was sensitization data needs now on tribehenin at 50.6 percent. So it's a high use concentration. And also, capric triglyceride, that's being used at 84 percent. Let me see. And then, Ron Hill, you wanted some clarification on the structure of tribehenate isostearate eicosadioate. Boy, tongue tier's. I call that tie. It is. Tie. Tongue tier. At any rate, that's what we were leaning towards -- not leaning, we would propose if I were the first one talking an insufficient data announcement.

DR. BERGFELD: Want to make comment on that Belsito's team?

DR. BERGFELD: Well, first of all, we've dealt with agents that can cause bleaching, etcetera. We simply say it's not a cosmetic function, and they should be formulated not to cause that. So, I don't need any more data on bleaching. We almost have a boilerplate there. This is not the first time we've looked at something that can cause pigmentary alterations.

DR. MARKS: So would you put that in the conclusion Don?

DR. BELSITO: No.

DR. MARKS: Or in the discussion?

DR. BELSITO: It's in the discussion.

DR. BERGFELD: Discussion.

DR. BELSITO: It's always been a discussion item. And then, if you want to look at some sensitization on fat, that's fine. We can look and ask if there's data. I wasn't really concerned. But I agree there's no data to support that high level for these. So, I mean, this is the first go around. We can ask for it and see what we get and then decide --

DR. MARKS: Yeah.

DR. BELSITO: -- what to do with that.

DR. MARKS: And then Beth, just to clarify, I thought there was going to be a Committee meeting on INCI names. Is that correct or not? And would the three ingredients Don mentioned, that have uses but no INCI -- are not in the INCI dictionary, would they occur in the dictionary in the future?

DR. JONAS: My understanding, and Carol can correct me if I'm wrong, the coconut triglyceride and the tallow triglyceride, according to INCI, Joanne is our expert, should just be coconut oil and tallow oil. So they were probably inappropriately recorded in VCRP. And then the third ingredient was C18-38 acid triglyceride, which we believe is a typo.

DR. EISENMANN: Instead of being 38, well there's a name, the 36. There's only one.

DR. JONAS: Mm-hmm.

DR. EISENMANN: So somebody put an eight instead of a six, is my guess. There's only one use of that.

DR. BERGFELD: So, if we go an insufficient data announcement, then we'd have to clarify the status of these three ingredients. And any opinions from the Belsito team of holding in an IDA? I know the Marks team has agreed.

DR. BELSITO: Well, it's the first time we've come across it. So, I mean, I think insufficient data --

DR. BERGFELD: Yeah.

DR. BELSITO: -- is fine.

DR. BERGFELD: Ron Hill, did you have a comment?

DR. HILL: Yeah. I didn't have the concerns about the sensitization, other than a matter of principle for the ones that he talked about. But I'd pointed out that we have the C10-4040 isoalkyl acid triglyceride. And we haven't dealt with that acid component before in some of the more exotic iso on a small number of occasions, we've seen some sensitization from those. So it was that one. And then I pointed out that we don't have, for the triethylhexanoin, which is the triethylhexal, we don't have any dermal irritation or sensitization on that one. So those are the two I was concerned about for sensitization, not the ones that, even though they were at higher concentrations. Because I doubted those could read-across. The one structure that I mentioned, and I ask that it go ahead and be left in right now. That eicosadioate, appears to be the long chain, 20 carbon dicarboxylic acid, with a carboxyl group on each end. So, instead of having a simple triglyceride where you have glyceride and three fatty acids that actually sets up a link between two. And I don't have any toxicology concerns that I'm aware of. It's just structurally different than the rest of them. And the one other time that it came up, it was appropriate to leave it in, because of the nature of the ingredient class. But I just questioned whether it belonged here, because we really have fatty acid triglycerides. But I'd sort of asked that it not be thrown out at the moment, until I thought about it some more, until we got 100 percent clarification of that structure. Because we couldn't bring up a structure in chemical abstracts. And the one in NIH database might be flawed.

DR. BERGFELD: All right. I think that can be done by the next time we deal with this. Any other comments about what would be needed with the insufficient data announcement? Then we'll move --. Go ahead Monice.

MS. FIUME: I just wanted to get clarification for those ingredients that are in the VCRP, but not in the INCI dictionary, because I don't know if everything was on the same page. If they're still being removed. If we're asking for formal clarification. And what is going to be done with those.

DR. BELSITO: Well, I think that we're, I mean, from our standpoint, if we can get formal clarification that they are, in fact, misnomers or typos. And that they are, in fact, cosmetic or just delete them.

DR. JONAS: Delete them.

DR. BELSITO: Okay.

DR. JONAS: Our recommendation is delete them.

DR. BELSITO: Right. Delete them.

DR. BERGFELD: Okay.

DR. BELSITO: Which is what we had recommended.

DR. MARKS: Right.

DR. BERGFELD: All right. Any other comments?

DR. HILL: This is the first time I remember having seen cod liver oil. And so I had just asked them to see if we could get a distribution of the fatty acids in that, because it was mentioned that there omega minus three's in that. And I don't think that changes anything that I would conclude.

DR. BERGFELD: Okay.

DR. HILL: Just to see if we could get that information given that we hadn't seen it before.

DR. BERGFELD: All right. Anything -- other comments? Or requests? Seeing none, then I'll move on. This is going to go out as insufficient data announcement. I think we've clarified what the needs are.

Belsito Team – April 10, 2017

DR. BELSITO: So we're going to triglycerides. So this is a combination of 25 previously reviewed ingredients with 29 for which safety hadn't been assessed. At the June 2016 meeting we agreed to include trilaurin and 22 additional glyceryl triesters and two ionic ingredients. And to review trihydroxystearin. So there was a possibility raised of also including 27 more ingredients that were put into the safety assessment. And we have put in but we haven't received concentration of use, simply because we haven't signed off on whether they belong there yet. So probably the first thing we need to do is sign off on those 27. We have updated frequency of use and concentrations for the others. So the first question as always goes to you Dan and my colleagues about the recommendations for the addition of those others.

DR. LIEBLER: So I agree with reopening and adding all of the new ingredients.

DR. BELSITO: Okay.

MS. FIUME: Can I add something? We received comments from counsel earlier last week. And three of the ingredients that were added were only found in the VCRP. And I couldn't cross reference at all to the INCI Database. They stated that they will leave that

DR. BELSITO: This is the coconut triglyceride the tallow triglyceride.

MS. FIUME: Yes. And there's a third one.

DR. BELSITO: Short chain.

MS. FIUME: C18-38.

DR. BELSITO: Right.

MS. FIUME: So they believe the C18-38 may be a typographical error. But there's no proof of it so whether or not it belongs. But for the coconut triglycerides they believe that it's coconut oil. Which has been reviewed and re reviewed. So they do not know whether or not it should be included in this report. And that tallow triglyceride is tallow. And the same comment should it be included in this report.

DR. BELSITO: Okay. So we just actually had this discussion with the polyurethanes. Because there's something labeled polyurethane that doesn't exist in the INCI Dictionary. And the way we decided, and correct me if misquote our decision. Was that they not be included in the use table. That somewhere in the report, either as a star in the use table or in cosmetic use. That our reports to the VCRP of these ingredients, they are not listed in the INCI Dictionary.

We don't know how they're used or for what purpose they're used or what concentration. And we are not looking at the safety of those specific ingredients. And then we eliminate them, we never even, I mean, probably just put in words in the cosmetic use section and not include it in the table at all.

MS. FIUME: Okay. And then I will leave those three from that list in the introduction section.

DR. BELSITO: So we're going with the addons.

DR. SNYDER: Seem like some of these other ones are kind of all in that same group. Didn't we review them previously or not? This seems some of the names seem very familiar.

MS. FIUME: From what I found they were not.

DR. BELSITO: So the impurities we have the polycyclic aromatic hydrocarbons. With crude oil being reduced to below ten parts per billion. That was for the triundecanoin from the prior report. And I suppose I said. do we need the usual boilerplate in the discussion regarding this? Six thousand uses, wow.

DR. SNYDER: What happen 600 to 6000, 673.

DR. BELSITO: It's not a typo. Yeah. Caprylic capric triglyceride.

DR. SNYDER: Up to 54 percent in lipstick.

DR. BELSITO: Yeah.

DR. SNYDER: 763 in 2003.

DR. LIEBLER: And there's 6000 lipsticks.

DR. BELSITO: No, no, no. This is not just lipsticks 54 percent in lipstick is actually for

MR. KLAASSEN: 6000 cosmetics.

DR. BELSITO: It's also caprylic capric triglyceride.

MS. FIUME: I mean, because there's 598 eyeshadows, there's 583 lipsticks.

DR. BELSITO: 84 percent in perfumes.

MR. ANSELL: Sometimes they just file each shade as a separate product.

MS. FIUME: Because there's 11,037 moisturizing formulations that have it.

DR. LIEBLER: That have ingredients in this family.

MR. FIUME: That have the caprylic capric Triglyceride.

MR. ANSELL: Really. That sounds like a lot. Because I don't think they're

MS. FIUME: I'll check

MR. ANSELL: Doesn't seem to me the VCRP has any.

MS. FIUME: I usually cut and paste but...

MR. KLAASSEN: My wife doesn't ask me to go to the store to buy one. If I had to decide which one (inaudible) thousand.

DR. BELSITO: Okay. So we need the inhalation boilerplate, we need the penetration enhancement.

MR. ANSELL: Over 1000 I can believe.

DR. BELSITO: We're you okay with those reproductive effects in animals?

MALE SPEAKER: (Inaudible)

DR. BELSITO: There were some reproductive effects with trycaprylin and that authors postulated that the differences could be due to normal variations in Long Island or Long Evans rats. Same thing with a carcinogenicity study just too much fat.

DR. SNYDER: I didn't see anything, yeah.

DR. BELSITO: Okay. So on the dermal irritation and sensitization, there was application with tanning butter formulation containing 22 percent caprylic capric triglyceride. At a dose (inaudible) five times a week. Application of a perfume softener formulation containing 4 percent shave skin. Why I target this then I'm on the wrong one.

There was one that was undiluted caprylic triglyceride was non irritating. Slight to moderate everything reserved intact in the braided skin. A rabbit swelling of four week application of that butter formulation containing 22 percent caprylic capric triglyceride at a dose. But I mean, I said it's likely due to the other 78 percent of the materials. Since a 100 percent had no effect and I don't think that's helpful. It just adds confusion and I would delete that study. It's not a pure study. Do you see which one I'm talking about?

MS. FIUME: No.

DR. BELSITO: Page 29 of the PDF. The 1, 2, 3, 4th paragraph down starting with undiluted caprylic capric triglyceride was not irritating. And then slight to moderate aerothermal was observed and intact in the braided skin of rabbits. Four weeks application of a butter formulation containing 22 percent.

MS. FIUME: So Dr. Belsito, that was from the original reports?

DR. BELSITO: I say.

MS. FIUME: So do you want me to delete it or leave it in?

DR. BELSITO: I don't know, what's the usual thing. You just copy everything from the original reports?

MS. FIUME: We usually take it from the summary.

DR. BELSITO: I just think that, you know, it follows a sentence that goes, "undiluted is totally non irritating and guess what, 22 percent is." That makes no sense. It only makes sense if you remember that there's 78 percent of other stuff in there that you don't know what it is. You know, there's 78 percent other stuff that's causing the irritation.

So I just don't think it's very helpful information. And if it could be deleted I would delete that sentence. And if you can't if the custom is just to carry over the statement, then that's fine too. I don't even think enough of it that we need to have it in the discussion.

Then on page 31 again, you getting some irritation coming up with triheptanoin. I really don't think these are irritating but then the question becomes when formulated to be non irritating. I don't know I'm just throwing that out there. I don't think we need to but... What do you guys think about the irritation data here? I think it's pretty negligible.

DR. SNYDER: (Inaudible).

DR. BELSITO: So the discussion the botanical boilerplate obviously. Penetration enhancement 1, 2 diester obviously didn't type something correctly 1 2 diester something reviewed. Was there a 1 2 diester issue Dan?

DR. LIEBLER: Well basically, the next related group of ingredients which will be the glycerol 1 2 diester.

DR. BELSITO: So it probably said 1 2 diesters continue to be reviewed. Or that we're not reviewing the 1 2 diester. Do we need that with discussion?

MALE SPEAKER: Different.

DR. BELSITO: Do we need anything about 1, 2 diesters in the discussion.

DR. LIEBLER: I don't think so.

DR. BELSITO: I'm not sure either since it's totally misspelled. Bleaching is not a cosmetic function. So whatever one had that bleaching effect, should not be used at a concentration that could cause that. And we're not reviewing the materials that were reported to VCRP that are not in the dictionary.

MS. FIUME: Does go the (inaudible) as well?

DR. BELSITO: I don't know. I leave that up to my teammates to (inaudible).

MR. LIBELER: Just put it in the intro that those are synonymous and if they were already been reviewed then reference them.

DR. BELSITO: Okay. Which was the one that had bleaching as a function in the dictionary?

MS. FIUME: I believe it's Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride.

DR. BELSITO: That's all one molecule.

MS. FIUME: Yes.

MR. ANSELL: I find that kind of surprising.

MS. FIUME: Reported function and actual function we find often are not the same.

MR. ANSELL: There's no criteria for a manufacturer to claim whatever, they want in that section of the dictionary.

DR. LIEBLER: That's what I would call in my lab an egregious hypothesis.

DR. BELSITO: So safe as used.

MS. FIUME: Dr. Belsito, did you want anything mentioned about the possible 1 4 dioxane? They're not additive (inaudible).

DR. LIEBLER: I saw the mention of that and thought, what. And I realized it was a don't worry about this.

DR. BELSITO: Oh. I know what I was talking about the 1 2 diesters for the diglyceride in the report glyceryl dilaurate. Our prior conclusion, it was safe in the present practices of use and concentration. Providing the content of 1 2 diesters is not high enough to induce epidermal hyperplasia. So does that go into our discussion?

DR. LIEBLER: I seem more of a purity issue. If you have 1 2 diesters and those two have signaling effects starting. And so your triglycerides would need to be high purity essentially.

DR. BELSITO: Right. In the discussion of some of these that have been brought back in, we specifically mention 2 diesters. And the limit was below that that would cause epidermal hyperplasia. Do we want that statement again in the discussion?

DR. LIEBLER: I think you can have it as a discussion it doesn't need to be in a conclusion.

DR. BELSITO: So what I'm looking then page 42 table 3. The second group of compounds, there's glycerin and then the next group is the diglycerides.

DR. LIEBLER: Yeah.

DR. BELSITO: And you see a conclusion.

DR. LIEBLER: Sure. Yeah. Only some of these diglycerides are capable of doing anything like that. It's an unusual conclusion. We haven't done anything like that since I been on the panel

DR. BELSITO: Oh, we done some.

DR. LIEBLER: (Inaudible) way back. Yeah, I know. I think I have to scroll back up to impurities and look at the data on percentages of purity. The only specific mentions of impurities for this huge family are triundecanoin. Contains no impurities or residues of catalyst or solvents. And then caprylic capric triglyceride only known impurities are free fatty acids and small amount of glycerol. It doesn't say anything about diglycerides or diacylglycerols. So some diacylglycerols are active signaling molecules (inaudible). And...

DR. BELSITO: But who's a (inaudible) Tom Slaga.

DR. LIEBLER: But not all of them are created equal in terms of their ability to (inaudible).

DR. BELSITO: Right.

DR. LIEBLER: Many of these that could be produced by cleaving any or fatty acid chain off of this. Actually, you need to have the I think it's the two position cleave you'd have (inaudible) diacylglycerols would be the.

MS. FIUME: That was the discussion we reported it.

DR. BELSITO: Okay.

DR. LIEBLER: Yeah. I mean, I think incorporating that into the conclusion which was probably overly conservative then. I still...

DR. BELSITO: So put in the discussion but not the conclusion?

MS. FIUME: This type of assignment should go into the discussion?

DR. BELSITO: Yeah.

DR. LIEBLER: Right.

DR. BELSITO: But not conclusion. Safe as used for conclusion.

DR. LIEBLER: And this report was in this previous report it was in the conclusion

DR. BELSITO: Right.

DR. LIEBLER: which is why I mentioned it was an unusual conclusion by our standards these days. I think it's appropriate end of discussion in that same language could be lifted.

MS. FIUME: Doesn't say (inaudible).

DR. LIEBLER: To be included I think that would be fine. We should get Tom's say so. Get his input, I'm sure he will.

DR. BELSITO: I'm sure we'll get Ron's too. Okay anything else on this, Paul?

DR. SNYDER: It's an overkill really.

MR. KLAASSEN: Over cautious.

DR. SNYDER: Over cautious but that's okay.

DR. BELSITO: Discussions can be over cautious.

DR. LIEBLER: But back when this was done last this was a more new hot topic. Which probably informs the (inaudible)

DR. BELSITO: Paul you were.

DR. SNYDER: Well, I'm just worried

DR. BELSITO: Code work (inaudible)

DR. SNYDER: Digging a little bit deeper into the repro and the carci studies. So those references were all previous CIR reports. But then there's didn't bring forward any of the discussion from those reports as to why we weren't concerned back then. And we should be concerned now. Was there any wording in there or?

MS. FIUME: I brought the discussions from the trihydroxystearin and trilaurin reports forward. The other report caprylic triglyceride didn't have discussion. But the discussions I had I did bring into the report. They follow the summary.

DR. SNYDER: I mean, it's just three short paragraphs though (inaudible)

MS. FIUME: And that's all they're minutes are in I did include the minutes in the package.

DR. SNYDER: I'll go back and look at those. I may have heard of it but I just don't remember.

MS. FIUME: Dr. Belsito, you didn't mention it but the inhalation boilerplate as well?

DR. BELSITO: Yes. I thought I did.

DR. SNYDER: Yes. Penetration and inhalation.

MS. FIUME: Sorry I missed that.

Marks Team – April 11, 2017

DR. MARKS: Let me see here. Next is triglycerides. And Monice is still up on the hot seat Oh, here we go.

This is an amended safety assessment of triglycerides. And this is a small point, but we continue to use the word, "cosmetic." Should it be changed to, "personal care products?" That's just a out in left field, so to speak, throwing that in now, but

DR. HILL: I think I asked that, I think I asked that with more details a few meetings back, and we decided that we all knew what we meant.

DR. MARKS: Yes. Okay.

DR. GILL: I'm personally thinking personal care products you get into the OTCs as well.

DR. MARKS: Yes. Okay. I just kind of okay.

DR. SADRIEH: The word, "cosmetics," is what's in the regulation, so that was the term that's currently used.

DR. MARKS: In regulations.

DR. GILL: Correct.

DR. MARKS: Okay. Let me see here. Monice, do you want to maybe I should ask you. "However, because a decision to include the additional ingredients was never finalized, use concentrations for these ingredients have not yet been surveyed." That's going to be important.

So 25 ingredients in this amended safety assessment were previously reviewed and found to be safe. The 29 additional ingredients, the first thing would be are all the ingredients now, the 25 plus 29, okay.

DR. HILL: So I had an issue with one.

DR. SHANK: The one that causes skin bleaching?

DR. HILL: No.

DR. SHANK: Oh. Which one was that?

DR. SHANK: (inaudible) triglyceride I don't think should be added.

DR. HILL: I wonder how I mean, you feel that that's actually a real effect, the skin bleaching from that?

DR. SHANK: That I don't know. That's what's in the report so

DR. MARKS: So you don't want it added because of its effect, or because it chemically doesn't fit into the triglycerides because we don't eliminate it if has a toxic effect. We just say either insufficient or unsafe. And that one again was

DR. EISENMANN: But you're including Omega 3 in this report. No. I mean should Omega 3 it's in general, when you're looking at the proposing the fatty acid report Omega 3s are not there. Should they be here? I was looking for it would be helpful a description of what are the boundaries of this group so you include everything from acetic acid to does it matter is there anything that would be metabolized different based on where the double bonds are or

DR. HILL: So for me the only one that I had a problem with was the icosin dioic acid.

DR. MARKS: In terms of

DR. HILL: In terms of structure or relatedness because in that particular case you've got more than one carboxive group in which case the basis structure of the triglyceride would change unless I'm missing something.

DR. MARKS: Before we get to that one, let's go back to Ron Shank. The concern you had was, let me see. Where is it on this listed? Which subgroup is it under? There were linear change, branched, had a long name.

DR. HILL: The skin bleaching is what you're looking for?

DR. MARKS: Yes. That was under the linear mix change in the first page. Was that the one?

DR. SHANK: I'm on Table 1. Which page are you on?

DR. MARKS: Table 1. Is that the one where it has all the I'm on this. This one here, Ron where it has a list of ingredients, and then what data we have on them. I'm sorry again. Was it discosal hexynoic

DR. SHANK: It is called (discoahexinoid, dicoso pantinoid (inaudible) triglycerides.

DR. MARKS: And that causes bleaching.

DR. SHANKS: That's what it says.

DR. MARKS: And what page

DR. MARKS: And usually, we don't add things to reports that cause a change in the conclusion, right?

MS. FIUME: Dr. Shank, are you going by its listed function, or

DR. SHANK: Well, Page 21

DR. MARKS: What used to be no brainers, but it's hard to believe we can add, if we eliminate that 28 other additional ingredients and it's a no brainer.

MS. FIUME: So I think the confusion is the dictionary will list functions, and often we have things that are listed such as skin bleaching agents and we make a statement that that's not a cosmetic function, therefore, that type of use is not being evaluated in the report. So we haven't ruled it out because of the function. If there are test data that show it's a skin bleaching agent, then it's usually addressed somehow in the safety evaluation, either the discussion or the conclusion, but there were multiple functions listed for that ingredient, and as I said, we usually will make a note that the panel isn't reviewing function as a skin bleaching agent.

DR. SHANK: Really? Okay.

DR. HILL: Hovic (inaudible) acid. That's another one that we saw.

DR. MARKS: What page is that on where it talks about the skin bleaching? And there's nothing

MS. FIUME: I'll find the page in Table 1. It's listed under the functions in Table 1. And it's also listed in a paragraph on page 21.

DR. MARKS: 21. Okay. So, Ron Shank, how do you want to handle that? Do you want to do in the discussion where we don't 21. Let me see here.

DR. SHANK: But of we come across an ingredient that causes skin bleaching we need to set a limit for say it's not safe.

DR. HILL: He set a limit.

DR. MARKS: Yes. We certainly have done

DR. HILL: (inaudible) concentration dependency.

DR. HILL: That's why I asked if it was even real. I mean, I guess hypothetically that things could somehow modulate the action as tearsinase as one possible activity.

DR. SHANK: Well, apparently, it is in use and not a cosmetic use.

MS. FIUME: Well, it's a listed function, but Carol, correct me if I'm wrong, just because the function is listed doesn't mean it's actual effect. If Bart were here, he'd be taking great he's not very thrilled with the functions sometimes because skin conditioning agent is thrown in there all the time, he'll say. But, yes, just because it's listed as a function doesn't mean it's a shown effect.

DR. SHANK: Okay.

MS. FIUME: Is my understanding.

DR. SHANK: Okay.

DR. MARKS: Can we be explicit with that? It says a reported function of this ingredient, skin bleaching agent. The skin bleaching agent is not a cosmetic function, therefore, use in that manner is not being assessed in this report. Can we say we expect it's not only not being assessed in this report, but we don't feel that it's actually being used or doesn't have that effect?

But I agree with you, Ron, when you say

MS. SADRIEH: Maybe I should clarify. The (inaudible) based on claims, and so the product is regulated based on the claim that it makes. The claim has to be a cosmetic claim. So if it makes a skin bleaching claim that would not be a cosmetic claim. So that would be a drug claim. So I think any ingredient could potentially have an effect on the structure and function if one were to look at it, but for the purposes of the cosmetic, it's making cosmetic claims. And I guess if you were looking at the bleaching effect that would be an efficacy and not a safety sort of assessment, and they're making a safety assessment from my understanding.

DR. MARKS: Yes. Except that we've had ingredients before where they've had a skin bleach in effect. That was not their function.

MS. SADRIEH: Well, maybe the lightening or brightening. They were not bleaching.

DR. MARKS: No. There were some that caused depigmentation, and we declared it either unsafe or insufficient because of that effect.

And I see the conundrum here because if it says that's one of the uses, is it really a use or is it really an effect.

DR. SHANK: Is it an effect?

DR. MARKS: And we have no literature to suggest that it really is a bleaching agent.

MS. FIUME: Not that I've found. So when we started including functions in the introduction, there was a lot of discussion about the language and reported it's actually reported similar to (inaudible), we don't know that it has that effect. It's just reported that it could possibly have that function.

So I know it's very confusing.

DR. MARKS: No. I would just I would probably put another sentence in there that maybe would reassure us is despite it being reported that this is a function, we have no data to suggest that it actually is a bleaching agent.

DR. SHANK: Shouldn't we request that be there?

DR. MARKS: Insufficient.

MS. SADRIEH: That's not a cosmetic function. That wouldn't be a cosmetic function.

DR. SHANK: It doesn't matter.

MS. SADRIEH: So you really wouldn't be looking at that data.

DR. SHANK: That doesn't matter if it has a deleterious effect.

MS. SADRIEH: Well, silocytic acid is for acne, you know, but it's used in cosmetics not for basically treating acne. You know, you're looking at the safety of it for the cosmetic use.

DR. SHANK: Yes. That's right. But if the chemical has a skin bleaching effect, we can't say it's safe for use in cosmetics unless we know it doesn't have that effect in cosmetics.

DR. MARKS: So why don't we just put in, we can put an insufficient data announcement and see whether or not we can find something that will substantiate whether it has any bleaching or not?

Obviously, if there's no study looking at it, and we don't we'll have to proceed, but I hear both of your points. I agree with Ron Shank that that's a safety concern even though that would be a drug function if it's in a cosmetic and it has that

DR. SHANK: And causes that effect.

DR. MARKS: causes that effect, that's a safety issue.

DR. SHANK: That's right. Now, that's so reopening this is the issue, so I guess it should at least be reopened, but the conclusion is going to change.

DR. MARKS: Well, it has to change since we're adding a lot of new ingredients.

DR. SHANK: Well

DR. MARKS: So just adding the new ingredients changes the conclusion. Wish this was just a shorter chemical ingredient. Triglyceride. And I had some sensitization need so even though we're going to be seconding, I'm going to say I want to see sensitization on three. I don't know whether we want to get to that yet, but I agree with you about the bleaching. We need to clarify that. Clarify skin bleaching use for the DDOPT. I don't know how you say it, Ron. It's a mouthful. The D D O P T

DR. SHANK: There you go.

DR. MARKS: ingredient. That's how I'm going to refer to it, DDOPT. Okay. So we want the skin bleaching, clarify that whether it really is have that use.

And then the sensitization I wanted tribehenin at 50.6 percent. Let me go back to that's been used at that percentage, and we only have an HRIPT of 0.3 percent. So there's a big difference between the data we have as a safe for sensitization and the use of it.

MS. FIUME: You said Tribehenin?

DR. MARKS: Yes. Tribehenin I have that's being used, and it's being used in lots of cosmetics. 723 uses. The highest concentration or Read On is 50.6, and on page 65, we have a HRIPT with safe at 0.3 percent. So there's more than a tenfold difference.

DR. SHANK: But we have several that are in use at 100 percent, or testing at 100 percent.

DR. MARKS: Yes. Can you read across those? Let me

DR. SHANK: Table 13, which is page 54. So can you read across those tested at 100 percent were not irritating or sensitizing.

DR. MARKS: Yes. One of them was triheptanin, tanoin. That was at 100 percent with guinea max, but I don't know. I didn't feel that you could, but maybe they're both linear chain, saturated liner chains. One's tri, triheptenoin, and the one I'm concerned about is tribenoin. And then I had the same concern about caprylic and capric triglyceride. There's over 6,000 uses.

DR. SHANK: That was tested at 100 percent.

DR. MARKS: I didn't have it at 100. I have it a 4 percent with guinea pig. Where is the hundred on that? That was page 107. Let me see.

DR. SHANK: It was Table 13, page 54.

DR. MARKS: Oh, I know. That's in the original report.

DR. SHANK: That's just irritation.

DR. MARKS: Yes. I went back to the original report from 107, and that was the highest concentration for sensitization. Did you see a different sensitization concentration, Ron? The one I pulled was from the original (inaudible) on page 107.

DR. SHANK: Actually, it turns out to be just irritation.

DR. MARKS: Yes.

DR. HILL: So I had a different take on sensitization since you're on the subject matter. I didn't have a problem with that one, but we have had

DR. MARKS: 65, yeah, and I went back to the original. Actually, going back to tribenoin. That was I went back to the original on that, also page 65, and that was .3 percent HRIPT.

So, again, much different between what had been tested and the use now, and there's lots of uses. Im talking about 6,000. There's got to be an HRIPT at 84 percent. I just can't imagine, or at least a higher one.

And I wasn't reassured totally that if you had triheptenoin at 100 percent was okay with a guinea pig would applied to these others.

DR. SHANK: Okay.

DR. HILL: I believe it would.

DR. MARKS: You believe it would.

DR. HILL: My take is different on this which is that we've got, when we've seen sensitization in this kind of molecule, it's come with some of these branchlings, and the one that bothered me was the triethylhexal or triethylhexanolin because we have some past experience past experience with ethylhexnoic acid.

And then the C 40, C 10 C 40, it actually says C 10 to iso alkyl acid triglyceride where we have no data whatsoever on

these isotriglycerides. And there was an isonananate. We at one point in time

saw sensitization. Otherwise, as a class, you wouldn't expect that there's anything would lead us to think that sensitization would be an issue.

But these iso ones, particularly the C 10 to C 40 iso alky acid triglyceride, that's another story, and there's no data.

And then similarly, we don't have any sensitization, anything on the triethylhexanoin, or hexanoin. I wouldn't say it that way, but

DR. MARKS: The triethylhexanoin.

DR. HILL: Yes. And then looking at the first read across table in the report, but

DR. MARKS: Yes. That one, you're right. The local lymph node assay showed it may be a sensitizer.

DR. HILL: Which one?

DR. MARKS: The triethylhexanoin or

DR. HILL: (inaudible)?

DR. MARKS: Yes. Well, it's not totally reassuring because the local lymph node assay show it may be a sensitizer. So I kind of, okay, maybe a sensitizer, but I was focused more on we don't have any reported uses for that, but I was focused more on the trihex

DR. HILL: I'm not sure you're looking at the same one I was looking at then because triethylhexanoin, and assuming that her table on page 7 is accurate, there's no sensitization and there is use.

DR. MARKS: Okay. You're on page 7.

DR. HILL: Yeah.

DR. MARKS: The one I had identified was the trihydroxy stearin

DR. HILL: Yeah.

DR. MARKS: which has 273 uses, and 15 percent concentration, and my question is can you read across. Page 63.

DR. HILL: I guess my comfort level there was that that's a naturally occurring and fairly pervasive at least the stearic acid and (inaudible), the hydroxy stearic acid and that we, if we reacted to that we'd all be in trouble. That was just my take on that one.

DR. MARKS: Yes. I guess whenever I that used to be my thought years ago that if it's a natural occurring substance, but we know that individuals have delayed type hypersensitivity, the corticosteroids. And we have circulating corticosteroids. We take certain corticosteroids, apply it to the skin and they become sensitized.

DR. HILL: Hydrox stearates though are present in practically every biological membranes, and we traffic those pervasively. So unless this is not faithful to the endogenous hydroxy stearate, which I think it probably is, I don't have any reason to believe otherwise, I don't believe there's a problem with that one.

it's these unusual branched acids in the triglycerides where I don't have any information about what they are, and these iso alky acid triglyceride where I get a little more worried because we've seen past sensitization with certain of these more exotic synthetic branched, not always, but a few. But I still want to remove that one ingredient by the way.

DR. MARKS: Which one is that?

DR. HILL: That's the page 8 is one, it's the first place, but that's in her pre report table. And then it shows up again in the cert strategy, and then

DR. MARKS: So which ingredient is it you want to remove?

DR. HILL: If you can get to page 8, it's the first one on page 8. And thee's a CA number

DR. MARKS: What's the name?

DR. HILL: Yeah, okay. So it is Tribehenate, Isostearate, Eicosandioate, and it's the Eicosandioate that is the flag because it's diacid. It's a 20 carbon diacid where there's an acid group on each end best I can tell so that you don't have a triglyceride, just this glycerol with one or three fatty acids as crust, as crust link, and a very different structure.

I don't have any reason to suspect anything, but it's structurally quite different.

And then if we don't want to remove it, for me it's insufficient.

DR. MARKS: I C O S A N D I O T E. Structural. Okay. Do you have any problems with removing it Ron or Tom?

DR. SLAGA: I don't.

DR. SHANK: No.

DR. MARKS: Okay.

DR. HILL: And we want to this is a Monice, we want to capture that structure because the INCI table and the structure that's in there doesn't enlighten that we have a different acid here as part of that structure, and there's a CA number that goes with that. It's like 941,000 something or other.

MS. FIUME: If it were to stay in you would want the structure and the table?

DR. HILL: I would say if maybe I'm thinking, because otherwise it's just a stray. Maybe you could put in for the moment make sure we capture that structure, but I still feel like we'll say insufficient at the end for me. But that's okay.

DR. MARKS: Yes, we'll, tomorrow propose we move on and mention that it structurally is different and let you comment on it.

DR. HILL: It's in use, so that's why I think we might get some additional information that we haven't gotten yet. If we reopen, right, which we are

DR. MARKS: Yes. I don't think there's any question that we'll

DR. HILL: Go after that? See if we can get it?

DR. MARKS: open it at least in my mind. There'll be an amended report that we're going to add 29, possibly 28 if we remove the skin bleaching agent, the DDOPT, and possibly 27 if we remove the TIE. I'm going to abbreviate that.

DR. EISENMANN: Can we talk briefly about the three ingredients that were in the VCRP that are INCInase, coconut triglyceride and tallow triglyceride? Wouldn't you consider that's coconut oil which we've reviewed three times and it's in the list to be reviewed in 2018. And isn't tallow triglyceride tallow? So do those really need to be in this report because we've already reviewed them because it's just a different name.

And the other one is a, I mean, it could be more purified. It's just the two triglycerides and maybe the oils have a little bit of other, but, basically, you've reviewed them. I'm not sure why you would need to do them again.

The other one, I don't care whether or not you include it at C something to 38 instead of 36. I suspect, in this one use report I suspect it's a typo, but I don't care if that's in there or not, but the tallow triglyceride and coconut triglyceride alternative names for something you've already reviewed I think.

DR. MARKS: So were they the 25 previously reviewed, or are they part of the 29 additional ingredients?

DR. EISENMANN: They're in different reports all together.

MS. FIUME: Currently, Dr. Marks, they're part of the 29 additional ingredients. They were only found in the VCRP. I couldn't find the synonym or a technical name matching them in the INCI database.

So for right now, they were put in here not knowing for sure exactly what they were.

DR. EISENMANN: But when Joann reviewed, the INCI person reviewed the VCRP, she stuck them in coconut oil, and she stuck it in tallow, the tallow triglycerides.

DR. MARKS: Well, can't we just change it to 27 previously reviewed ingredients, and in the, somewhere in there indicate that these two tallows were previously reviewed under different names?

DR. EISENMANN: I would just not put them in here because you've already

DR. MARKS: Well, you could say that to the 25 previous reviewed.

DR. EISENMANN: Well, I mean, reviewed in different reports.

DR. MARKS: Yes. No, I hear you. But if you're going to eliminate two that have been previously reviewed, how about the other 25? I would include it and just note that they're the same ingredient with different names, and they've been previously reviewed with, I presume, a safe conclusion.

DR. EISENMANN: I just think it's kind of funny that you've already reviewed the coconut oil in three different reports, and here is the fourth, and then you're proposing to review it another time in a report next year. So, I don't know. I'm just

MS. FIUME: As I said, right now the reasoning in here because there was no cross reference in the dictionary, so I included them based on the name without having

DR. EISENMANN: Correct. I think that's fine. But I think at this point, it would be necessary we've reviewed them in our reports it's not necessary for them also to be in this report.

DR. MARKS: Tom, Ron, Ron, how do you want to proceed with this? To me it's, I'm not sure I'd say procedural unless it was either insufficient or unsafe.

DR. SLAGA: We already have a bunch that have been reviewed and just flip it in that section. Right?

DR. MARKS: Yes, exactly. That's what I thought. That it being previously reviewed doesn't eliminate it from here even though it's been multiple times. We're including at this point 25 previously reviewed. We can just make it 27 previously reviewed and

additional of which two may be eliminated in the future. What do you want to do

DR. SHANK: That sounds good.

DR. MARKS: Yes. Okay. So I'll be seconding presumably tomorrow an insufficient data announcement for this amended report, and what we want in the data we want to see the needs are clarified as skin bleaching use for the DDOPT. I won't repeat that whole long name.

I still would like to see sensitization needs for the tribenhenoin 50.6 percent since we're sending an insufficient data notice. The same for the capryllic, capric triglyceride at 84 percent. And I will eliminate the trihydro oxy stearan. I'll mention it since it's a natural constituent. And then remove the tribenhenoin iso stearate, Eicosandioate structure because it's different.

DR. HILL: I think I'd like to see it kept for right now and clarification of the structure, and then we can make a decision at a future date

DR. MARKS: Okay. So I'll say clarify. That would be another need.

DR. HILL: But on the sensitization I would like to see the C 10 C 40 iso akyl

DR. MARKS: Clarify. The C 10 C 40, which one's that?

DR. HILL: C 10 40, oh, hang on. I'll give you the right name.

DR. MARKS: So add that to it. You don't feel we need the trihydroxi stearin

DR. HILL: I don't.

DR. MARKS: since it's a natural product?

DR. HILL: It's because that fatty acid that's on that triglyceride means that the triglycerides that have that in already are fairly pervasive. Now, how many actually have all three of them being that probably not biologically but I wasn't worried about that.

And then the other one was the triethylhexin. I'm trying to find both of those names so that I give them to you correctly. Which table are you looking at? In the Conclusion?

DR. MARKS: No. I always go back to the table that gives us what data points we have, and then I add them.

DR. HILL: All the way at the beginning?

DR. MARKS: Yes. All the way at the beginning where it has, it's divided into linear chains, linear mixed chain link, and then branched chain, acetylated hydroxy acid triglycerides.

DR. HILL: Some of those are mischaracterized, but that's irrelevant at this stage.

DR. MARKS: Well, you can annex You can I'm going to let you offline meet with Monice and Bart, and say

DR. HILL: I think I probably noted it in here, and that's probably yeah, so that is offline. But let me go back to that table. So page

DR. MARKS: So it begins on page 45.

DR. HILL: Oh. All right. Page 45 is the table you're looking at?

DR. MARKS: Yes.

DR. HILL: Okay. Hang on.

DR. MARKS: Oh, no, I'm sorry. That's the use table. No, I it's right after the beginning, you know, Ron.

DR. HILL: All the way back to the beginning of the

DR. MARKS: That's right.

DR. HILL: That's what I thought you had had. All right. So that's where I am at. So page 7 and 8

DR. MARKS: Okay.

DR. HILL: All right. So it would be the first one on page 7 where I wanted to see sensitization.

DR. MARKS: So that's which one

DR. HILL: Except the coconut triglycerides. After that, there's a header that says, "Branched Chain," and it says triethylhexanoin.

DR. MARKS: So you wanted to see the C 10 40?

DR. HILL: And then the C 10 40 iso akyl acid triglyceride. That one too. So there's two of them on that page.

DR. MARKS: Okay.

DR. HILL: The first one

DR. MARKS: There's no data

DR. HILL: The first one of the branch chain

DR. MARKS: The triethylhexanoin

DR. HILL: That one.

DR. MARKS: Okay.

DR. HILL: Because we've seen sensitization for the ethylhexanoic acid.

DR. MARKS: Yep. Okay. I got you. Because that's right. The local lymph node assay showed it may be a sensitizer, but we have no

DR. HILL: It's shaky.

DR. MARKS: guinea pig or HRIPT to confirm whether at what concentration, if at all.

DR. HILL: And the C 1 to 40 iso akyl acid, I don't think we've seen that acid in any context before. If we have, I surely don't remember it. And we have no data on that, but it does seem to be in use.

DR. MARKS: Triethylhexanoin, and then the and we don't have use concentration or I don't have any use on that. And then the C 10 40

DR. HILL: Iso akyl. This table doesn't show that?

DR. MARKS: iso akyl acid triglycerides. Yeah, I don't have any use on that either or concentration. So we may not get anything, but we can certainly ask. Okay.

DR. HILL: One more thing.

DR. MARKS: Yes.

DR. HILL: I don't think I've ever seen anywhere where we've had the fatty acid distribution in cod liver oil.

DR. EISENMANN: That's (inaudible).

DR. MARKS: Pardon?

DR. EISENMANN: The main fatty acids are Omega 3s

DR. HILL: Omega 3s, yeah, which I don't think it, it doesn't raise any safety concerns. I would just like to see the distribution added to the report.

DR. MARKS: Okay. Any other comments about this?

MS. SADRIEH: I just want to say if you're keeping the tallow in there, you may want to make sure that the language regarding BSC is consistent with what you have in the previous reports for, other reports that include tallow.

DR. MARKS: Okay. Got that?

DR. HILL: Yep.

DR. MARKS: Any other comments?

MS. FIUME: Can I I'm sorry.

DR. MARKS: No, go ahead, Monice.

MS. FIUME: So with the triethylhexanoin in a previous report we have that's (inaudible) just not a sensitizer. Is that at all useful information?

DR. HILL: Yes, it is.

MS. FIUME: Is the human HRIPT in which it was used as a solvent and tested as a control?

DR. MARKS: Yeah.

MS. FIUME: No reactions were observed during induction or challenge. That's all the details that were provided.

DR. MARKS: Do we have a percentage that it was tested compared to what the use is here?

MS. FIUME: It just said that it was used as a solvent and tested as a control.

DR. HILL: Okay. Yeah, I would say the relative concentration would come into play because I remember that concern with that acid was very concentration dependent. We had to pass a threshold just (inaudible) anything.

DR. MARKS: So you still would like to see

DR. HILL: I think I would like to see it, but if we get information to suggest that the concentration as it was tested was fairly high, I mean, as a solvent suggests it probably was.

DR. MARKS: You would think so, yes. Sounds like if a solvent it was probably done neat. And that was satiro

MS. FIUME: Satiro ethylhexanoate. There were no additional details provided. That was all that I had.

DR. HILL: That would put in the same I mean, it's not a triglyceride, but it would put us in the same molecular weight regime, and I would think if we didn't see any sensitization there we probably wouldn't see it here either. I mean, if the data is available because it is an active commercial use then we ought to get it.

DR. MARKS: Well, do you think referring to that previous report will be enough for you, Ron Hill? Seems to me triethyl versus satiral

DR. HILL: Like I say, I think if we see that it is tested at a fairly high concentration then I think I'm pretty comfortable.

DR. MARKS: Well, it's going to be an insufficient data announcement so

Okay. any other comments?

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 using 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. Belsito 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: Draft Final Amended Report for Panel Review
Release Date: November 10, 2017
Panel Meeting Date: December 4-5, 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 51 triglycerides; 25 of these ingredients were previously reviewed by the Panel, and 26 are reviewed herein for the first time. 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. The Panel reviewed relevant new data, including frequency and concentration of use, and considered the data from previous CIR reports. The Panel concluded the 51 triglycerides reviewed in this report are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The 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 Final Report on the Safety Assessment of Trilaurin and 22 additional glyceryl triesters was published,⁴ and in 1980, the Final Report of the Safety Assessment for Caprylic/Capric Triglyceride was published.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 now included in this re-review:

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

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 each report was reviewed 15+ years ago and they all comprise triglycerides, i.e., fatty acid triesters of glycerin, and because the collection of these ingredients in one report enables the assembly of reinforcing and complementary test data, the Panel determined these reports should be re-reviewed together in one document; this family is referred to as the triglycerides.

Also included in this assessment are 26 triglycerides named in the web-based *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)* that have not been reviewed:

Acetic/Linoleic/Palmitic Triglyceride	Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride
C8-12 Acid Triglyceride	Glyceryl Tri-Hydrogenated Rosinate
C12-18 Acid Triglyceride	Glyceryl Tripalmitate/Palm Kernelate/Olivate/Macadamate/Rapeseedate
C18-36 Acid Triglyceride	Hydrogenated C12-18 Triglycerides
Capric/Lauric/Myristic/Oleic Triglyceride	Isomerized Safflower Glycerides
Caprylic/Capric/Lauric Triglyceride	Jobba Oil/Caprylic/Capric Triglyceride Esters
Caprylic/Capric/Linoleic Triglyceride	Lauric/Palmitic/Oleic Triglyceride
Caprylic/Capric/Myristic/Stearic Triglyceride	Oleic/Linoleic Triglyceride
Caprylic/Capric/Palmitic/Stearic Triglyceride	Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride
Caprylic/Capric/Stearic Triglyceride	Palmitic/Stearic Triglyceride
C10-40 Isoalkyl Acid Triglyceride	Ricinoleic/Caproic/Caprylic/Capric Triglyceride
Cod Liver/Mink/Tallow Triglyceride	Trilinolenin
C10-18 Triglycerides	Tripelargonin

A consolidated list of the 51 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 is given in [Table 2](#).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (<http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <http://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

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 safe in the present practices of use and concentration provided the content of 1,2-diester 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 in the same 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.

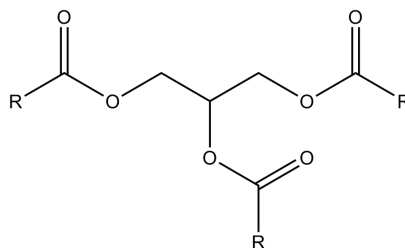


Figure 1. Triglycerides, wherein each “RC(O)-“ is a fatty acid residue

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

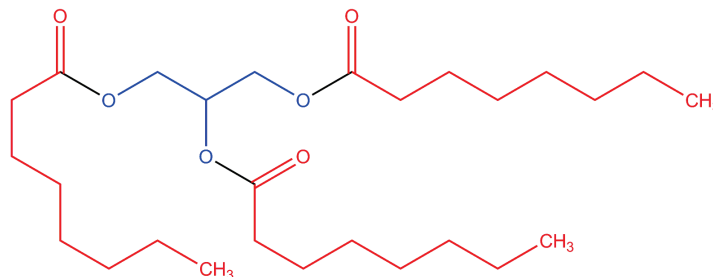


Figure 2. Tricaprylin (the triester of **caprylic acids** with glycerin)

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 4](#).

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 200°C. Another method of production is the reduction of triricinolein.¹

Trilaurin may be produced by reacting glycerin with lauric acid or glycerin with lauroyl chloride (reagent: pyridine or quinoline).⁴ The reaction of lauric acid with glycerin is another method of production. Triolein may be prepared by the esterification of oleic acid. Tripalmitin can be prepared from glycerin and palmitic acid in the presence of either Twitchell reagent or trifluoroacetic anhydride. Tristearin may be prepared from stearic acid and glycerin in the presence of Al_2O_3 . Triundecanoin is produced by esterification of undecanoic acid and glycerin. 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 glycerin 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 glycerin, 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 glycerin.

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.

The following are method of manufacture schemes for Caprylic/Capric Triglyceride (medium-chain triglycerides (MCT); terminology used in a FDA foods Generally Recognized as Safe (GRAS) notification, defined as triglycerides with alkyl chain lengths from 8 to 10 carbons long) ([Figure 3](#))¹¹ and medium- and long-chain triacylglycerol (MLCT)-oil (terminology used in a FDA foods GRAS notification, defined as triglycerides with alkyl chain lengths from 8 to 24 carbons long) ([Figure 4](#)):¹²

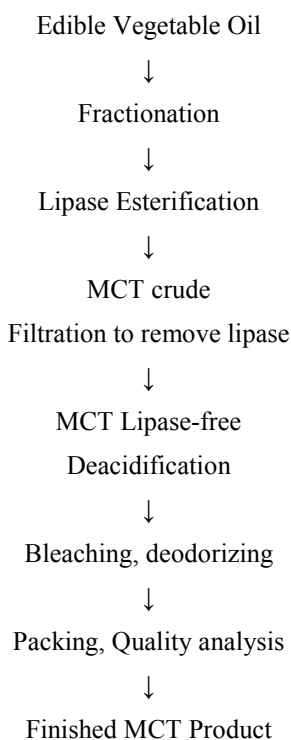


Figure 3. Caprylic/Capric Triglyceride (MCT) production scheme

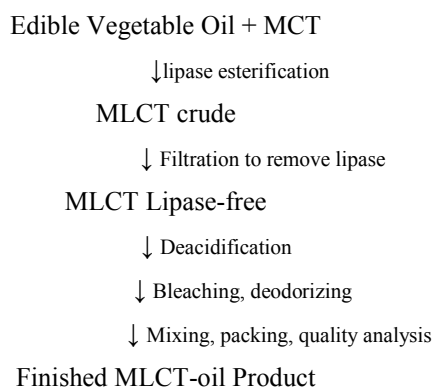


Figure 4. MLCT production scheme

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% glycerin.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 these ingredients 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, 30 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.¹³ Tribehenin has the next highest frequency of use, with 723 reported uses, followed by Triethylhexanoin, with 601 reported uses. (Table 5; Table 6)

Use concentration survey data were collected in 2015/2016 (and updated in 2017) for some of ingredients,¹⁴ and in 2017 for the remaining ingredients.¹⁵ 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 5). Caprylic/Capric Triglyceride has the next highest maximum use concentration in leave-ons, with concentrations of 95.6% in face and neck products.

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 previous 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.^{5,6} Concentrations of use have also increased.^{6,14} In 2003, the maximum leave-on concentration of use for this ingredients was 84%, it is now reported to 95.6%; maximum concentrations of use increased for eye area, non-coloring hair, hair coloring, nail, and baby product formulations. The increase in baby products was quite notable, increasing from 0.8% to 52%.

The 21 triglycerides not currently reported to be in use, according to VCRP and concentration of use survey data, are listed in Table 7.

In some cases, reports of use were received from the VCRP, but no concentration of use data were provided. For example, Trilinolenin is reported to be used in 2 formulations,¹⁶ but no use concentration data were provided. In other cases, no uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example,

Caprylic/Capric/Linoleic Triglyceride was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 52.1% in body and hand product formulations.¹⁵ It should be presumed that Caprylic/Capric/Linoleic Triglyceride is used in at least one cosmetic formulation for each category for which it is reported to be used.

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, Caprylic/Capric Triglyceride is used at up to 83.3% in eye lotions, 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, Caprylic/Capric Triglyceride and Triethylhexanoin are reported to be used at maximum concentrations of 38% in spray body and hand formulations and 36% in perfumes, respectively, and 16% and 14.7%, respectively, in face powders. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters $>10\text{ }\mu\text{m}$, with propellant sprays yielding a greater fraction of droplets/particles $<10\text{ }\mu\text{m}$ 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 Caprylic/Capric Triglyceride is used at up to 0.99% in spray deodorant formulations. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.²⁰ However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

All 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 175.105), 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 (21CFR 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.*¹

*Trilaurin has been detected in pharmaceutical excipients.*⁴ *Tricaprylin has been used as an energy source for burn 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 sizing, 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 is approved for use as direct multipurpose food additives (21CFR172.861).

Caprylic/Capric Triglyceride and Triglycerides (general)

The FDA received a GRAS notification request for triglycerides (C8-C24) for use as a food ingredient, such that the total daily consumption would not exceed 31 g/day.¹² The FDA responded that the tailored triglycerides ingredient (12% Caprylic/Capric Triglyceride) 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% Caprylic/Capric Triglyceride) ingredient.

Caprylic/Capric Triglyceride, is 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, Caprylic/Capric Triglyceride, olive oil, and fish oil; recommended dosing is 1 to 2 g/kg/day, not exceeding 2.5 g/kg/day.

TOXICOKINETIC STUDIES

Dermal Penetration

In mice and guinea pigs, little skin penetration was observed.⁴ In the mice, ¹⁴C-Triolein (undiluted or in hydrophilic ointment) did not penetrate into the body organs of mice, and the oil remained localized at the application site at 48 h post application.

Penetration Enhancement

Tricaprylin enhanced the skin penetration of drugs in vivo (Wistar rats) and in vitro (hairless mice).⁴ The skin penetration enhancement of drugs in the presence of Triolein has been reported.

Absorption, Distribution, Metabolism, and Excretion

Metabolism data indicate that most triglycerides (or glyceryl triesters) are split into monoglycerides, free fatty acids, and glycerin in the small intestine and absorbed by the intestinal mucosa⁴

When absorbed from the digestive tract, Caprylic/Capric Triglyceride is hydrolyzed, and the fatty acids are catabolized to C₂ fragments which may be further metabolized either to CO₂ or to form long-chain fatty acids.⁵ Caprylic/Capric Triglyceride can undergo hydrolysis by enzymatic or chemical means to produce free fatty acids, partial glycerides, and glycerin. 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 C₆-acid.

Caprylic/Capric Triglyceride and Triglycerides (general)

Oral absorption and metabolism of foods containing long-chain triglycerides (LCT) mixtures (alkyl chain lengths greater than 12 (C > 12)) differ from those containing Caprylic/Capric Triglyceride.²⁸ C > 12 are degraded by salivary, intestinal and pancreatic lipases into two fatty acids and a monoacyl glycerol, whereas, Caprylic/Capric Triglyceride is degraded by the same enzymes into three fatty acids and the simple glycerol backbone. Caprylic/Capric Triglyceride is readily absorbed from the small intestine directly into the bloodstream and transported to the liver for hepatic metabolism, while C > 12 are incorporated into chylomicrons and enter the lymphatic system. Caprylic/Capric Triglyceride is readily broken down to carbon dioxide and two-carbon fragments, while C > 12 are re-esterified to triacylglycerols and either metabolized for energy or stored in adipose tissue.

Tripelargonin and Triethylhexanoin

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

Groups of 5 newborn Rhesus (*Macaca mulatta*) monkeys were administered 8.4 ml/kg bw Tripelargonin, Triethylhexanoin, or water (control) via nasogastric (NG) tube.²⁹ Plasma C8:0 and C9:0 fatty acids and whole blood D-(-)-3-hydroxybutyrate (3HB) levels were measured 0, 1, and 3 h after dosing. Free fatty acid concentrations and ketone 3HB increased with time. C8 and C9 levels did not differ at 1 or 3 h, but at 1 h, blood 3HB concentrations were higher with Triethylhexanoin compared to animals dosed with Tripelargonin.

Groups of 8 New Zealand male rabbits were given a Tripelargonin/LCT (7/3 wt/wt) emulsion via a total parenteral nutrition (TPN) infusion regimen 7 h/day for 11 days.³⁰ The 3HB concentrations were significantly decreased, and plasma concentrations of propionic, acetic, butyric, and valeric acids were significantly increased. Following overnight fasting on days 9 and 12, fatty glycerol concentrations were statistically significantly increased compared to controls that were fed a standard diet, and on day 12, fasted rabbits were found to have increased triglyceride and non-esterified fatty acid levels.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

In acute oral toxicity studies in which Trihydroxystearin was tested using albino rats, the LD₅₀ was not achieved at a dose of 5 g/kg and no deaths were reported.¹

Acute oral LD₅₀ values range from 5 g/kg in mice (Tribehenin) to > 20 g/kg in rats (Tristearin).⁴ In other acute oral toxicity studies, Triethylhexanoin [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 LD₅₀ 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 μ l/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 μ m or less, represented 1.97 μ l/l of the test substance. No adverse effects were observed.

The acute dermal and oral toxicity studies summarized below are described in [Table 8](#).

The dermal LD₅₀ in rats was >2 g/kg (the highest dose tested) for both Triheptanoin³¹ and Tristearin.³² The oral LD₅₀ was >2 g/kg for Triisostearin in mice and rats,³³ >2 g/kg Triolein in mice,³⁴ >5 g/kg Triheptanoin in mice, and >48 g/kg Triethylhexanoin³⁵ in rats. The oral LD₅₀ of an MLCT oil was >5 g/kg in rats.²⁸ A single dose of 8.4 ml/kg bw Tripelargonin and Triethylhexanoin, administered via NG tube, did not affect activity level or induce narcolepsy in newborn Rhesus (*Macaca mulatta*) monkeys.²⁹

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 effects were observed.

The short-term oral and intravenous (i.v.) toxicity studies summarized below are described in Table 9.

In 28-day gavage studies in Han-Wistar rats, dosing with 3.12 g/kg 33% Caprylic/Capric Triglyceride did not produce any signs of toxicity,³⁶ 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.³⁷ These changes were reversible. In Göttingen minipigs, clinical signs of toxicity were observed with 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.³⁸ In rats, a no-observed adverse effect level (NOAEL) of 10 mg/kg bw/day was reported in a 30 day study with Caprylic/Capric Triglyceride,³⁹ and a NOAEL of 3500 mg/kg/day was reported with MLCT.²⁸ 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.²⁸

No adverse effects were observed in a study in which rabbits were given a Tripelargonin/LCT emulsion via a TPN infusion regimen for 7 h/day for 11 days.^{30,40}

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 9.

Three-month feeding studies were performed with Caprylic/Capric Triglyceride in rats³⁹ and dogs.⁴¹ The NOAELs were 5% and 15%, respectively, and no toxicologically-relevant signs of toxicity were observed at the highest doses.

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 (10 ml/kg group) and significant increases in the liver (2 ml/kg) and adrenal gland weights (2 and 10 ml/kg) 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 9.⁴²

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Tricaprylin (≤10 ml/kg) was not teratogenic in mice or rats when administered orally.⁴ In another study on reproductive effects, a uterine injection on 0.1 ml Tricaprylin was effective in producing fusion of the endometrial epithelium (symplesma formation) and decidualization of the stroma in pseudopregnant New Zealand white rabbits. The oral administration of 4750 mg/kg/day Triethylhexanoin [Trioctanoin] on days 6-13 of gestation 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 0.5 mmol/kg bw Triethylhexanoin [Trioctanoin; was the vehicle control in a teratogenicity study] on days 8 and 12 of gestation 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.⁴³ 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 (only) 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 statistically significant 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 study 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.” The adverse effects of trichloroacetonitrile in Tricaprylin were seen at doses as low as 1 mg/kg/d and included a number of different kinds of heart defects.

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, Triethylhexanoin [Trioctanoin], Triolein, Tristearin, and Triisostearin were not mutagenic in S. typhimurium strains. However, Triethylhexanoin [Trioctanoin] was mutagenic in the spot test for gene mutations. In other tests, no clastogenic activity was noted when Triethylhexanoin [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 10](#).

Tristearin (5000 µg/plate)³² and Tricaprylin (concentration not stated)³⁵ 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 Triisostearin 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).⁴⁴

A lipid emulsion that comprises a mixture of soybean oil, Caprylic/Capric Triglyceride, 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 0.25 ml 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 (dose not specified) 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.

Undiluted Triisostearin and a 20% solution of Tribehenin (0.5 ml) in liquid paraffin were, at most, mildly irritating when applied to the skin of rabbits.⁴ Undiluted Triethylhexanoin [Trioctanoin] and an eyeliner containing 36.3% Trilaurin did not induce cutaneous irritation in rabbits. Neither Tribehenin (test concentration not provided) nor Triethylhexanoin [Trioctanoin; 1% intradermal induction, 100% occlusive topical induction; 25% occlusive challenge] induced sensitization in the Magnusson-Kligman guinea pig maximization test. Triisostearin (0.02 ml/cm²) 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 91 test subjects.⁴ Triethylhexanoin [Trioctanoin; details not provided] did not induce skin irritation in 25 subjects. A lip enhancer cream containing 0.38% Tribehenin was not comedogenic and did not induce clinically significant skin irritation in any of the 18 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, Triethylhexanoin [Trioctanoin; details not provided] did not induce sensitization in a contact allergy test.

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 11](#).

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 6.³¹ 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.³³ No irritation was observed in 4-h patch tests with undiluted Tristearin,³² Caprylic/Capric Triglyceride,³⁹ or C8-C12 Acid Triglycerides.³⁹ Triheptanoin (100%)³¹ and Tristearin (50%)³² were not sensitizers in guinea pigs. Triisnonanoin was predicted to be non-irritating in an EpiSkin™ in vitro test.⁴⁴ However, in a mouse local lymph node assay (LLNA), it was predicted that Triisnonanoin may cause sensitization; results were negative with 25% and 50% Triisnonanoin, but positive when tested at 100%.⁴⁴

A facial oil containing 95.51% Caprylic/Capric Triglyceride was not an irritant in a 24-h single insult occlusive patch test in 17 human subjects,⁴⁵ and it was not a sensitizer in a human modified maximization patch test with 26 subjects.⁴⁶ In human repeated insult patch tests, a moisturizer containing 6% Tribehenin was not a sensitizer (102 subjects),⁴⁷ and a mixture containing 20% Tribehenin had no clinically significant potential for dermal irritation or sensitization (52 subjects).⁴⁸ Triolein was not a sensitizer in a chamber test; details were not provided.³⁵

PHOTOSENSITIZATION

Caprylic/Capric Triglyceride

The photosensitization potential of a facial oil containing 95.51% Caprylic/Capric Triglyceride was evaluated in a RIPT photocontact allergenicity assay completed in 27 subjects.⁴⁹ For induction, an occlusive patch consisting of 40 mg of the test material spread uniformly onto a 2 x 2 cm (10 mg/cm²) cotton cloth was applied to the lower back of each subject for 24 h; immediately following patch removal, the test site was exposed to two minimal erythema doses (MEDs) from a xenon arc solar simulator. This procedure was repeated 2x/wk for 3 wks, for a total of 6 induction applications. The light source was a 150 W compact xenon arc solar simulator (Solar Light Company) equipped with a UV-reflecting dichroic mirror and a 1 mm thick Schott WG320 filter; a 1 mm thick UG11 filter was also used. The solar spectrum (SSR waveband) was used to

determine the individual MED. The size of the irradiated field at skin level was approximately a 1cm diameter circle. Total irradiance at skin level was 90.0 mW/cm². The UVA intensity was 52.5 mW/cm².

Following a 10-day non-treatment period, a challenge patch was applied for 24 h to a previously untreated site on the opposite side of the back, followed by exposure to ½ MED of solar simulated radiation plus 4 J/cm² of UVA. (For the challenge, a 1 mm thick Schott WG-345 filter was added to eliminate the UVB component (290-320 nm) and to produce a continuous broadband UVA extending from 320 to 410nm.) An unirradiated site treated with the test product served as a "dark" control. The sites were examined at 48 and 72 hours after irradiation for evidence of photocontact sensitization. The facial oil containing 95.51% Caprylic/Capric Triglyceride did not possess a detectable photocontact-sensitizing potential in human skin.

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. Triethylhexanoin [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 12](#).

Undiluted Triheptanoin,³¹ Tristearin,³² Caprylic/Capric Triglyceride,³⁹ and C8-12 Acid Triglyceride,³⁹ as well as Triisostearin at an unspecified concentration,³³ 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.⁴⁴

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 51 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-one of the 51 ingredients included in this safety assessment are in use, and Caprylic/Capric Triglyceride has the highest frequency of use (6000 formulations). According to the results of a concentration of use survey conducted by the Council, 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.

Oral absorption and metabolism of foods containing LCT mixtures differ from those containing Caprylic/Capric Triglyceride. C > 12 are degraded by salivary, intestinal and pancreatic lipases into two fatty acids and a monoacyl glycerol, whereas, Caprylic/Capric Triglyceride is degraded by the same enzymes into three fatty acids and the simple glycerol backbone.

In newborn Rhesus monkeys administered a single dose of Tripelargonin or Triethylhexanoin via NG tube, free fatty acid concentrations and ketone 3HB increased with time. In New Zealand male rabbits given a Tripelargonin/LCT emulsion via a TPN infusion regimen 7 h/day for 11 days, 3HB concentrations were significantly decreased and plasma concentrations of short-chain fatty acids were significantly increased.

In acute toxicity testing, the dermal LD₅₀ in rats was > 2 g/kg (the highest dose tested) for both Triheptanoin and Tristearin. The oral LD₅₀ 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 LD₅₀ of a MLCT oil was > 5 g/kg in rats. A single dose of 8.4 ml/kg bw Tripelargonin and Triethylhexanoin, administered via NG tube, did not affect activity level or induce narcolepsy in newborn Rhesus monkeys.

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 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. No adverse effects were observed in a study in which rabbits were given a Tripelargonin/LCT emulsion via a TPN infusion regimen for 7 h/day for 11 days.

Short-term and subchronic feeding studies were conducted with Caprylic/Capric Triglyceride. In rats, a NOAEL of 10 mg/kg bw/day was reported in a 30 day study with Caprylic/Capric Triglyceride, and a NOAEL of 3500 mg/kg/day was reported with mixture of triglycerides with alkyl chain lengths C8-C24. In a human study, no adverse effects were observed in a placebo-controlled double-blind study in which healthy subjects ingested 42 g/day of the C8-C24 mixture. Three-month feeding studies were performed with Caprylic/Capric Triglyceride in rats and dogs, and the NOAELs were 5% and 15%, respectively; no toxicologically-relevant signs of toxicity were observed at the highest doses.

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

Tricaprylin was used as a vehicle in an oral (gavage) 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 Triisononanoin 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, Caprylic/Capric Triglyceride, 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. Triisononanoin was predicted to be non-irritating in an EpiSkin™ in vitro test. However, in a mouse LLNA, it was predicted that Triisononanoin may cause sensitization; results were negative with 25% and 50% Triisononanoin but positive when tested at 100%.

In human testing, a facial oil containing 95.51% Caprylic/Capric Triglyceride was not an irritant in a 24-h single insult occlusive patch test in 17 subjects, was not a sensitizer in a human modified maximization patch test with 26 subjects, and was not a photosensitizer. In HRIPTs, a moisturizer containing 6% Tribehenin was not a sensitizer (102 subjects), and a mixture containing 20% Tribehenin had no clinically significant potential for dermal irritation or sensitization (52 subjects). Triolein was not a sensitizer in a chamber test; details were not provided.

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. Triisononoin 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

In accordance with its procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years. The Panel has issued three final reports on the safety of 25 triglycerides, i.e., fatty acid triesters of glycerin, in the past 15+ years. The Panel previously concluded that Trihydroxystearin (2000), Caprylic/Capric Triglyceride (1980; reaffirmed in 2003), and a family of ingredients that included Trilaurin and 22 additional glyceryl triesters (2001) are safe as used in cosmetics. Additionally, the Panel determined that it was appropriate to include 26 triglycerides that have not yet been reviewed. The collection of these ingredients in one report enables the assembly of reinforcing and complementary test data. Safety profiles of these ingredients are consistent with roles of most constituents as dietary components and safe conclusions in previous reports.

Upon initial review of the safety of the triglycerides as used in cosmetics at its April 10-11, 2017 meeting, the Panel determined additional data were needed to assess the safety of these ingredients and issued an Insufficient Data Announcement (IDA). Many, but not all, of the data requests were satisfied.

The main focus of the IDA was for irritation and sensitization data at concentration of use on four ingredients (i.e., Tribehenin, Caprylic/Capric Triglyceride, Triethylhexanoin, and C10-40 Isoalkyl Acid Triglyceride). Data were received for two of the four ingredients (i.e., Tribehenin and Caprylic/Capric Triglyceride), and the Panel acknowledged the negative results obtained in a guinea pig maximization study (1% intradermal induction, 100% occlusive topical induction; 25% occlusive challenge) that was reported in the previous (2001) report. Although data were not received on all four ingredients included in the IDA, the Panel stated that the weight of the evidence was very strong to support the safety of all the ingredients included in this report, and therefore their data needs were satisfied.

Approximately half of the ingredients 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. Also, in 2003, the maximum leave-on concentration of use for Caprylic/Capric Triglyceride was 84%, it is now reported to 95.6% in face and neck products.

One reported possible function of Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride is skin bleaching agent. In the United States, skin bleaching agent is not considered a cosmetic function, and therefore use in that manner is not being assessed in this report.

During its original review of Trilaurin and other glyceryl triesters, 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. In a tumor inhibition study, Trilaurin was found to inhibit the formation of neoplasms initiated by DMBA and promoted by croton oil. However, the Panel stated that no restrictions were warranted for any of these ingredients.

High purity is needed for the triglycerides. In 2007, the Panel published a final report on a diglycerides, and concluded that the ingredients in the diglyceride family are safe in the present practices of use and concentration provided the content of 1,2-diester is not high enough to induce epidermal hyperplasia. The Panel discussed that there was an increased level of concern because of data regarding the induction of protein kinase C (PKC) and the tumor promotion potential of 1,2-diacylglycerols. The Panel noted that, nominally, glyceryl-1,3-diester contain 1,2-diester, raising the concern that 1,2-diester could potentially induce hyperplasia. The Panel did note that these compounds are more likely to cause these effects when the fatty acid chain length is ≤ 14 carbons, when one fatty acid is saturated and one is not, and when given at high doses, repeatedly.

Based on existing information from a previous CIR safety assessment, 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. However, the Panel recognized that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals, and the Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The Panel acknowledged that some of the triglycerides may be formed from plant-derived or animal-derived constituents. The Panel thus expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to sufficiently limit amounts of such impurities in an ingredient before blending them into cosmetic formulations. Additionally, the Panel considered the risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. Although tallow may be used in

the manufacture of Cod Liver/Mink/Tallow Triglyceride and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the U.S. FDA that tallow derivatives are not risk materials for transmission of infectious agents.

Finally, the Panel discussed the issue of incidental inhalation exposure, as some of the triglycerides are used in cosmetic sprays 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. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>

CONCLUSION

The CIR Expert Panel concluded that the following 51 triglycerides are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

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

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

TABLES

Table 1. Triglycerides included in this report

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

Note: ingredients that were previously reviewed are indicated in blue

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

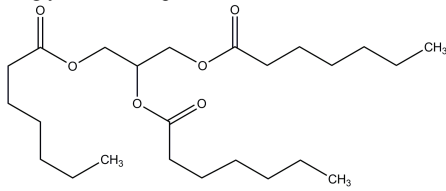
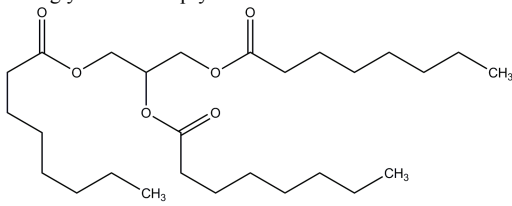
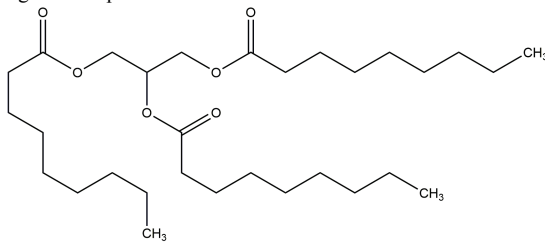
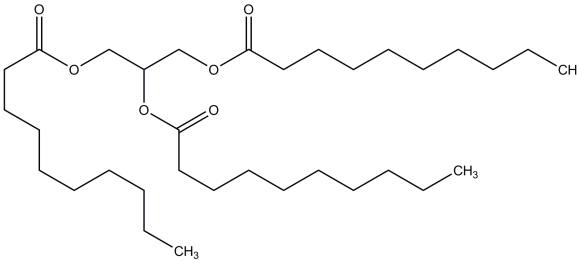
Ingredient/CAS No.	Definition & Structure	Function(s)
<i>Linear chain saturated triglycerides</i>		
Triheptanoin 620-67-7	<p>Triheptanoin is the triester of glycerin and heptanoic acid. It conforms to the formula:</p> 	<p>skin conditioning agent – occlusive; viscosity increasing agent – nonaqueous</p>
Tricaprylin 538-23-8	<p>Tricaprylin is the triester of glycerin and caprylic acid. It conforms to the formula:</p> 	<p>fragrance ingredient; skin conditioning agent – occlusive</p>
Tripelargonin 126-53-4	<p>Tripelargonin is the organic compound that conforms to the formula:</p> 	<p>skin conditioning agent – emollient</p>
Tricaprin 621-71-6	<p>Tricaprin is the triester of glycerin and capric acid. It conforms to the formula:</p> 	<p>fragrance ingredient; skin conditioning agent – occlusive</p>

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

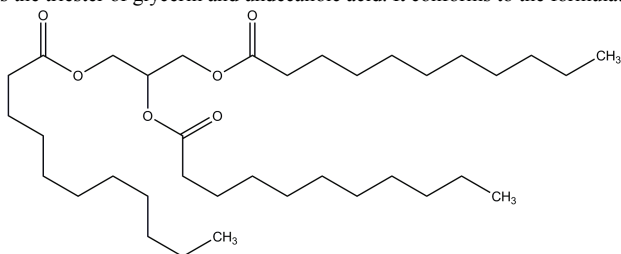
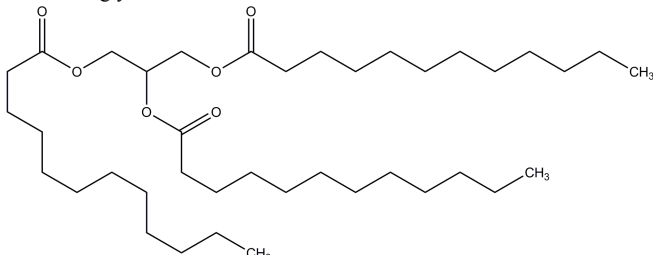
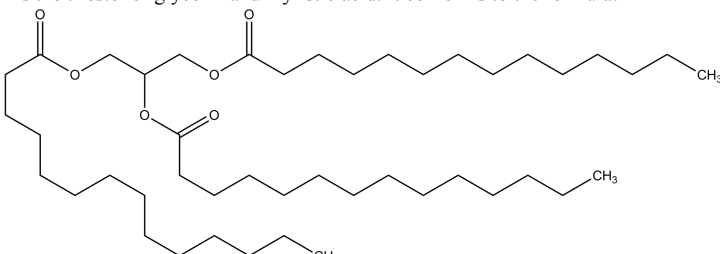
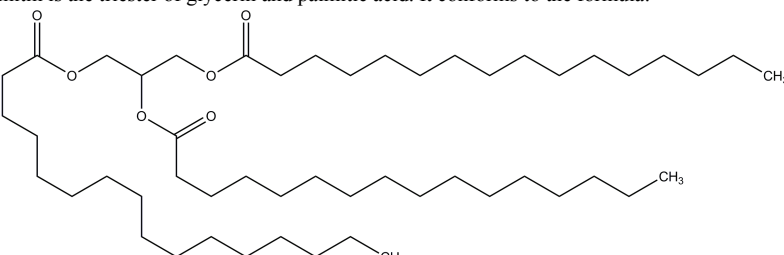
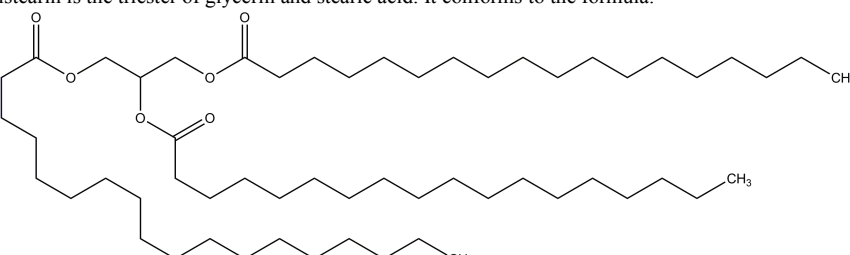
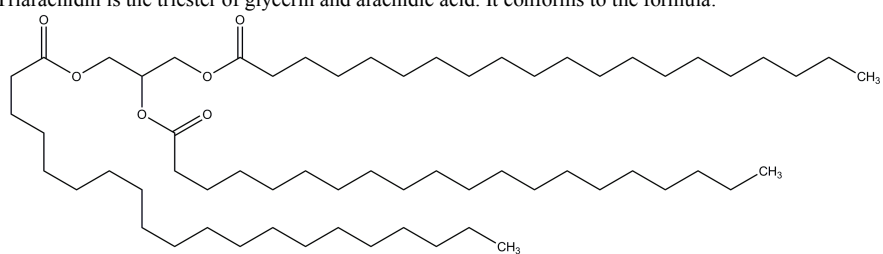
Ingredient/CAS No.	Definition & Structure	Function(s)
Triundecanoin 13552-80-2	Triundecanoin is the triester of glycerin and undecanoic acid. It conforms to the formula: 	hair conditioning agent; skin conditioning agent – occlusive
Trilaurin 538-24-9	Trilaurin is the triester of glycerin and lauric acid. 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

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

Ingredient/CAS No.	Definition & Structure	Function(s)
Tribehenin 18641-57-1	<p>Tribehenin is the triester of glycerin and behenic acid. It conforms to the formula:</p>	skin conditioning agent – occlusive
Linear, mixed chain length saturated triglycerides		
Glyceryl Stearate Diacetate 84931-78-2	<p>Glyceryl Stearate Diacetate is the organic compound that conforms to the formula:</p>	skin conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Caprylic/Capric Triglyceride 65381-09-1 73398-61-5	<p>Caprylic/Capric Triglyceride is the mixed triester of glycerin and caprylic and capric acids.</p> <p>[wherein RC(O)- is the residue of caprylic (C8) or capric (C10) acid.]</p>	fragrance ingredient; skin conditioning agent – occlusive; solvent
Caprylic/Capric/Lauric Triglyceride 123465-33-8	<p>Caprylic/Capric/Lauric Triglyceride is the mixed triester of glycerin with caprylic, capric and lauric acids.</p> <p>[wherein RC(O)- is the residue of caprylic (C8), capric (C10), or lauric (C12) acid.]</p>	skin conditioning agent – occlusive
C8-12 Acid Triglyceride	<p>C8-12 Acid Triglyceride is the triester of glycerin and a mixture of saturated acids containing 8 to 12 carbons in the alkyl chain.</p> <p>[wherein RC(O)- is the residue of a fatty acid 8, 10, or 12 carbons in length]</p>	skin conditioning agent – occlusive; solvent; viscosity increasing agent - nonaqueous
Caprylic/Capric/Myristic/Stearic Triglyceride	<p>Caprylic/Capric/Myristic/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric, myristic and stearic acids.</p> <p>[wherein RC(O)- is the residue of caprylic, capric, myristic or stearic acid.]</p>	skin conditioning agent – occlusive

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

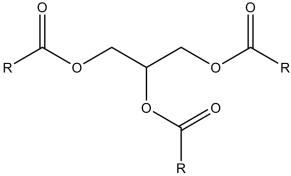
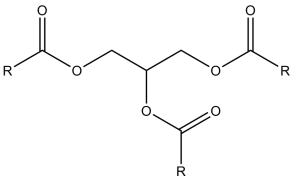
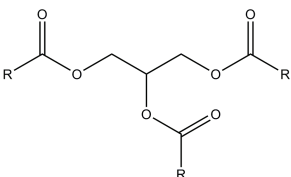
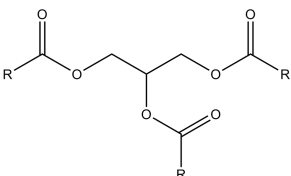
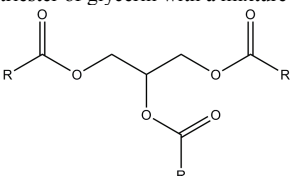
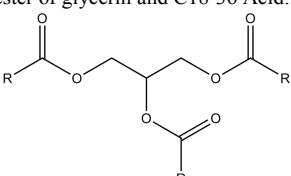
Ingredient/CAS No.	Definition & Structure	Function(s)
Caprylic/Capric/Palmitic/Stearic Triglyceride	Caprylic/Capric/Palmitic/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric, palmitic and stearic acids.	skin conditioning agent – occlusive
<div data-bbox="678 216 966 390">  </div> <div data-bbox="631 415 1271 436">[wherein RC(O)- is the residue of caprylic, capric, palmitic or stearic acid.]</div>		
Caprylic/Capric/Stearic Triglyceride	Caprylic/Capric/Stearic Triglyceride is the mixed triester of glycerin with caprylic, capric and stearic acids.	skin conditioning agent – occlusive
<div data-bbox="678 493 966 667">  </div> <div data-bbox="708 693 1271 714">[wherein RC(O)- is the residue of caprylic, capric, or stearic acid.]</div>		
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.	skin conditioning agent – occlusive; solvents
<div data-bbox="678 770 966 945">  </div> <div data-bbox="548 970 1271 991">[wherein RC(O)- is the residue of a fatty acid 10, 12, 14, 16, or 18 carbons in length]</div>		
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.	skin conditioning agent – occlusive; solvent; viscosity increasing agent - nonaqueous
<div data-bbox="678 1050 966 1224">  </div> <div data-bbox="581 1228 1271 1249">[wherein RC(O)- is the residue of a fatty acid 12, 14, 16, or 18 carbons in length]</div>		
Palmitic/Stearic Triglyceride	Palmitic/Stearic Triglyceride is the triester of glycerin with a mixture of palmitic and stearic acids	viscosity increasing agent - nonaqueous
<div data-bbox="678 1281 966 1455">  </div> <div data-bbox="777 1480 1271 1501">[wherein RC(O)- is the residue of palmitic or stearic acid]</div>		
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	skin conditioning agent – occlusive
<div data-bbox="678 1533 966 1707">  </div> <div data-bbox="391 1732 1271 1753">[wherein RC(O)- is the residue of a fatty acid 18, 20, 22, 24, 26, 28, 30, 32, 34, or 36 carbons in length]</div>		

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. (7:|CIR Staff)

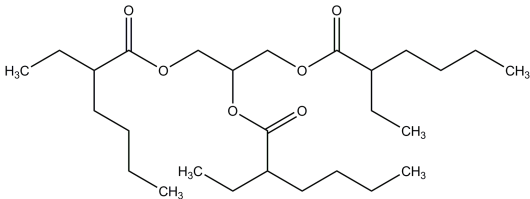
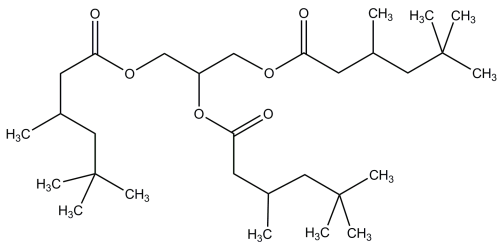
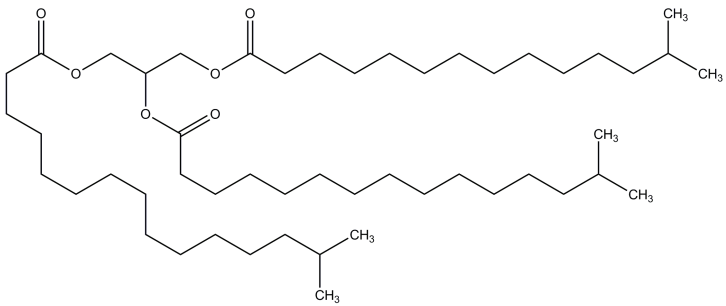
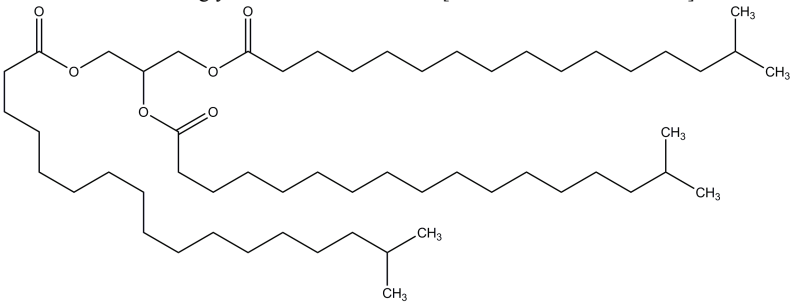
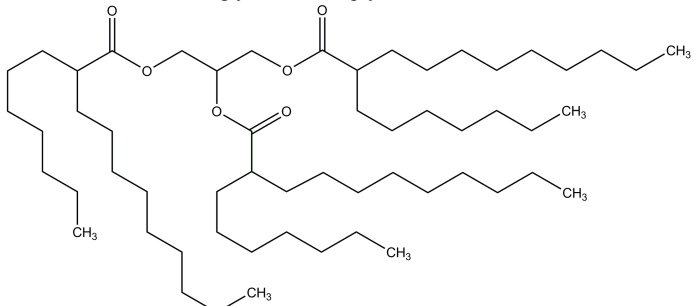
Ingredient/CAS No.	Definition & Structure	Function(s)
<i>Branched chain triglycerides</i>		
Triethylhexanoin (previously named Trioctanoin) 7360-38-5	Triethylhexanoin is the triester of glycerin and 2-ethylhexanoic acid. It conforms generally to the formula: 	fragrance ingredient; hair conditioning agent; 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])

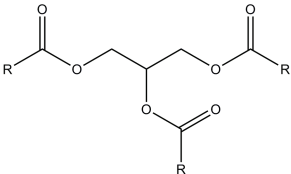
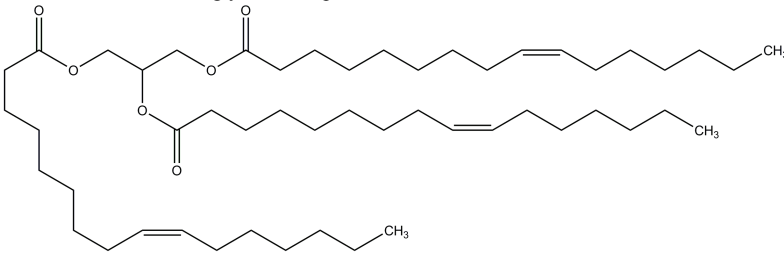
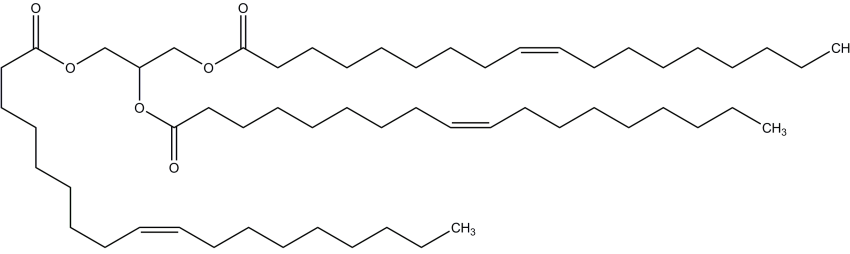
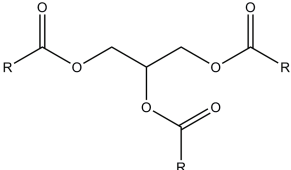
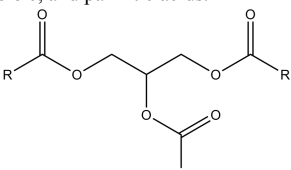
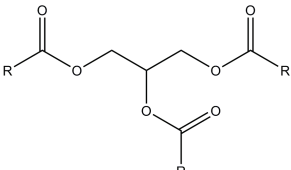
Ingredient/CAS No.	Definition & Structure	Function(s)
Branched, mixed length chain triglyceride		
C10-40 Isoalkyl Acid Triglyceride	<p>C10-40 Isoalkyl Acid Triglyceride is the triester of glycerin and C10-40 Isoalkyl Acid.</p>  <p>[wherein RC(O)- is the residue of a branched fatty acid 10 to 40 carbons in length]</p>	hair conditioning agent; skin conditioning agent – emollient; viscosity increasing agent - nonaqueous
Unsaturated chain & hydroxy acid triglycerides		
Tripalmitolein 129784-33-4 20246-55-3	<p>Tripalmitolein is the triester of glycerin and palmitoleic acid. It conforms to the formula:</p> 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Triolein 122-32-7 6915-08-8	<p>Triolein is the triester of glycerin and oleic acid. It conforms to the formula:</p> 	skin protectant; skin conditioning agent – emollient, occlusive, misc; viscosity increasing agent - nonaqueous
Oleic/Linoleic Triglyceride	<p>Oleic/Linoleic Triglyceride is the mixed triester of glycerin with oleic and linoleic acids.</p>  <p>[wherein RC(O)- is the residue of oleic or linoleic acid]</p>	skin conditioning agent – occlusive
Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride	<p>Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride is the mixed triester of glycerin with docosahexenoic, docosapentenoic, oleic, and palmitic acids.</p>  <p>[wherein RC(O)- is the residue of docosahexenoic, docosapentenoic, oleic, or palmitic acid.]</p>	skin bleaching agent; skin protectant; skin conditioning agent – misc
Isomerized Safflower Glycerides	<p>Isomerized Safflower Glycerides is the product formed by the esterification of glycerin and isomerized safflower acid.</p>  <p>[wherein RC(O)- is the residue of a fatty acid derived from safflower oil, which is approximately 68% linoleic, 25% oleic, and 2% palmitic]⁵⁰</p>	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])

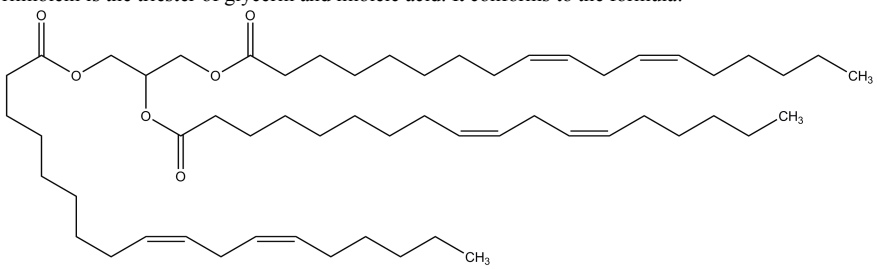
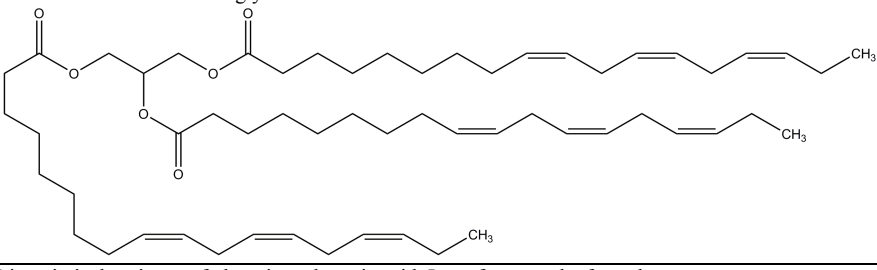
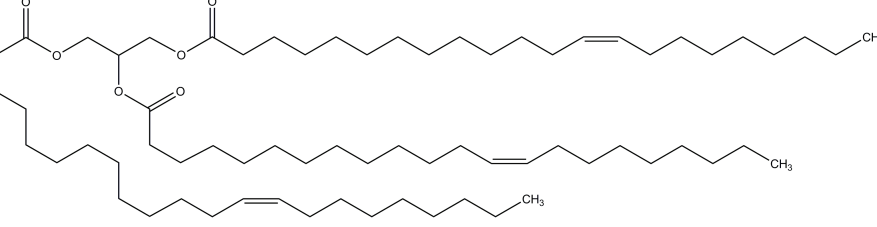
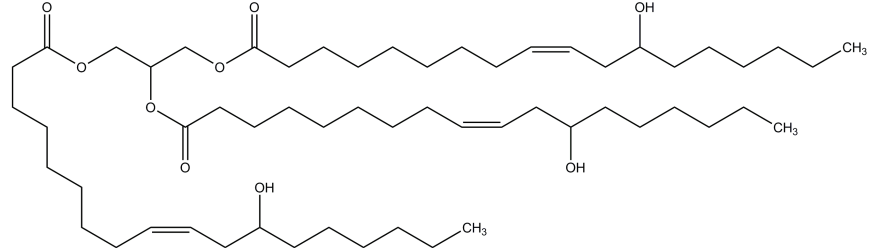
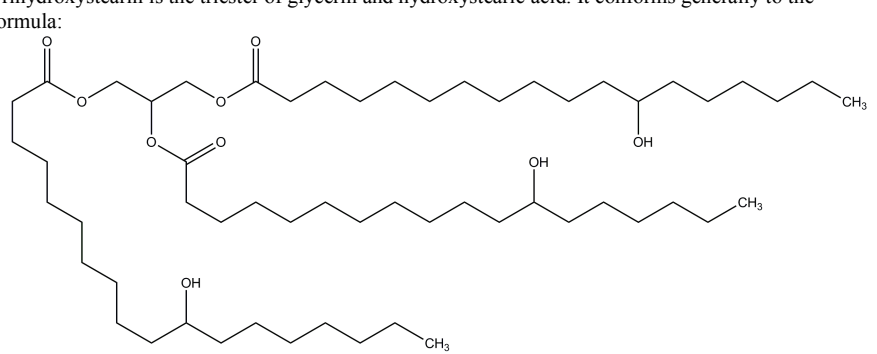
Ingredient/CAS No.	Definition & Structure	Function(s)
Trilinolein 537-40-6	<p>Trilinolein is the triester of glycerin and linoleic acid. It conforms to the formula:</p> 	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Trilinolenin 14465-68-0	<p>Trilinolenin is the triester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

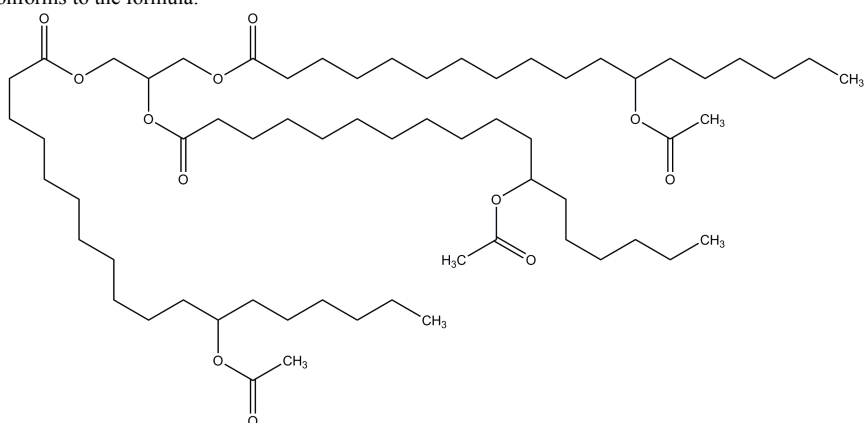
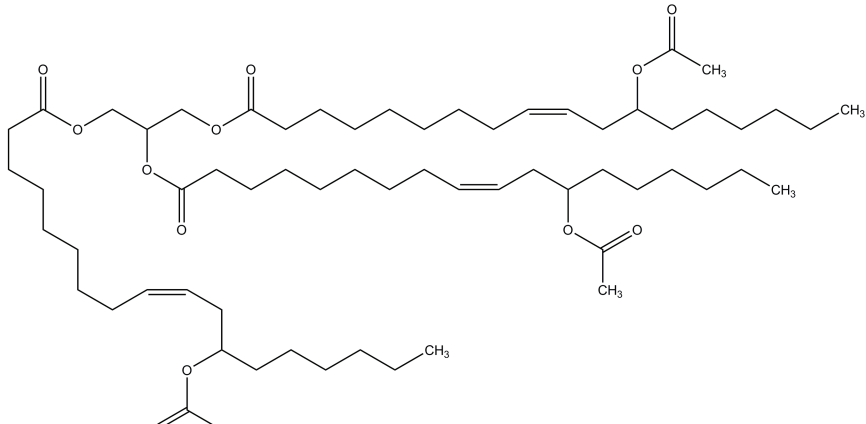
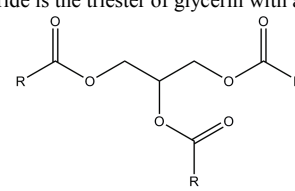
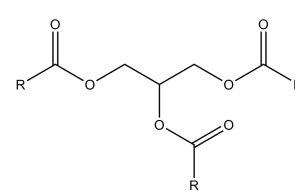
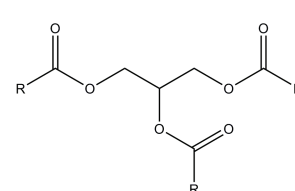
Ingredient/CAS No.	Definition & Structure	Function(s)
Acetylated hydroxyacid triglycerides		
Glyceryl Triacetyl Hydroxystearate 27233-00-7	<p>Glyceryl Triacetyl Hydroxystearate is the triester of glycerin and acetyl hydroxystearic acid. It conforms to the formula:</p> 	skin conditioning agent - emollient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

Table 2. Definitions, idealized structures, and functions of the ingredients in this safety assessment. (7)(CIR Staff)

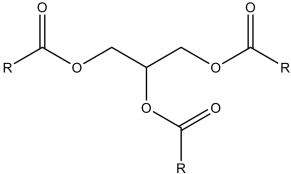
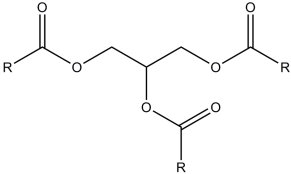
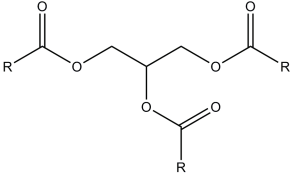
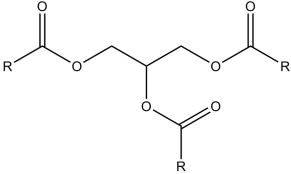
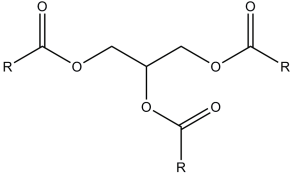
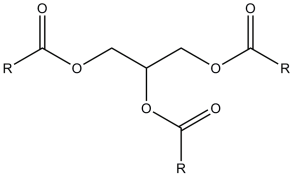
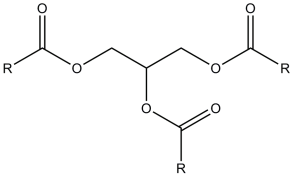
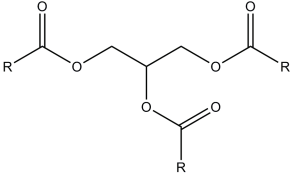
Ingredient/CAS No.	Definition & Structure	Function(s)
Cod Liver/Mink/Tallow Triglyceride	<p>Cod Liver/Mink/Tallow Triglyceride is a mixed triester of glycerin with the fatty acids derived from cod liver oil, mink oil, and tallow</p>  <p>[wherein RC(O)- is the residue of a fatty acid derived from cod liver oil (which is approximately 16.2% oleic acid, 11.9% docosahexaenoic acid, 10.4% palmitic acid, 9.4% gondoic acid (20:1 <i>n</i>-9), 9.3% eicosapentaenoic acid, 7.8% cetoleic acid (22:1 <i>n</i>-11), 6.5% palmitoleic acid, 4.4% cis-vaccenic acid, 3.6% myristic acid, 2.6% stearic acid, 2.4% moroctic acid, 1.6% gadoleic acid (20:1 <i>n</i>-11), 1.5% linoleic acid,⁵¹ 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),⁵² 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)⁵³].</p>	skin conditioning agent – emollient; skin conditioning agent - occlusive
Glyceryl Tri-Hydrogenated Rosinate	<p>Glyceryl Tri-Hydrogenated Rosinate is a triester of glycerin and the partially hydrogenated acids derived from Rosin</p>  <p>[wherein RC(O)- is the residue of the partially hydrogenated acids derived from rosin.].</p>	surfactant – emulsifying agent
Glyceryl Tripalmitate/ Palm Kernelate/Olivate/ Macadamiate/ Rapeseedate	<p>Glyceryl Tripalmitate/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.</p>  <p>[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)]⁵⁰</p>	skin conditioning agent – emollient
Hydrogenated C12-18 Triglycerides	<p>Hydrogenated C12-18 Triglycerides is the end-product of controlled hydrogenation of C12-18 triglycerides.</p>  <p>[wherein RC(O)- is the residue of hydrogenated of C12-18 acids]</p>	skin conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Jjoba Oil/Caprylic/Capric Triglyceride Esters	<p>Jjoba Oil/Caprylic/Capric Triglyceride Esters is the product obtained by the transesterification of Simmondsia Chinensis (Jjoba) Seed Oil with Caprylic/Capric Triglyceride.</p>  <p>[wherein RC(O)- is the residue of caprylic acid, capric acid, and a fatty acid derived from jjoba, which is approximately 83%as combinations of arachidic and behenic acids⁵⁴]</p>	skin protectant; skin conditioning agent – emollient

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

Ingredient/CAS No.	Definition & Structure	Function(s)
Lauric/Palmitic/Oleic Triglyceride	Lauric/Palmitic/Oleic Triglyceride is a mixed triester of glycerin with lauric, palmitic and oleic acids.	skin conditioning agent – occlusive
		
[wherein RC(O)- is the residue of lauric, palmitic, or oleic acid]		
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.	skin conditioning agent – occlusive
		
[wherein RC(O)- is the residue of oleic, palmitic, lauric, myristic, or linoleic acid]		
Ricinoleic/Caproic/Caprylic/Capric Triglyceride	Ricinoleic/Caproic/Caprylic/Capric Triglyceride is the mixed triester of glycerin with ricinoleic, caproic, caprylic and capric acids.	skin conditioning agent – occlusive
		
[wherein RC(O)- is the residue of ricinoleic, caproic, caprylic, or capric acid]		

Note: ingredients that were previously reviewed are indicated in blue

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 Hydroxystearate, 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 Olivatate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Glyceryl Rosinate, Glyceryl 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	55
Caprylic/Capric/Coco Glycerides	safe for use as a cosmetic ingredient	56
Carthamus Tinctorius (Safflower) Seed Oil	safe in the present practices of use and concentration	50
Coconut Acid; Cocos Nucifera (Coconut) Oil	safe for use as a cosmetic ingredient	50
Cocoglycerides; Hydrogenated Coco-Glycerides	safe for use as a cosmetic ingredient	56
Elaeis Guineensis (Palm) Oil; Elaeis Guineensis (Palm) Kernel Oil	safe in the present practices of use and concentration	50
Hydroxystearic Acid	safe as a cosmetic ingredient in the present practices of use	57
Isostearic Acid	safe as a cosmetic ingredient in the present practices of use	57
Lauric Acid	safe in the present practices of use and concentration	58
Macadamia Nut Oil	safe in the present practices of use and concentration	50
Mink Oil	safe in the present practices of use and concentration	52
Myristic Acid	safe in the present practices of use and concentration	59
Glyceryl Dimyristate		
Glyceryl Isostearate/Dimyristate		
Oleic Acid	safe in the present practices of use and concentration	58
Olive Acid; Olea Europaea (Olive) Fruit Oil	safe in the present practices of use and concentration	50
Palmitic Acid	safe in the present practices of use and concentration	58
Pelargonic Acid	safe in the present practices of use and concentration	60
Rapeseed Acid; Hydrogenated Rapeseed Oil	safe in the present practices of use and concentration	50
Ricinoleic Acid; Ricinus Communis (Castor) Seed Oil; Hydrogenated Castor Oil	safe in the present practices of use and concentration	61
Shea Oleine	safe in cosmetics in the present practices of use and concentration when formulated to be non-sensitizing	62
Simmondsia Chinensis (Jojoba) Seed Oil	safe in the present practices of use and concentration	63
Soy Acid; Hydrogenated Soybean Oil	safe in the present practices of use and concentration	50
Stearic Acid	safe in the present practices of use and concentration	58
Tallow; Tallow Glyceride; Hydrogenated Tallow Glyceride; Tallow Glycerides; Hydrogenated Tallow Glycerides	safe as a cosmetic ingredient in the present practices of use	53

Table 4. Physical and Chemical Properties

	form	molecular weight	melting point (°C)	specific gravity	density	solubility	refractive index	o/w partition coefficient	saponification value	acid value	hydroxyl value
Triheptanoin ³¹	liquid	428.6	-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)				
Tripelargonin ⁶⁴		512.76			0.959 (at 20°C)			10.915			
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 ether; 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 ³⁵	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 ³⁵			
Triisostearin ⁴	Light yellow, oily substance							8.98 (calc)	185-210	3 max	30 max
Triolein ⁴	Colorless to yellowish oily liquid polymorphic	885.47	-32 ³⁵		0.8988 (at 60°C)	Practically insoluble in water; slightly soluble in alcohol; soluble in chloroform, 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 5. Current¹³⁻¹⁵ and historical^{1,4-6} frequency and concentration of use of triglycerides according to duration and exposure

Table 3: 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 ⁶	2017	1998	2017	1998
Totals*	6000	763	0.0000067-95.6	0.00001-84	20	3	1-19.6	9
Leave-On	5403	704	0.0000067-95.6	0.00001-84	20	3	1-19.6	9
Rinse-Off	574	59	0.0000067-89.2	0.002-10	NR	NR	NR	NR
Diluted for (Bath) Use	23	NR	0.099	7-78	NR	NR	NR	NR
Eye Area	1063	207	1-83.3	0.008-49	NR	NR	NR	NR
Incidental Ingestion	585	75	1.2-54	0.002-54	20	2	1-19.6	9
Incidental Inhalation-Spray	122; 1446 ^a ; 1356 ^b	30; 150 ^a ; 104 ^b	0.019-38.6; 0.00001-28.8 ^a ; 0.0034-1.3 ^b	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	3.2-16; 0.0034-1.3 ^b ; 0.67-95.6 ^c	0.01-22; 0.06-48 ^b ; 0.8 ^c	NR	NR	NR	NR
Dermal Contact	5195	672	0.000021-95.6	0.00005-84	NR	NR	NR	NR
Deodorant (underarm)	6 ^b	1 ^b	not spray: 0.000021-9; spray: 0.09-0.99	0.00005-5 ^b	NR	NR	NR	NR
Hair - Non-Coloring	161	10	0.0000067-89.2	0.00005-18	NR	1	NR	NR
Hair-Coloring	22	1	0.00002-4.1	NR	NR	NR	NR	NR
Nail	17	5	0.08-50	0.2-15	NR	NR	1-19.6	NR
Mucous Membrane	698	75	0.0001-55.7	0.002-78	20	2	NR	9
Baby Products	37	5	3.2-52	0.8	NR	NR	NR	NR
	Glyceryl Triacetyl Ricinoleate				Tribehenin			
	2017	1998	2017	1998	2017	1998	2017	1998
Totals*	17	32	1-49.2	8	723	42	0.002-15	0.31-6
Duration of Use								
Leave-On	17	32	1-49.2	8	695	38	0.002-15	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	0.002-8	0.32-6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	5.1	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	2017	1998	2017	1998	2017	1998
Totals*	51	NR	0.75	NR	262	47 ^c	70	0.0002-12.7
Leave-On	47	NR	0.75	NR	256	47	66	0.0002-11
Rinse-Off	4	NR	0.75	NR	6	NR	4	0.25-12.7
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Eye Area	5	NR	NR	NR	111	3	5	2-8
Incidental Ingestion	3	NR	NR	NR	37	11	15	0.035-5
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
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
Dermal Contact	47	NR	0.75	NR	221	34	51	0.0002-11
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.5-10
Hair - Non-Coloring	1	NR	NR	NR	4	NR	3	0.25-7
Hair-Coloring	NR	NR	0.75	NR	NR	2	NR	12.7
Nail	NR	NR	NR	NR	NR	NR	1	NR
Mucous Membrane	3	NR	NR	NR	37	11	15	0.035-5
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

Table 5. Current¹³⁻¹⁵ and historical^{1,4-6} frequency and concentration of use of triglycerides according to duration and exposure

Table 3. 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 (%)	
	Triethylhexanoïn (previously Trioctanoïn)				Triheptanoïn			
	2017	1998	2017	1998	2017	1998	2017	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				Triisononanoïn			
	2017	1997	2017	1997	2017	1998	2017	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	2017	1998	2017	1998	2017	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 5. Current¹³⁻¹⁵ and historical^{1,4-6} 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	2017	1998	2017	1998	2017	1998
Totals*	27	2	0.00048-0.017	NR	27	10	0.12-8	1-2
Leave-On	12	2	0.0048-0.017	NR	27	10	0.12-8	1-2
Rinse-Off	15	NR	0.00048-0.0048	NR	NR	NR	2	NR
Diluted for (Bath) Use	NR	NR	0.00048	NR	NR	NR	NR	NR
Eye Area	NR	NR	NR	NR	3	1	0.2-8	2
Incidental Ingestion	NR	NR	0.0048	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 ^e	1
Dermal Contact	27	2	0.00048-0.017	NR	27	10	0.12	1-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	0.12-8	NR
Hair - Non-Coloring	NR	NR	0.00048	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	0.00048-0.0048	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	0.00053-0.14	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	0.00053-0.025	NR	2	1	1	2
Diluted for (Bath) Use	NR	NR	0.00053	NR	NR	NR	NR	NR
Eye Area	3	NR	0.005-14	NR	8	NR	0.094-19.3	NR
Incidental Ingestion	68	NR	0.0008-0.0053	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 ^e	NR
Dermal Contact	39	NR	0.00053-0.14	NR	12	1	0.094-19.3	2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	0.00053	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	0.00053-0.0053	NR	1	NR	15.6	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Tristearin				Triundecanoil ^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

Table 6. Frequency¹³ and concentration of use^{14,15} previously unreviewed triglycerides

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	C12-18 Acid Triglyceride		C18-36 Acid Triglyceride		Caprylic/Capric/Lauric Triglyceride	
Totals*	18	0.2-0.33	216	0.64-26.1	4	NR
Duration of Use						
Leave-On	18	0.2-0.33	216	0.64-26.1	4	NR
Rinse-Off	NR	NR	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	2	0.2-0.33	92	0.76-4.5	NR	NR
Incidental Ingestion	14	NR	NR	1.3-26.1	NR	NR
Incidental Inhalation-Spray	1 ^a	NR	3; 1 ^a , 5 ^b ;	9.2; 11 ^a	2 ^a , 2 ^b	NR
Incidental Inhalation-Powder	1; 1 ^a	NR	1 ^a	NR	2 ^a	NR
Dermal Contact	4	0.2-0.33	134	0.64-20	3	NR
Deodorant (underarm)	NR	NR	NR	0.64-3.5	NR	NR
Hair - Non-Coloring	NR	NR	3	11	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	NR
Mucous Membrane	14	NR	NR	1.3-26.1	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Caprylic/Capric/Linoleic Triglyceride		Caprylic/Capric/Myristic/Stearic Triglyceride		Caprylic/Capric/Stearic Triglyceride	
Totals*	NR	0.001-52.1	229	0.015-15.3	22	1-17.7
Duration of Use						
Leave-On	NR	0.001-52.1	217	0.015-15.3	21	1-17.7
Rinse Off	NR	NR	12	0.1-8	1	2
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	29	0.075-15.3	3	1.3-17.7
Incidental Ingestion	NR	NR	7	1.9-8.6	1	NR
Incidental Inhalation-Spray	NR	NR	1; 156 ^a , 18 ^b	0.1-6 ^a	6; 7 ^a , 2 ^b	NR
Incidental Inhalation-Powder	NR	0.001-52.1 ^c	156 ^a	0.18-8 ^c	7 ^a	1 ^c
Dermal Contact	NR	0.001-52.1	221	0.015-15.3	18	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	0.1-5	3	2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	12	1.9-8.6	2	NR
Baby Products	NR	NR	NR	NR	NR	NR

	C10-40 Isoalkyl Acid Triglyceride		C10-18 Triglycerides		Glyceryl Tri-Hydrogenated Rosinate	
Totals*	1	NR	93	0.0049-48.4	NR	61
Duration of Use						
Leave-On	1	NR	91	0.0049-48.4	NR	NR
Rinse-Off	NR	NR	1	0.0049-0.25	NR	61
Diluted for (Bath) Use	NR	NR	1	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	23	3.5-43.9	NR	NR
Incidental Ingestion	1	NR	11	0.1-48.4	NR	NR
Incidental Inhalation-Spray	NR	NR	22 ^a , 22 ^b	1.3 ^a	NR	NR
Incidental Inhalation-Powder	NR	NR	1; 22 ^a , 1 ^c	0.1-2.7; 0.0049-5 ^c	NR	NR
Dermal Contact	NR	NR	82	0.0049-43.9	NR	61
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.25	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	12	0.1-48.4	NR	NR
Baby Products	NR	NR	1	NR	NR	NR

Table 6. Frequency¹³ and concentration of use^{14,15} previously unreviewed triglycerides

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Hydrogenated C12-18 Triglycerides		Palmitic/Stearic Triglyceride		Trilinolenin^d	
Totals*	12	1-39.3	6	NR	2	NR
Duration of Use						
<i>Leave-On</i>	10	1-39.3	6	NR	2	NR
<i>Rinse-Off</i>	2	NR	NR	NR	NR	NR
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	39.3	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1 ^a , 5 ^b	NR	2 ^a , 3 ^b	NR	2 ^a	NR
Incidental Inhalation-Powder	1 ^a	NR	2 ^a , 1 ^c	NR	2 ^a	NR
Dermal Contact	12	1-39.3	6	NR	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	NR	NR
Baby Products	NR	NR	1	NR	NR	NR

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

^a 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 as Linoleic Acid Triglyceride in VCRP

NR – no reported use

Table 7. Ingredients not reported to be in use¹³⁻¹⁵

Acetic/Linoleic/Palmitic Triglyceride	Glyceryl Tripalmitate/Palm Kernelate/Olivate/Macadamate/Rapeseedate	Triarachidin
C8-12 Acid Triglyceride	Isomerized Safflower Glycerides	Trierucin
Capric/Lauric/Myristic/Oleic Triglyceride	Jobba Oil/Caprylic/Capric Triglyceride Esters	Triheptylundecanoin
Caprylic/Capric/Palmitic/Stearic Triglyceride	Lauric/Palmitic/Oleic Triglyceride	Triisopalmitin
Cod Liver/Mink/Tallow Triglyceride	Oleic/Linoleic Triglyceride	Tripalmitolein
Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride	Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride	Tripelargonin
Glyceryl Stearate Diacetate	Ricinoleic/Caproic/Caprylic/Capric Triglyceride	Triricinolein

Table 8. Acute Toxicity Studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Procedure	LD ₅₀ /observations	Reference
DERMAL						
Triheptanoin	rats	5/sex	none	24 h semi-occlusive patch with 2 g/kg	>2 g/kg	³¹
Tristearin	rats	5/sex	corn oil	24 h semi-occlusive patch with 2 g/kg	>2 g/kg	³²
ORAL						
Triheptanoin	NMRI mice	5 males	none	5 g/kg by gavage	>5 g/kg	³¹
Tripelargonin; Triethylhexanoin	newborn Rhesus (<i>Macaca mulatta</i>) monkeys	5	none	8.4 ml/kg bw by nasogastric tube	Did not affect alertness or activity level; did not induce narcolepsy	²⁹
Triethylhexanoin	rats	not provided	not provided	not specified	>48 g/kg	³⁵
Triisostearin	Swiss mice	5 females	none	2 g/kg by gavage	>2 g/kg	³³
Triisostearin	Sprague-Dawley rats	5/sex	none	2 g/kg by gavage	>2 g/kg	³³
Triolein	Wistar rats	5/sex	none	2 g/kg by gavage	>2 g/kg	³⁴
MLCT	Wistar rats	5/sex	none	5 g/kg MLCT oil or mixed rapeseed and soybean oils (7:3; control) by gavage	>5 g/kg	²⁸

Abbreviations: MLCT – medium- and long-chain triacylglycerol (length C8 -C24)

Table 9. Short-Term, Subchronic, and Chronic Oral Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
SHORT-TERM TOXICITY STUDIES							
<i>ANIMAL</i>							
ORAL							
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	³⁶
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% carboxymethylcellulose/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 histiocytosis 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	³⁷
Caprylic/Capric Triglyceride	Göttingen minipigs, 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% methylcellulose/0.1% Tween 80 in water (2 ml/kg/day)	<u>0.5 and 2 ml/kg/day</u> : transient tremors, abnormal feces color, and increased triglycerides. <u>2 ml/kg/day</u> : also, reduced motor activity, decreased food intake, respiratory signs (2/6 animals) and increased 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 researchers to aspiration pneumonia) No changes in organ weights or gross or microscopic lesions were observed, and no toxicologically-relevant changes in hematology or urinalysis parameters were noted	³⁸
Caprylic/Capric Triglyceride	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 g/kg bw/day reduced food consumption, softened feces, ruffled fur were observed in the high dose group during the first days of the study	³⁹
MLCT	Wistar rats; 20 males/group	6 wks	none	diet containing 7% MLCT or rapeseed oil (control) (equiv to 3.5 g/kg/day)	6-wk dietary study	NOAEL = 3.5 g/kg/day no adverse effects were observed feed consumption, total carcass protein, and serum cholesterol values were statistically significantly increased; total body fat was statistically significantly decreased	²⁸
PARENTERAL							
Tripelargonin/LCT (7/3 wt/wt) emulsion	New Zealand rabbits; 8 male	11 days	none	46.5% of total daily energy	TPN infusions 7 h/day; controls were given isocaloric amounts of a standard food; the animals were killed on day 12	No signs of toxicity; no effect on organ weights or liver lipid concentrations; macroscopic, but not microscopic, changes were noted in the liver	^{30,40}

Table 9. Short-Term, Subchronic, and Chronic Oral Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
HUMAN							
MLCT	20 healthy males and females	4 wks		“bread” containing mixed rapeseed and soybean oils (7:3; controls) or MLCT; 42 g oil/day consumed	placebo-controlled double blind study ; hematology and urinalysis were conducted at study initiation and study termination; liver and renal function were measured; body wts and body mass index were measured	no adverse effects	28
SUBCHRONIC TOXICITY STUDIES							
Caprylic/Capric Triglyceride	Wistar rats, 20/sex	90 days	none	1 and 5%	dietary study, in accord with OECD TG 408; changes in organ weights were not measured; microscopic examination was not performed	NOAEL = 5% no signs of systemic toxicity; all animals survived until study termination; no effects on body weight gain, hematology, clinical chemistry, urinalysis, or gross pathology	39
Caprylic/Capric Triglyceride	Beagle dogs, 4/sex	91 days	none	0, 5, 10, and 15%	3-h feeding regimen for the course of the study; dry dog food with beef tallow; animals were observed daily; body weight and feed consumption were measured; hematology, serum chemistry, and urine analysis were performed	NOAEL = 15% No toxicologically-significant clinical signs of toxicity; no significant differences in body wts or feed consumption; 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	41
CHRONIC TOXICITY STUDIES							
oil consisting of: 64% Triheptanoin 34% diheptanoin 2% monoheptanoin	Wistar rats, 10 males	9 mos	none	control diet with either 30% or 50% substitution of soybean oil with test oil	animals were exposed to <i>ad libitum</i> ; controls were fed AIN-3 diet (lipid source is exclusively soybean oil); body wts were measured; biochemistry analysis (for hepatic and renal function) was performed; the liver, kidneys, and small intestine were examined microscopically	no toxic effects were observed	42

Abbreviations: LCT – long chain triglyceride (length C_{16:0} – C_{18:3}); MLCT – medium- and long-chain triacylglycerol (length C₈ - C₂₄); NOAEL – no-observable adverse effect level; OECD – Organisation for Economic Cooperation and Development; TG – test guideline; TPN – total parenteral nutrition

Table 10. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Tristearin	5000 µg/plate	95% ethanol	<i>S. typhimurium</i> 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	32
Caprylic/Capric Triglyceride	not stated	not stated	not stated	Ames test	negative	35
Triethylhexanoïn	50-5000 µg/plate	DMSO	<i>S. typhimurium</i> 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
Triethylhexanoïn	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
Triisononanoïn	50-5000 µg/plate	acetone	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100 <i>Escherichia coli</i> WP2uvrA	Ames test, with and without metabolic activation; solvent and appropriate positive controls were used	negative	44
Triisononanoïn	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	44
Triisononanoïn	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	44
lipid emulsion comprised of Caprylic/Capric Triglyceride, soybean oil, olive oil, and fish oil	not provided	not provided	<i>S. typhimurium</i>	Ames test (details not provided)	negative	27
lipid emulsion comprised of Caprylic/Capric Triglyceride, soybean oil, olive oil, and fish oil	not provided	not provided	human lymphocytes	chromosomal aberration assay (details not provided)	negative	27
lipid emulsion comprised of Caprylic/Capric Triglyceride, soybean oil, olive oil, and fish oil	not provided	not provided	V79 cells	HPRT gene mutation assay (details not provided)	negative	27
MLCT	313-5000 µg/plate	sodium phosphate buffer	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100 <i>E. coli</i> WP2uvrA	Ames test, with and without metabolic activation; solvent and appropriate positive controls were used	negative	28
IN VIVO						
lipid emulsion comprised of Caprylic/Capric Triglyceride, soybean oil, 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; MLCT – medium- and long-chain triacylglycerol (length C8 -C24); OECD – Organisation for Economic Cooperation and Development; TG – test guideline

Table 11. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IN VITRO					
Triisononanoïn	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	44
ANIMAL					
Triheptanoïn	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 <u>30-60 min</u> : very slight to well-defined erythema in all animals <u>24-72 h</u> : moderate to severe erythema and severe edema with brown discolorations and dryness, with sanguineous lacerations and scaling in 1 animal <u>72 h</u> : 1 animal showed moderate redness of the skin, with dry skin and severe extensive subcutaneous hemorrhage <u>6 days</u> : scaling was observed in all animals <u>10-14 days</u> : all animals were normal	31
Triheptanoïn	undiluted, 0.5 ml	NZW rabbits, 3 males	4- h semi-occlusive patches were applied in accord with OECD TG 404	<u>1 h</u> : very slight and slight erythema in 1 and 2 animals, respectively. <u>24 h</u> : very slight edema in one of the latter animals very slight and slight erythema in 2 and 1 animals, respectively. <u>48 h</u> : very slight edema in the latter. <u>48 and 72 h</u> : very slight erythema in 2 animals, with very slight edema in one	31
Triheptanoïn	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	31
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	32
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	32
Caprylic/Capric Triglyceride	undiluted, 0.5 ml	NZW rabbits, 6	4-h semi-occlusive patches	not irritating no erythema or edema were observed	39
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	39
Triisononanoïn	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%	44
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	<u>1 and 24 h</u> : well-defined erythema observed in 3/3 animals <u>48 h</u> : slight erythema persisted in 2/3 animals <u>72 h</u> : erythema cleared completely no edema was observed in any animal at any time point	33

Table 11. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
HUMAN					
facial oil containing 95.51% Caprylic/Capric Triglyceride	applied neat	17 subjects	SIOPT; 24 h patch	not irritating; PII = 0	45
facial oil containing 95.51% Caprylic/Capric Triglyceride		26 subjects	modified maximization test procedure; 5 occlusive patches (2 cm x 2 cm) were applied for 48-72 h; the test sites were pretreated with 0.25% SLS one day prior to patching. Challenge was conducted following a 14-day non-treatment period; an occlusive patch with 5.0% SLS was applied for 1 h, followed by application of a test patch for 48 h; controls were patched with a sham patch following SLS pretreatment	not a sensitizer	46
moisturizer containing 6% Tribehenin	applied neat; 0.01 g (pink solid paste)	102 subjects	HRIPT; 24-h occlusive patches (2 cm x 2 cm) were applied to the upper back 3 x/wk for 3 wks; challenge was performed following an 8-19 day non-treatment period with a 24-h occlusive patch to a previously untreated site	no adverse events were reported not a sensitizer	47
mixture containing 20% Tribehenin	0.2 g	52 subjects	HRIPT; 24-h occlusive patches (1 in x 1 in) were applied to the upper back 3 x/wk for 3 wks; challenge was performed following a 2 wk non-treatment period with a 24-h occlusive patch to a previously untreated site	8 subjects had a response on a least one day of induction, ranging from barely perceptible (+) to moderate (score of 2; 1 occurrence); at challenge, one subject had a mild reaction at the 72 h reading and a barely perceptible reaction with dryness at a 96-h follow-up evaluation. The researchers stated that none of these responses were considered clinically significant, and concluded there was no clinically significant potential for dermal irritation or sensitization	48
Triolein	not stated	human subjects; number not stated	chamber test; details not provided	not a sensitizer	35

Abbreviations: HRIPT – human repeated insult patch test; LLNA – local lymph node assay; NZW – New Zealand White; OECD – Organisation for Economic Cooperation and Development; PII – primary irritation index; SI – stimulation index; SIOPT - single insult occlusive patch test; SLS – sodium lauryl sulfate; TG – test guideline

Table 12. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IN VITRO					
Triisononanoil	undiluted, 30 µl	HCE model	In vitro eye irritation test using the SkinEthic™ reconstructed model	predicted to be non-irritating	44
ANIMAL					
Triheptanoil	undiluted, 0.1 ml	rabbits, 3 males	24 h instillation into one eye	non-irritating	31
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	52
Caprylic/Capric Triglyceride	undiluted, 0.1 ml	NZW rabbits, 6	single instillation into one eye; 72-h observation period	non-irritating	39
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	39
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	53

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 Trihydroxystearin¹

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, Canterbury, 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, Canterbury, 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

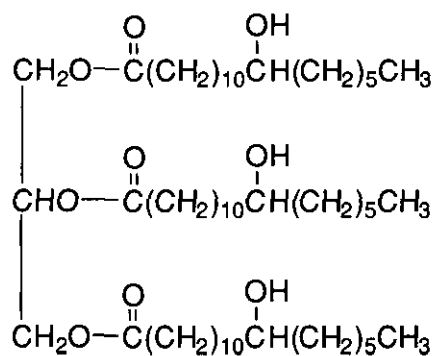
One method of production of Trihydroxystearin involved the hydrogenation of castor oil, in the presence of the reagent nickel, at a temperature of 200°C. Another method of production is the reduction of triricinolein (Scientific & Technical Information Network International 1996b).

Reactivity

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

Received 3 February 2000; accepted 3 May 2000.

¹Reviewed 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.

**FIGURE 1**

Chemical formula for Trihydroxystearin (Wenninger, Canterbury, 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, Canterbury, 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

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

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 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 non-treatment period. The LD₅₀ 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 $\mu\text{g}/\text{plate}$ (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 tricapylin for 80 weeks). The high dose group received a total dose of 80 mg delivered in a total of 8 ml of tricapylin.

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. Semioclusive 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 semioclusive 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 $\geq 0.1\%$ to 50%; Glyceryl Stearate/SE is used in over 200 cosmetic products at concentrations of $\geq 0.1\%$ 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 LD₅₀ 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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²Available 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, Trimyrustin, Trioctanoin, Triolein, Tripalmitin, Tripalmitolein, Triricinolein, Tristearin, Triundecanoin, Glyceryl Triacetyl Hydroxystearate, Glyceryl Triacetyl Ricinoleate, and Glyceryl Stearate Diacetate¹

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 non-aqueous 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, sub-chronic, 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, Trimyrustin, 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.

Received 19 September 2001; accepted 11 October 2001.

¹Reviewed 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.

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, Triisononanoil, Triisostearin, Trilaurin, Trilinolein, Trimyristin, Trioctanoin, Tripalmitin, Tristearin, Glyceryl Triacetyl Hydroxystearate, and Glyceryl Triacetyl Ricinoleate.

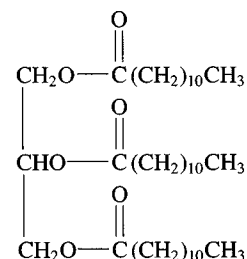
Information is available on the constituent chemicals and on related cosmetic ingredients. Glycerin is classified as a generally recognized as safe (GRAS) food ingredient based on a literature review published in 1973 (Informatics, Inc., 1973). The Cosmetic Ingredient Review (CIR) Expert Panel concluded 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).

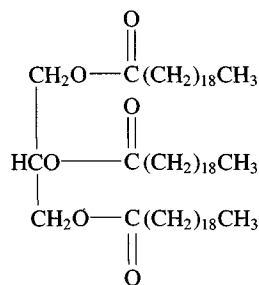
TABLE 2
Descriptions/specifications of Glyceryl Triesters

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

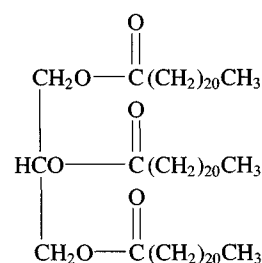
Triarachidin (CAS No. 620-64-4) is the triester of glycerin and arachidic acid (q.v.) that conforms to the following formula (Wenninger and McEwen 1997):



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

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

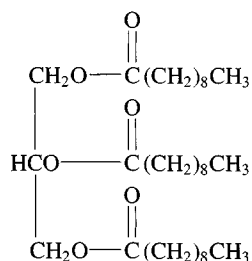
Tribehenin (CAS No. 18641-57-1) is a cream-colored solid with a faint odor (Unichema International 1992). It is the triester of glycerin and behenic acid that conforms to the following formula (Wenninger and McEwen 1997):



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)

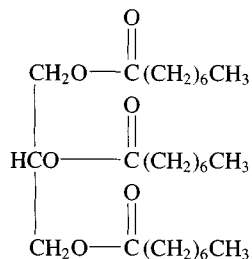
Tricaprin (CAS No. 621-71-6) is the triester of glycerin and capric acid that conforms to the following formula (Wenninger and McEwen 1997):



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

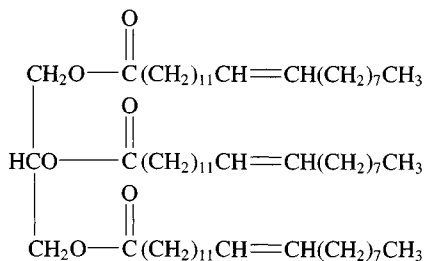
Tricaprylin (CAS No. 538-23-8) is the triester of glycerin and caprylic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

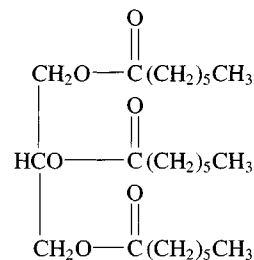
Trierucin (CAS No. 2752-99-0) is the triester of glycerin and erucic acid that conforms to the following formula:



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)

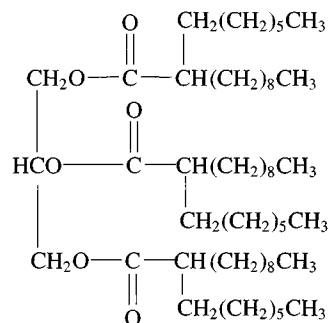
Triheptanoin (CAS No. 620-67-7) is the triester of glycerin and heptanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

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

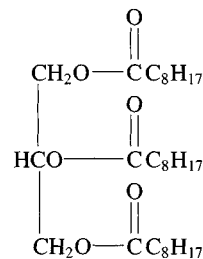
Triheptylundecanoin (CAS No. 105214-66-2) is the triester of glycerin and heptylundecanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

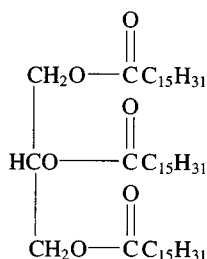
Triisononanoin is the triester of glycerin and a branched-chain nonanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

- 1,2,3-Propanetriol Triisononanoate
- 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):



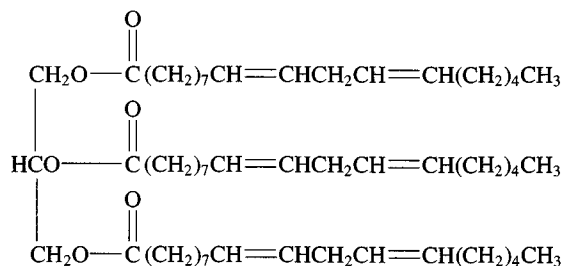
Other names (Wenninger and McEwen 1997) for Triisopalmitin include:

- 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):

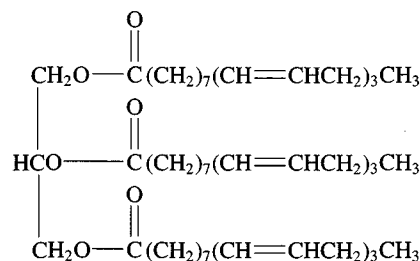


Other names (Wenninger and McEwen 1997) for this chemical include:

- 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-Octadecadienoate)

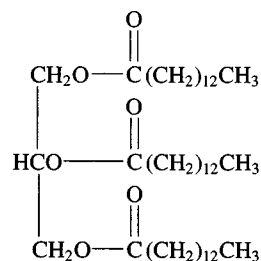
Trilinolenin (CAS No. 14465-68-0) is the triester of glycerin and linolenic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

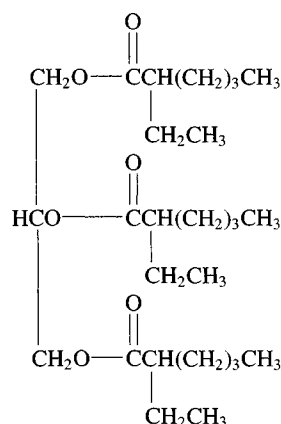
Trimyristin (CAS No. 555-45-3) is present in many vegetable fats and oils, notably in coconut oil and nutmeg butter (Budavari 1989). It is the triester of glycerin and myristic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

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

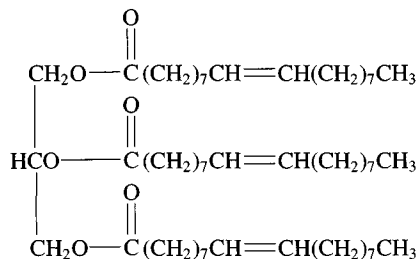
Trioctanoin (CAS No. 7360-38-5) is a colorless to pale yellow, transparent oily liquid with negligible odor (Unichema International 1996). It is the triester of glycerin and 2-ethylhexanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



Other names (Wenninger and McEwen 1997) for Trioctanoil 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

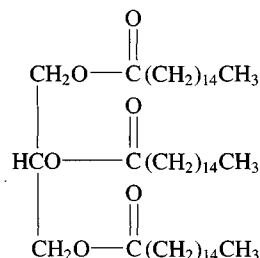
Triolein (CAS No. 122-32-7) is the predominating constituent in expressed almond oil, lard, and many of the more fluid animal oils and those of vegetable origin (Gennaro 1990). It is the triester of glycerin and oleic acid that conforms to the following formula (Wenninger and McEwen 1997):



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-Octadecenoate)

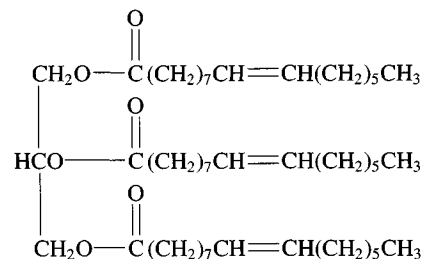
Tripalmitin (CAS No. 555-44-2) predominates in palm oil and coconut oil (Gennaro 1990). It is the triester of glycerin and palmitic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

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

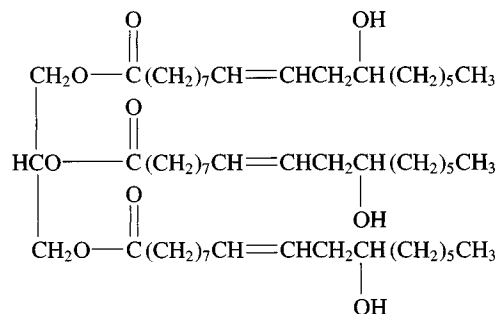
Tripalmitolein (CAS Nos. 20246-55-3 and 129784-33-4) is the triester of glycerin and palmitoleic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

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

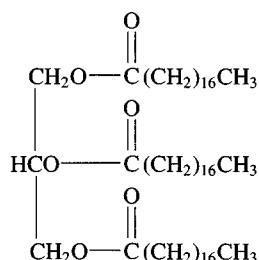


Other names (Wenninger and McEwen 1997) for Tricinolein include:

- Glyceryl Tricinoleate
- 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

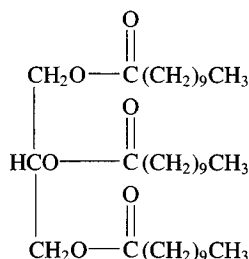
stearic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

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

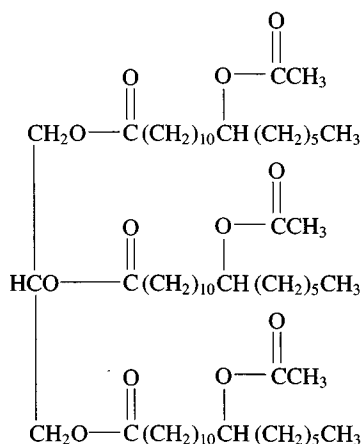
Triundecanoin (CAS No. 13552-80-2) is the triester of glycerin and undecanoic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

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

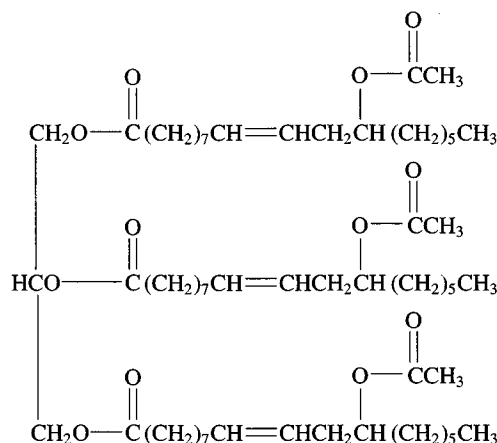
Glyceryl Triacetyl Hydroxystearate (CAS No. 27233-00-7) is the triester of glycerin and acetyl hydroxystearic acid that conforms to the following formula (Wenninger and McEwen 1997):



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

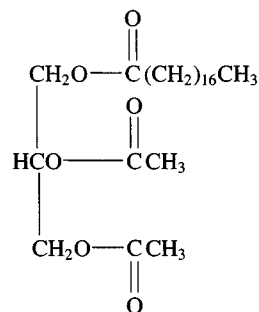
Glyceryl Triacetyl Ricinoleate (CAS No. 101-34-8) is the triester of glycerin and acetyl ricinoleic acid that conforms to the following formula (Wenninger and McEwen, 1997):



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-Shirkhodae 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
Trimyrustin	as above
Triolein	as above
Tripalmitin	as above
Tripalmitolein	as above
Tricinnolein	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, Trimyrustin, 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, Trimyrustin, 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, Trimyrustin, 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
Triisononanoïn		
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 Triisononanoïn 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%
Eyeliners	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%
Triisononanoil	
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%
Trioctanoil	
Eyebrow pencil	10%
Eyeliners	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 mono-glycerides, 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} ($0.5 \mu\text{Ci}$). Doses were administered by gastric probe after 15 to 18 hours of fasting. Cumulative $^{14}\text{CO}_2$ elimination curves of the percentage of radioactive carbon dioxide relative to the dose ingested indicated that the amount of $^{14}\text{CO}_2$ 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- C^{14}) (a.k.a. C^{14} -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% C^{14} -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, C^{14} -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- C^{14} -Trioleate. The percentage of administered Glycerol 1- C^{14} -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- C^{14}]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- C^{14}]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 C^{14} -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- C^{14}]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- C^{14}]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- C^{14}]Triolein and [1- C^{14}]Tripalmitin are summarized below:

When groups of rats were dosed with [I- C^{14}]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 [$1-^{14}\text{C}$]Tripalmitin in bran pellets. Absorption was expressed as the percentage of that which left the stomach. The mean percentage absorption reported was $70\% \pm 5\%$ (Hamilton, Webb, and Dawson 1969).

Following the oral administration of a Glycerol-tri($1-^{14}\text{C}$)-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 $1-^{14}\text{C}$ -Trilinolein emulsion (50 μl). Groups of two to four animals were killed at the following intervals, after which testes were excised: $\frac{1}{4}$, $\frac{1}{2}$, 1, 3, 6, 12, 24, 36, and 48 hours. Results indicated that radioactive $1-^{14}\text{C}$ -linoleic acid was released from $1-^{14}\text{C}$ -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 $1-^{14}\text{C}$ -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, $26.7\% \pm 5.2\%$ of the administered radioactivity was recovered as expired $^{14}\text{CO}_2$ in 150 minutes. After pancreatectomy, $^{14}\text{CO}_2$ 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- $[1-^{14}\text{C}]$ octanoate), and the long-chain triglyceride (LCT), Trilinolein (glycerol tri- $[1-^{14}\text{C}]$ 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 $[^{14}\text{C}]$ MCT, and group 2 was fed a 75%:25% (vol:vol) admixture of $[^{14}\text{C}]$ MCT:unlabeled LCT lipid emulsion. Group 3 was fed $[^{14}\text{C}]$ 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 $\mu\text{g}/\text{ml}$ 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 $0.3\% \pm 0.2\%$. The percutaneous absorption of Triolein was greatest ($4.7\% \pm 0.8\%$) in the presence of PBS + gentamicin + bovine serum albumin and least in the presence of PBS + gentamycin + PEG-20 oleyl ether ($0.2\% \pm 0.1\%$). 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 [^3H]-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 Wretling 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 LD₅₀ of 3,700 ± 194 mg/kg was reported (Wretling 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 ($\times 10^4/\text{mm}^3$) 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 ($\times 10^2/\text{mm}^3$) 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 significant 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 LD₅₀, where LD₅₀ 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 Blendern 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 semioclusive 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/cm²) 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)F₁ female mice. In the first experiment, 44 T-stock females were used. Forty-seven T-stock females and 37 (C3H × C57BL)F₁ 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)F₁ 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 10⁹ to 10¹⁰ 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 revertants 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 μ g/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 μ g/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 μ g/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 CO₂ 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 ($10^6/\mu\text{l}$) 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 Ponomarev 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 6 β -hydroxyperoxy-4-cholesten-3-one (in Triolein or sesame oil) and with sesame oil (control). Groups of BALB/c mice were injected with 6 β -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, 6 β -hydroxyperoxy-4-cholesten-3-one (5 mg) in sesame oil and Triolein produced 9% and 18% sarcomas, respectively. In Balb/c mice, 6 β -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, 6 β -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 6 β -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, 6 β -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, 6 β -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 μ g/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 to 11 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 (symplesma 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 LD₁₀ 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 (B6C3F₁/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 $4.5\% \pm 1.7\%$. 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)

[¹³C]-Trioctanoin was administered orally to five normal term neonates and five growing preterm infants. ¹³C enrichment in carbon dioxide was analyzed using isotope ratio mass spectrometry; oxidation rates over 6 hours were calculated. The peak for ¹³C 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 [¹³C]-Trioctanoin were $46.2\% \pm 3.6\%$ in preterm infants and

$53.5\% \pm 13.8\%$ 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 μ Ci [¹⁴C]-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-1-¹⁴C as ¹⁴CO₂ 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 μ Ci [¹⁴C]-Triolein. The quantity of expired ¹⁴CO₂ was estimated from measurements of specific activity of ¹⁴CO₂ 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, ¹⁴CO₂ was expired at a slow, but constant rate (Pedersen and Marqversen 1981).

The fate of orally administered [1-¹³C]- and [8-¹³C]-Triolein was evaluated using four healthy human subjects (two males, two females). In the first experiment, 100 mg of [1-¹³C]-Triolein was administered orally (postprandial). One week later in a second experiment, the four subjects received 100 mg of [8-¹³C]-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. ¹³C 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 [1-¹³C]-Triolein was recovered in the serum TG fraction, compared to 10% to 60% of the [8-¹³C]-Triolein dose. Thus, after administration of [8-¹³C]-Triolein, the TG oleic acid in serum was significantly more highly enriched (significantly higher enrichment peak) in ¹³C than after [1-¹³C]-Triolein administration. This difference could have been due to faster elimination of [1-¹³C]-Triolein from the serum. ¹³C enrichment in other fatty acids of the TG fraction as well as phospholipid and cholesterol ester fractions were in the range of natural ¹³C abundance (Metges, Kempe, and Wolfram 1994).

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

Tripalmitin (C16)

The metabolic fate of a triglyceride oral load labeled with [1,1,1-¹³C₃]-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/m². Sunflower oil (30 g) enriched with 300 mg of [1,1,1-¹³C₃]-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. [1-¹³C]-palmitate appeared in the plasma TG at 90 minutes, and the mole percent excess (MPE) of [1-¹³C]-palmitate in TG increased and reached a plateau after 240 minutes. At 240 minutes, the MPE of [1-¹³C]-palmitate was significantly greater in NEFA than in TG. At the conclusion of the study, the MPE of [1-¹³C]-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 [1-¹³C]-palmitate infusion. The average BMI for these subjects was 21 kg/m³. Albumin-bound [1-¹³C]-palmitate was infused intravenously for 150 minutes, and blood samples were collected at 120 and 150 minutes. Hepatic reesterification of intravenously infused [1-¹³C]-palmitate was estimated from the appearance of labeled palmitate in TG. A constant ¹³C-palmitate enrichment of 1.6 ± 0.2 MPE was noted in NEFA after 120 minutes of [1-¹³C]-palmitate infusion. However, [¹³C]-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 [1,1,1-¹³C₃]-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 μ l) 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, Trimyrustin, 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, Trimyrustin, 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, although 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 LD₅₀ 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 (symplesma 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 Tri-caprylin 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, Trimyrustin, 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 C₂ fragments which may be further metabolized either to CO₂ or to form long-chain fatty acids.

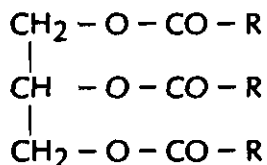
It has a very low toxicity to man and animals as shown by tests involving oral ingestion, intraperitoneal and intramuscular injection, skin and eye irritation tests, skin sensitization, percutaneous toxicity and finally, by two generation feeding studies.

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)*:



R represents the alkyl moieties primarily of C₈, caprylic (octanoic) and C₁₀, 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).

*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 C₆-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.

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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

CAPRYLIC/CAPRIC TRIGLYCERIDE

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

Ingredient	Cosmetic Product Type	Concentration (%)	Number of Product Formulations
Caprylic/Capric Triglyceride	Cleansing (cold creams, cleansing lotions, liquids and pads)	> 10 to 25	1
		> 5 to 10	1
		> 1 to 5	1
		> 0.1 to 1	1
	Face, body and hands (excluding shaving preparations)	> 10 to 25	3
		> 5 to 10	8
		> 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 liquids	> 10 to 25	2
		> 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.

Its 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, 1977¹; 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) ¹
12.5 ml	Mouse (10F)	0		
20.0 ml	Mouse (10F)	20	> 25 ml	(Consultox, 1977) ¹
25.0 ml	Mouse (10F)	10		
4.5 ml	Rat (10M)*	0		
9.0 ml	Rat (10M)*	0	> 36 ml	(Rheinischen, 1971) ²
18.0 ml	Rat (10M)*	0		
36.0 ml	Rat (10M)*	0		
5.0 g	Rat (5M, 5F)	0	> 5 g	(Henkel, 1977) ¹
5.0g	Rat (5M, 5F)	0	> 5 g	(Henkel, A1835) ¹
5.0g	Rat (5M, 5F)	0	> 5 g	(PVO, 1976a) ¹
5.0 g**	Rat (5M, 5F)	0	> 5 g	(PVO, 1976b) ¹

* 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 μ l/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 μ m or less, represented 1.97 μ l/l 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

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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 Officiel 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

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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) ³
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) ³
6 (sex unspec.)	Full strength	Draize et al., same as above.	0.25	Mild irrit. potential	(Henkel A1838) ³
3M, 3F	Full strength	"	0.00	Non-irrit.	(PVO, 1976a) ³
3M, 3F	Full strength ²	"	0.05	Non-irrit.	(PVO, 1976b) ³
6 (sex unspec.)	Full strength	Draize et al.,	0.92	Mild irrit.	(Warf, 1975) ³

¹PII - Primary irritation index.²Also contains 3% polyoxyethylene sorbitan stearate (emulsifier), 0.2% preservative (not specified) and water to 100%.³Approximately 50% Caprylic/Capric Triglyceride in coconut oil.⁴J. official de la Republique, 1971³.

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)³.

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.

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

Observation after ten days revealed no effect; however, this report did not indicate whether there was evidence of irritation at any earlier time (Rheinschen, 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

¹Available 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 F₁ generation was fed as the F₀ generation had been and showed a weight gain comparable to that of control rats on an oleo oil diet (Harkins and Sorett, 1968).

¹Available 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 cm²) 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

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C₂ fragments which may be further metabolized either to CO₂ 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%

^aReported to be in use, but no concentration of use was provided.

^bOriginally, Face and Neck and Body and Hand were combined as one category, but now they are separated.

^c43% in a spray product.

^dWrinkle 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 con-

centration” (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 80μ . Typically less than 1% are below 10μ , 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 $10 \mu\text{g/L}$ (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	—	$\leq 1\%$	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	$\leq 0.1\%$	0.7%–1%
Other eye makeup preparations	—	18	—	0.7%–1%
Perfumes	9	9	$> 0.1\%$ –1%	0.3%–0.8%
Sachets	11	9	$\leq 1\%$	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	$\leq 0.1\%$	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
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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

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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
TRIEPTANOIN	1	07C - Foundations
TRIEPTANOIN	2	07E - Lipstick
TRIEPTANOIN	1	10E - Other Personal Cleanliness Products
TRIEPTANOIN	2	12A - Cleansing
TRIEPTANOIN	4	12C - Face and Neck (exc shave)
TRIEPTANOIN	2	12D - Body and Hand (exc shave)
TRIEPTANOIN	12	12F - Moisturizing
TRIEPTANOIN	1	12G - Night
TRIEPTANOIN	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
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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 HYDROXYSTEAF	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
C12-18 ACID TRIGLYCERIDE	2	03B - Eyeliner
C12-18 ACID TRIGLYCERIDE	1	07B - Face Powders
C12-18 ACID TRIGLYCERIDE	14	07E - Lipstick
C12-18 ACID TRIGLYCERIDE	1	12C - Face and Neck (exc shave)
C18-36 ACID TRIGLYCERIDE	2	03B - Eyeliner
C18-36 ACID TRIGLYCERIDE	5	03C - Eye Shadow
C18-36 ACID TRIGLYCERIDE	78	03F - Mascara
C18-36 ACID TRIGLYCERIDE	7	03G - Other Eye Makeup Preparations
C18-36 ACID TRIGLYCERIDE	3	04E - Other Fragrance Preparation
C18-36 ACID TRIGLYCERIDE	2	05G - Tonics, Dressings, and Other Hair Grooming Aids
C18-36 ACID TRIGLYCERIDE	1	05I - Other Hair Preparations
C18-36 ACID TRIGLYCERIDE	17	07C - Foundations
C18-36 ACID TRIGLYCERIDE	70	07E - Lipstick
C18-36 ACID TRIGLYCERIDE	26	07I - Other Makeup Preparations
C18-36 ACID TRIGLYCERIDE	1	08B - Cuticle Softeners
C18-36 ACID TRIGLYCERIDE	1	12C - Face and Neck (exc shave)
C18-36 ACID TRIGLYCERIDE	2	12F - Moisturizing
C18-36 ACID TRIGLYCERIDE	1	12J - Other Skin Care Preps
C18-38 ACID TRIGLYCERIDE	1	03A - Eyebrow Pencil
C18-38 ACID TRIGLYCERIDE	1	03A - Eyebrow Pencil
CAPRYLIC/CAPRIC/LAURIC TRIGLYCERII	1	05G - Tonics, Dressings, and Other Hair Grooming Aids
CAPRYLIC/CAPRIC/LAURIC TRIGLYCERII	1	12D - Body and Hand (exc shave)
CAPRYLIC/CAPRIC/LAURIC TRIGLYCERII	1	12E - Foot Powders and Sprays

CAPRYLIC/CAPRIC/LAURIC TRIGLYCERID	1	12F - Moisturizing
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	11	03C - Eye Shadow
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	13	03D - Eye Lotion
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	5	03G - Other Eye Makeup Preparations
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	1	04E - Other Fragrance Preparation
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	1	05G - Tonics, Dressings, and Other Hair Grooming Aids
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	1	07A - Blushers (all types)
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	2	07C - Foundations
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	7	07E - Lipstick
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	1	07F - Makeup Bases
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	1	07I - Other Makeup Preparations
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	5	10A - Bath Soaps and Detergents
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	1	11E - Shaving Cream
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	6	12A - Cleansing
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	9	12C - Face and Neck (exc shave)
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	41	12D - Body and Hand (exc shave)
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	106	12F - Moisturizing
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	8	12G - Night
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	1	12J - Other Skin Care Preps
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	7	13B - Indoor Tanning Preparations
CAPRYLIC/CAPRIC/MYRISTIC/STEARIC T	2	13C - Other Suntan Preparations
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	1	03B - Eyeliner
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	1	03D - Eye Lotion
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	1	03G - Other Eye Makeup Preparations
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	3	04E - Other Fragrance Preparation
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	3	05G - Tonics, Dressings, and Other Hair Grooming Aids
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	1	07E - Lipstick
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	2	07I - Other Makeup Preparations
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	1	10A - Bath Soaps and Detergents
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	7	12D - Body and Hand (exc shave)
CAPRYLIC/CAPRIC/STEARIC TRIGLYCER	2	12F - Moisturizing
C10-40 ISOALKYL ACID TRIGLYCERIDE	1	07E - Lipstick
C10-18 TRIGLYCERIDES	1	01B - Baby Lotions, Oils, Powders, and Creams
C10-18 TRIGLYCERIDES	1	02A - Bath Oils, Tablets, and Salts
C10-18 TRIGLYCERIDES	3	03A - Eyebrow Pencil
C10-18 TRIGLYCERIDES	12	03B - Eyeliner
C10-18 TRIGLYCERIDES	2	03C - Eye Shadow
C10-18 TRIGLYCERIDES	2	03D - Eye Lotion
C10-18 TRIGLYCERIDES	4	03G - Other Eye Makeup Preparations
C10-18 TRIGLYCERIDES	1	07A - Blushers (all types)
C10-18 TRIGLYCERIDES	1	07B - Face Powders
C10-18 TRIGLYCERIDES	1	07C - Foundations
C10-18 TRIGLYCERIDES	11	07E - Lipstick
C10-18 TRIGLYCERIDES	7	07I - Other Makeup Preparations
C10-18 TRIGLYCERIDES	1	12A - Cleansing
C10-18 TRIGLYCERIDES	12	12C - Face and Neck (exc shave)
C10-18 TRIGLYCERIDES	10	12D - Body and Hand (exc shave)
C10-18 TRIGLYCERIDES	16	12F - Moisturizing
C10-18 TRIGLYCERIDES	4	12G - Night
C10-18 TRIGLYCERIDES	1	12I - Skin Fresheners
C10-18 TRIGLYCERIDES	2	12J - Other Skin Care Preps
C10-18 TRIGLYCERIDES	1	13B - Indoor Tanning Preparations
GLYCERYL TRIBEHENATE/ISOSTEARATE	5	03B - Eyeliner

GLYCERYL TRIBEHENATE/ISOSTEARATE	1	03F - Mascara
GLYCERYL TRIBEHENATE/ISOSTEARATE	1	05A - Hair Conditioner
GLYCERYL TRIBEHENATE/ISOSTEARATE	1	05G - Tonics, Dressings, and Other Hair Grooming Aids
GLYCERYL TRIBEHENATE/ISOSTEARATE	1	12D - Body and Hand (exc shave)
GLYCERYL TRIBEHENATE/ISOSTEARATE	1	12F - Moisturizing
HYDROGENATED C12-18 TRIGLYCERIDE	1	10E - Other Personal Cleanliness Products
HYDROGENATED C12-18 TRIGLYCERIDE	1	12A - Cleansing
HYDROGENATED C12-18 TRIGLYCERIDE	4	12C - Face and Neck (exc shave)
HYDROGENATED C12-18 TRIGLYCERIDE	1	12D - Body and Hand (exc shave)
HYDROGENATED C12-18 TRIGLYCERIDE	5	12F - Moisturizing
PALMITIC/STEARIC TRIGLYCERIDE	1	01B - Baby Lotions, Oils, Powders, and Creams
PALMITIC/STEARIC TRIGLYCERIDE	2	12C - Face and Neck (exc shave)
PALMITIC/STEARIC TRIGLYCERIDE	3	12F - Moisturizing
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LINOLENIC ACID TRIGLYCERIDE	2	12C - Face and Neck (exc shave)



Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: October 6, 2017

SUBJECT: Tentative Report: Amended Safety Assessment of Triglycerides as Used in Cosmetics

Introduction, Summary - It is not appropriate to call the ingredients in the original glyceryl triester report "related" - those ingredients are ingredients in the current report.

Introduction, Table 2 - Table 2 does not include any ingredients in green. Therefore, there are not any ingredients in this report that are "found in the VCRP but not in the *Dictionary*". The following statement should be deleted from the Introduction "(except those listed only in the VCRP and not the *Dictionary*)" and the footnote under Table 2 needs to be corrected.

Non-Cosmetic Use, old report summary - Please correct "bum patients" (should be burn) and "textile sizes" (should be sizing).

Short-Term, old report summary - Please correct: "no adverse were observed".

Short-Term, new information - Please include the dose (3.12 g/kg) used in the rat study with 33% Caprylic/Capric Triglyceride.

Subchronic, new information, Summary, Table 9 - Regarding the 3-month studies of Caprylic/Capric Triglyceride in rats and dogs, it would be helpful to state that no effects were observed at the highest concentrations tested. There could be higher NOAELs if higher concentrations were tested. Please use consistent units - 50,000 ppm is 5% (or 15% is 150,000 ppm) so that the dietary concentrations used in the two studies can be compared.

Chronic, old report summary - Please include the doses of Tricaprylin used in the chronic studies.

Chronic, new information, Summary, Table 9 - There is not enough information in the text or in Table 9 to estimate the dose of Triheptanoin in the 9-month rat feeding study. The oil used contained 64% Triheptanoin and it replaced 30% or 50% of the soybean oil in the diet. If available, the amount of soybean oil included in the control diet should be stated, then the amount of Triheptanoin in the diet could be calculated.

- Developmental and Reproductive Toxicity - Please include some indication of doses used in the DART studies summarized in the first paragraph of this section.
- Genotoxicity, Irritation and Sensitization, Summary, Table 10, Table 11 - The spelling of "Triisonanoin" needs to be corrected to "Triisononanoin" in multiple places in this report.
- Carcinogenicity, old report summary - Please include the dose used in the mouse intraperitoneal injection study of Tricaprylin.
- Anti-Carcinogenicity, old report summary - Please include the dose of Trilaurin used in the initiation and promotion study.
- Irritation and Sensitization, old report summary - Please include the doses/concentrations used in the dermal irritation and sensitization studies.
- Irritation and Sensitization, new information - Please provide a reference for the LLNA of Triisononanoin.
- Summary - The first paragraph says that there are 54 ingredients in the report when there are only 51 ingredients in the report.
- Discussion - It would be helpful to mention the guinea pig maximization test on Triethylhexanoin (1% injection, 100% dermal induction, 25% challenge) in the original report as also supporting the safety of this ingredient.
- Table 2 - Rather than showing the generic triglyceride structure multiple times for the Linear, mixed chain length saturated triglycerides, and the Mixed chain triglycerides, perhaps the generic structure could be shown once with the heading and indicate that the R groups are defined in the definitions.
- Table 3 - Shea oleine, which is Triolein from shea butter, should be added to this table as it has a conclusion of safe when formulated to be non-sensitizing.
- Table 4 - The molecular weight of Triheptanoin (-25) is not correct. It should be 428.6. As there are partition coefficients other than octanol/water, the type of value included in the partition coefficient column should be stated.
- Table 5 - The range of concentrations of Caprylic/Capric Triglycerides for baby products needs to be corrected from ".2-52" to "3.2-52".
- Table 9 - The column in which the concentration of the tested material is stated is not consistent. The concentration is in the Ingredient column in the first row and in the Dose column for other studies. It should be presented in the same column for all studies. How dietary studies are handled is also not consistent. Diet is correctly listed in the Vehicle column for some dietary studies, but it says "none" for other dietary studies.
- Table 9, Reference 28 - It is not clear what is meant by "bread containing MLCT ..." was the bread baked with the various oils, or were the oils placed on bread? Baking might change the oils and affect bioavailability.
- Table 11 - The units for the EC₅₀ (%) should be stated for the LLNA of Triisononanoin.