RE-REVIEW

PEGylated Oils

CIR EXPERT PANEL MEETING

MARCH 5-6, 2012

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Scientific Writer/Analyst
Date: January 24, 2012
Subject: Re-review of PEG-30, -33, -35, -36, -40 Castor Oil and PEG-30 and -40 Hydrogenated Castor Oil

In 1997, the CIR Final Report on the safety assessment of PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil concluded that "PEG-30, -33, -35, -36, and -40 castor oil are safe for use in cosmetics at concentrations up to 50% and that PEG-30 and -40 hydrogenated castor oil are safe for use at concentrations of up to 100%."A copy of the Final Report is included with this re-review.

Current uses of these PEGylated castor oils can be found in Table 4a. The FDA's VCRP database indicates that uses have decreased for PEG-30 castor oil, PEG-40 castor oil, and PEG-30 hydrogenated castor oil, with the most significant decrease occurring with PEG-40 castor oil which now has 87 reported uses. Increases in use are reported in the remaining PEGylated castor oils from the original report, with the most significant occurring in PEG-40 hydrogenated castor oil, which now has 1883 reported uses.

Numerous newly available studies discussing the use of PEG-35 Castor Oil and PEG-40 Hydrogenated Castor Oil (trade name Cremophor EL and Cremophor RH, respectively) as surfactants in drug delivery systems have been discovered in the published literature. Because these studies tend to focus on the efficacy of the drug that is being tested, only the most recent studies that indicate any information on dermal toxicity have been included in this re-review.

Because of similarities in chemical properties and cosmetic function, the PEGylated oils listed in Table 1 could be potentially added to the safety assessment on PEG-30 et al. The cosmetic ingredients proposed to be incorporated into an expanded report include components that have been previously reviewed and concluded to be safe for use by the CIR Panel, most notably the recent safety assessments on plant-derived fatty acid oils and PEGs with an average of 4 moles of ethylene oxide or greater. The relevant related CIR safety assessments are included in this rereview package.

Table 4b presents the current product formulation data for these proposed expansion ingredients. Currently, PEG-60 hydrogenated castor oil has the most uses with a total of 362. A survey of current use concentration will be conducted by the Personal Care Products Council if the CIR Expert Panel decides to expand this safety assessment.

The task for the Panel at this meeting is to determine whether the conclusion on PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil is still valid. If it is not, an amendment should be initiated. The Panel should also decide whether or not to reopen the safety assessment to add new ingredients. If the Panel decides to open to add new ingredients, the Panel should decide if all of the ingredients listed are appropriate for this ingredient group.

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PEGylated Oils

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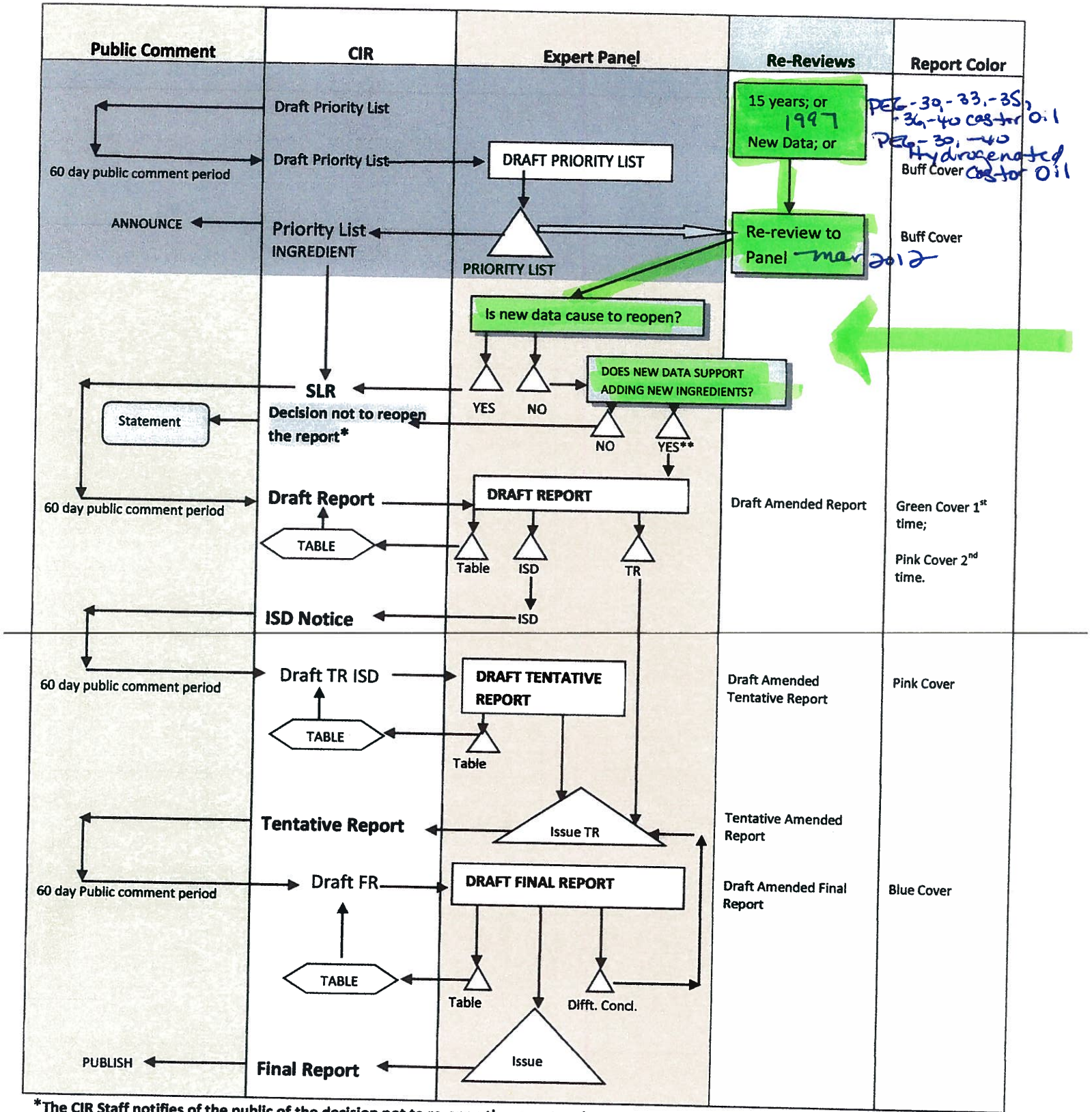
SAFETY ASSESSMENT FLOW CHART

Mar 2012



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

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

△ Expert Panel Decision

▭ Document for Panel Review

⇨ Option for Re-review

PEGylated Castor Oils History

Original Report: In 1997, the Expert Panel published the safety assessment for PEG Castor Oils with the conclusion that "PEG-30, -33, -35, -36, and -40 Castor Oil are safe for use in cosmetics at concentrations up to 50% and that PEG-30 and -40 Hydrogenated Castor Oil are safe for use at concentrations of up to 100%."

March 2012: The re-review of PEGylated Castor Oils was presented to the Panel.

SEARCH STRATEGY FOR PEGylated Castor Oils

December 2011/January 2012: SCIFINDER search for PEGylated Castor Oils- CAS NOs. 61791-12-6 and 61788-85-0 (generic), adverse effects, including toxicity

- Limited search to references published since 1995; 9 references came back.
- Limited search to books, clinical trials, journals, preprints, reports, and reviews; 9 references came back.

January 2012: SCIFINDER search for PEGylated Castor Oils – Possible expansion ingredients included, w/ generic CAS NO., adverse effects, including toxicity

- Limited search to books, clinical trials, journals, preprints, reports, and reviews; 54 references came back.

January 2012: SCIFINDER search for Cremophor, adverse effects, including toxicity

- Limited search to books, clinical trials, journals, preprints, reports, and reviews; 39 references came back.

	TOXLINE, minus PUBMED, limited to 1995-	PUBMED, limited to 1995-
61791-12-6	32	28
61788-85-0	23	28
Cremophor	59	822

Total references ordered: 23

Difficulty was experienced in searching for the expansion ingredients due to generic CAS No. (if one was available) and generic nature of ingredient names.

IF THE PANEL DECIDES TO ADD THE PROPOSED INGREDIENTS, A NEW SEARCH WILL BE PERFORMED USING TRADE NAMES.

Report

Re-Review

PEGylated Oils as Used in Cosmetics

March 5, 2012

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Christina L. Burnett, Scientific Analyst/Writer.

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INTRODUCTION

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

Since the original review, numerous additional published studies related to the noncosmetic use of PEG-35 castor oil and PEG-40 hydrogenated castor oil (trade name Cremophor EL and Cremophor RH, respectively) in drug delivery systems. A few of these studies are summarized in this re-review document.

Because of similarities in chemical properties and cosmetic function, the PEGylated oils listed in Table 1 could be potentially added to the safety assessment on PEG-30 et al. The cosmetic ingredients proposed to be incorporated into an expanded report include components that have been previously reviewed and concluded to be safe for use by the Cosmetic Ingredient Review Expert Panel, most notably the recent safety assessments on plant-derived fatty acid oils and polyethylene glycols (PEGs) with an average of 4 moles of ethylene oxide or greater. The ingredients, their conclusions, and published citations are found in Table 2.

CHEMISTRY

The definitions of the originally reviewed PEGylated castor oils and the proposed ingredients for the expansion of the safety assessment can be found in Table 3.

Just as oils and other PEGylated materials are mixtures, PEGylated Oils are mixtures. As most natural source oils are primarily triglycerides (and mono- and diglycerides) and fatty acids, PEGylated oils are primarily PEGylated glycerides, along with some PEGylated fatty acids. PEGylation of glycerides occurs not only as an etherification of the free alcohol groups of the glycerides with ethylene oxide groups, but also as a transesterification which results in net insertion of PEG groups between the glyceryl and fatty acid components of the glyceride.[2,3] For example, the primary component of castor oil, the ricinoleate triglyceride, is ethoxylated as shown in Figure 1, wherein n is equal to the number of ethylene oxide repeat units and need not be the same at all places of the molecule. It should be noted that n is not equal to X. In other words, wherein the value of X in PEG-X is equal to 2 (eg, PEG-2 Castor Oil), n is not equal to 2. Instead, X represents the number of stoichiometric equivalents of ethylene oxide that were added to one stoichiometric equivalent of castor oil. Therefore, the sum of all of the different n values in the mixture may be no more than X. Indeed, when one mole of ethylene oxide is reacted with one mole of fatty alcohol, adducts having ***no*** added ethylene oxide are the predominate material in the mixture.[2] Furthermore, wherein ethylene oxide reacts with castor oil it is approximately twice as likely that it will react at an ester site versus an alcohol site. Moreover, a percentage (13% in one specific case) of the ethylene oxide simply reacts with other molecules of ethylene oxide, resulting in some polyethylene glycols, unattached to glycerides or acid groups.

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

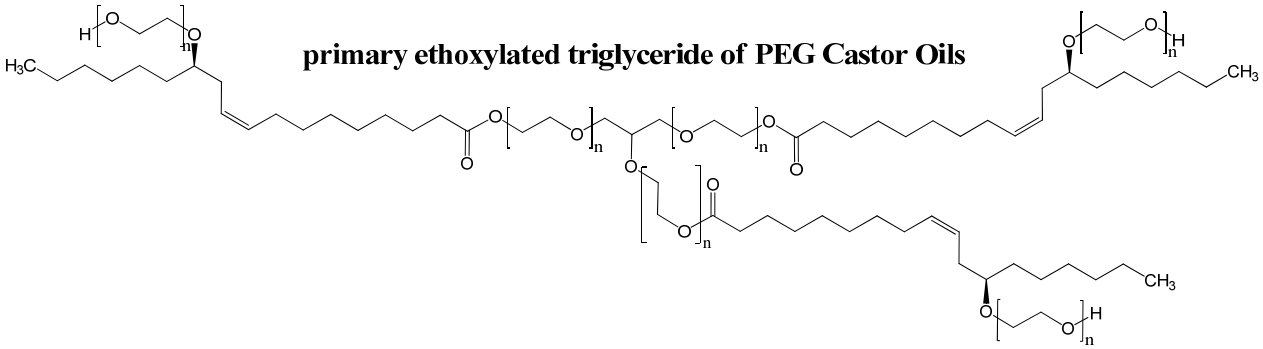

Figure 1. Glyceryl triricinoleyl polyethylene glycol

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

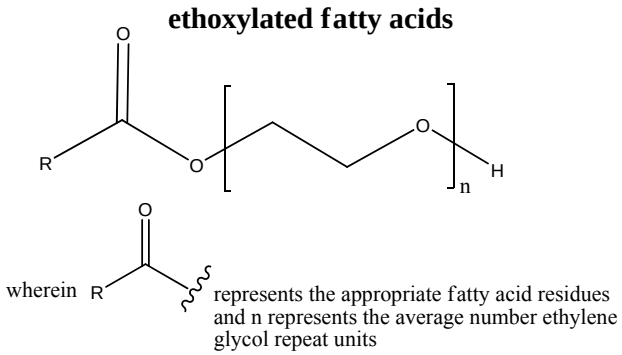

Figure 2. Fatty acid esterification

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

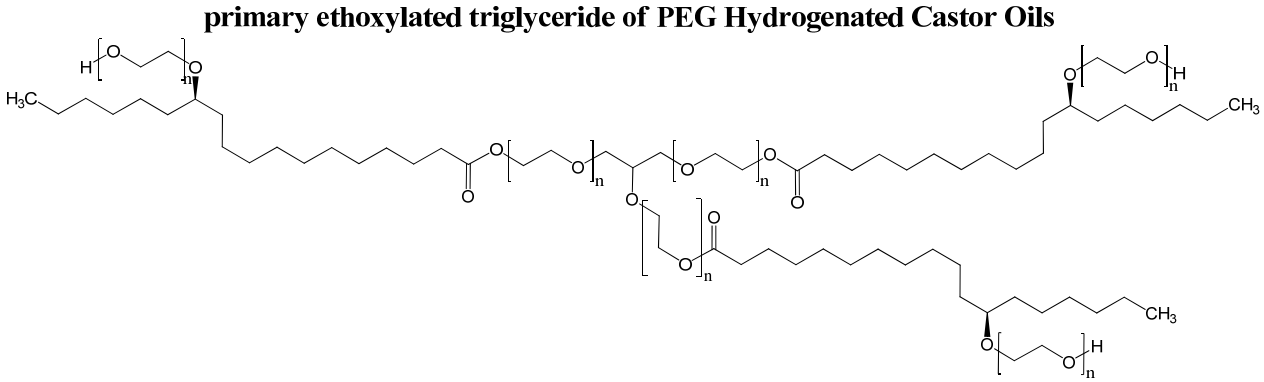

Figure 3. Glyceryl 12-hydroxystearyl polyethylene glycol

Physical and Chemical Properties

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

USE

Cosmetic

Table 4a presents the historical and current product formulation data for PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil. These PEGylated castor oils function primarily as surfactants that function as emulsifying or solubilizing agents in cosmetic formulations.[5] According to information supplied to the Food and Drug Administration (FDA) by industry 1997, PEG-40 hydrogenated castor oil had the most uses at 268, with the majority of the uses reported in leave-on products with a dermal exposure route.[1] The ingredient with the second most uses was PEG-40 castor oil with 170 uses, most in leave-on products with a dermal exposure route. An industry survey reported use concentrations for PEG-40 hydrogenated castor oil and PEG-40 castor oil of $\leq$ 10% and $\leq$ 5%, respectively. Currently, the FDA's Voluntary Cosmetic Registration Program (VCRP) database indicates that uses have decreased for PEG-30 castor oil, PEG-40 castor oil, and PEG-30 hydrogenated castor oil, with the most significant decrease occurring with PEG-40 castor oil which now has 87 reported uses.[6] Increases in use are reported in the remaining PEGylated castor oils from the original report, with the most significant occurring in PEG-40 hydrogenated castor oil, which now has 1883 reported uses. A survey of current use concentrations is currently being conducted by the Personal Care Products Council and will be provided as soon as it becomes available.

Table 4b presents the current product formulation data for the cosmetic ingredients proposed to be incorporated into an expanded report. Currently, the VCRP database indicate that of the proposed ingredients, PEG-60 hydrogenated castor oil

has the most uses of 362, with the majority in leave-on products with a dermal exposure route.[6] A survey of current use concentration will be conducted by the Personal Care Products Council if the CIR Expert Panel decides to expand this safety assessment.

The PEGylated castor oils are not restricted from use in any way under the rules governing cosmetic products in the European Union.[7]

Non-Cosmetic

PEG-30 castor oil and PEG-40 hydrogenated castor oil may be used as nonionic surfactants in oral, topical, and parenteral drug delivery systems.[3,4,8-14] PEGylated castor oil derivatives may also be used in animal feeds and textiles.[4]

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

TOXICOKINETICS

Absorption, Distribution, Metabolism, Excretion

The disposition of PEG-35 castor oil was determined in 31 cancer patients treated with a 1-h infusion of paclitaxel (87.8 mg PEG-35 castor oil per mg drug).[15] Dose levels of PEG-35 castor oil ranged from 70 to 100 mg/m^2. Plasma concentrations were measured. Clearance of PEG-35 castor oil appeared to be independent of infusion duration and the administered dose in the range studied (P =.797). Exposure measures increased in near proportion to an increase in dose. PEG-35 castor oil had a half-life and clearance of 35.7 $\pm$ 18.9 h and 0.216 $\pm$ 0.075 L/h, respectively (P < .00001). The volume of distribution at steady state was 9.48 $\pm$ 2.59 L and indicated limited distribution of the excipient outside of the central compartment. These results were compared to those of the excipient Tween 80, which had a shorter terminal half-life (0.607 $\pm$ 0.245 h) and total plasma clearance (7.70 $\pm$ 2.90 L/h). The other values were similar. The study concluded that use of PEG-35 castor oil as a formulation vehicle could result in drug interaction and excipient-related toxic side effects due to its rats of elimination.

Penetration Enhancement

A study of the development of a topical gel for treatment of acne vulgaris reports that various types of PEGS are hydrophilic penetration enhancers and are used in topical dermatological preparations.[8] The authors selected PEG-40 hydrogenated because of its properties as a very hydrophilic, non-ionic solubilizer for fat-soluble vitamins A, D, E, and K, and for its stability and clarity in alcohol solution.

TOXICOLOGICAL STUDIES

Acute Toxicity

Intravenous – Non-Human

PEG-X CASTOR OIL

Castor oil with an unspecified number of stoichiometric equivalents of ethylene oxide (just generically listed as Cremophor) that was mixed with dimethyl acetamide (DMA) was evaluated as a vehicle in a diabetes drug.[16] The mixture was composed of 23-45% DMA/10-12% Cremophor in water and the dose volume was 1.67 to 3 ml/kg. Groups of 3 New Zealand White rabbits received intravenously the test material, saline, insulin, or N-methyl-2-pyrrolidone (NMP) into the marginal ear vein. Blood was drawn just before injection and again at 0.25, 0.5, 1, 2, 4, and 24 h after injection to determine glycemia values. Glycemia after injection with the DMA/Cremophor mixture remained stable and within the normal range of 3.6 to 5.0 mmol/l. These results were comparable to the rabbits that received saline. In addition to these results, the test material did not elicit irritation at the site of injection.

PEG-60 HYDROGENATED CASTOR OIL

The toxicity of PEG-60 hydrogenated castor oil was evaluated in male and female beagle dogs, male and female cynomolgus monkeys, male New Zealand White rabbits, male Hartley guinea pigs, and male Sprague Dawley rats.[17] The test material was injected intravenously to groups of 3 dogs at 0.625, 1.25. 2.5. or 10 mg/kg; in groups of 3 monkeys or 5 rabbits at 50 or 100 mg/5 ml/kg; and in groups of 5 guinea pigs, and 5 rats at 10 or 100 mg/5 ml/kg. Blood pressure was monitored in the dogs before the injection and 10, 30, and 60 min after injection. Blood was taken in all animals to measure plasma histamine levels. In dogs, further histopathological examinations were performed on mast cells in the liver and skin. Clinical signs of toxicity were observed until 60 min after injection in all animals.

In dogs injected with 1.25, 2.5 or 10 mg/kg of the test material, blood pressure decreased and flush, swelling and itching were observed. Additionally in the 10 mg/kg dose group, a decrease in spontaneous motility was observed. An increase in histamine levels was observed in the 2.5 and 10 mg/kg dose groups. Degranulation was observed after injection in the mast cells of the skin, but not in the liver cells. No signs of toxicity were observed in monkeys, rabbits, guinea pigs or rats and there was no change in plasma histamine levels. The toxicity of PEG-60 hydrogenated castor oil may be species specific.[17]

CARCINOGENICITY

No new relevant studies were found in the published literature.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

PEG-35 CASTOR OIL

A skin irritation study of a pharmaceutical microemulsion that contained 20% w/w PEG-35 castor oil was performed in male guinea pigs (species not specified).[18] The hair on the backs of the guinea pigs was removed 24 h before treatment, and the animals were divided into a group with intact skin and a group with skin injury due to scarifying. These groups were again subdivided into single and multiple applications. There were a total of 5 guinea pigs in each subgroup. All guinea pigs received the test material and a control cream. Single application animals were treated for 24 h and the test sites were inspected for erythema and edema 1, 24, 48, and 72 h after material removal. Multiple application animals were treated for 24 h, followed by assessment for skin irritation 1 h after material removal, in a total of 7 applications. The test sites were observed for an additional 3 days after the last application. While very slight irritation was observed on average at the 1 h observation in guinea pigs treated with multiple applications with damaged skin, the average scores were still in the range that was considered to be "no irritation". No irritation was observed in any of the single application animals or in the intact skin of the multiple application animals. It was concluded that single and multiple applications of the microemulsion that contained 20% w/w PEG-35 castor oil did not cause irritation effects in guinea pigs.

PEG-40 HYDROGENTATED CASTOR OIL

A dermal irritation test was performed in mice (species and number not described) to investigate the potential irritancy microemulsion that contains 20% PEG-40 hydrogenated castor oil.[14] A single dose of 10 µl of the test microemulsion was applied to the left ear of the mouse. The right ear served as a control. The mice were observed for development of erthyma for 6 days. No signs of irritation were observed in the mice. The authors concluded that the formulation containing 20% PEG-40 hydrogenated castor oil would probably not irritate human skin.

The dermal irritancy potential of a microemulsion gel system that contained 20.66% PEG-40 hydrogenated castor oil as a surfactant was studied in male albino rats using the Draize method.[19] Animals were divided into 3 groups of 6: a negative control (no treatment), a positive control (0.8% aq. formalin), and the test formulation. The rats received a dose of 0.5 g of the formulation on a 5 cm^2 area on the shaved dorsal side daily for 3 consecutive days. Signs of erythema and edema were monitored daily for 3 days. After 3 days, the rats were killed and skin samples were taken for histopathological examination. No signs of irritation were observed in the test formulation. The controls yielded expected results. Histopathological examination found no apparent signs of skin irritation. The study concluded that the test formulation that contained 20.66% PEG-40 hydrogenated castor oil was not a skin irritant.

Ocular

PEG-35 CASTOR OIL

Several different formulations of a potential glaucoma drug in form of a nanoemulsion were tested for ocular irritation potential.[20] A few of these formulations contained PEG-35 castor oil as a surfactant. Groups of 6 New Zealand albino rabbits received test formulations that contained 0-13% PEG-35 castor oil. In each rabbit, the right eye received 50 µl of the tested formulation, while the left eye was used as a control. The rabbits received the test formulation every 2.5 h through a period of 7.5 h per day for 3 successive days and once on the fourth day. Eyes were examined according to the Draize method 1 and 24 h after the last instillation. The eyelids, cornea, iris, conjunctiva, and anterior chamber were inspected for inflammation or other toxic reactions. The eyes were then stained with fluorescein and examined under UV light to verify possible corneal lesion. A few nanoemulsion formulations that contained up to 13.5% PEG-35 castor oil were found to be non-irritating and tolerated well by the rabbit eye. Cross sections from the corneas of rabbits' eye after application of the tested formulations together with a control section showed that both corneal structure and integrity were unaffected by treatment.

CLINICAL USE

Case Studies

PEG-35 CASTOR OIL

A 40-year-old female undergoing chemotherapy treatment for breast cancer had a cutaneous lupus erythematosus-like reaction within 24 h of administration of the drug paclitaxel that contained the diluent, PEG-35 castor oil.[21] When treatment was switched to a paclitaxel that was bound with albumin, no lupus-like reactions were observed. The case study concluded that PEG-35 castor oil induced the lupus-like reaction and suggested that previously reported incidences of lupus-like reaction in chemotherapy patients was from this diluent and not from the chemotherapeutic agent.

Table 1. Proposed ingredients for PEGylated Oils report expansion.

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

* Oil component has not been previously reviewed by the CIR Expert Panel.

Table 2. Previous CIR safety assessments related to proposed expansion ingredients.

Ingredient(s)	Conclusion	Reference
Castor Oil and Hydrogenated Castor Oil	Safe for use in cosmetics in the present practices of use and concentration	IJT 16 (Suppl. 3):31-77, 2007
Plant-Derived Fatty Acid Oils	Safe for use in cosmetics in the present practices of use and concentration	CIR 2011
Polyethylene Glycols (PEGs) $\geq$ 4	Safe for use in cosmetics in the present practices of use and concentration	CIR 2010
Simmondsia Chinensis (Jojoba) Seed Oil	Safe for use in cosmetics in the present practices of use and concentration	CIR 2008
Mink Oil	Safe for use in cosmetics in the present practices of use and concentration	IJT 24 (Suppl.3):57-64, 2005

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

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

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

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

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

Ingredient CAS No.	Definition
PEG-40 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-40 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 40 moles of ethylene oxide. PEG-40 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with forty equivalents of ethylene oxide.
PEG-45 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-45 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 45 moles of ethylene oxide. PEG-45 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with forty-five equivalents of ethylene oxide.
PEG-50 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-50 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 50 moles of ethylene oxide. PEG-50 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty equivalents of ethylene oxide.
PEG-54 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-54 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 54 moles of ethylene oxide. PEG-54 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty-four equivalents of ethylene oxide.
PEG-55 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-55 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 55 moles of ethylene oxide. PEG-55 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty-five equivalents of ethylene oxide.
PEG-60 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-60 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 60 moles of ethylene oxide. PEG-60 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with sixty equivalents of ethylene oxide.
PEG-65 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-65 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 65 moles of ethylene oxide. PEG-65 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with sixty-five equivalents of ethylene oxide.
PEG-80 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-80 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 80 moles of ethylene oxide. PEG-80 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with eighty equivalents of ethylene oxide.
PEG-100 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-100 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 100 moles of ethylene oxide. PEG-100 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with one hundred equivalents of ethylene oxide.
PEG-200 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-200 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 200 moles of ethylene oxide. PEG-200 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with two hundred equivalents of ethylene oxide.
PEG-8 block added transester	
Hydrogenated Castor Oil PEG-8 Esters	Hydrogenated Castor Oil PEG-8 Esters is a product obtained by the transesterification of Hydrogenated Castor Oil and PEG-8.
PEGylated Hydrogenated Castor Oil Copolymer	
PEG-200 Hydrogenated Castor Oil/IPDI Copolymer	PEG-200 Hydrogenated Castor Oil/IPDI Copolymer is a copolymer of PEG-200 Hydrogenated Castor Oil and isophorone diisocyanate.
PEGylated Hydrogenated Castor Oil Diesters	
PEG-5 Hydrogenated Castor Oil Isostearate	PEG-5 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 5.
PEG-10 Hydrogenated Castor Oil Isostearate	PEG-10 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 10.
PEG-15 Hydrogenated Castor Oil Isostearate	PEG-15 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 15.
PEG-20 Hydrogenated Castor Oil Isostearate	PEG-20 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 20.
PEG-30 Hydrogenated Castor Oil Isostearate	PEG-30 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 30.
PEG-40 Hydrogenated Castor Oil Isostearate	PEG-40 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 40.
PEG-50 Hydrogenated Castor Oil Isostearate	PEG-50 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 50.
PEG-58 Hydrogenated Castor Oil Isostearate	PEG-58 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 58.
PEG-20 Hydrogenated Castor Oil Laurate [868047-47-6, generic to all PEG-X Hydrogenated Castor Oil]	PEG-20 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 20

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

Ingredient CAS No.	Definition
PEG-30 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-30 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 30.
PEG-40 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-40 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 40
PEG-50 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-50 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 50.
PEG-60 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-60 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 60.
PEG-20 Hydrogenated Castor Oil PCA Isostearate	PEG-20 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-20 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-30 Hydrogenated Castor Oil PCA Isostearate	PEG-30 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-30 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-40 Hydrogenated Castor Oil PCA Isostearate	PEG-40 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-40 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid
PEG-60 Hydrogenated Castor Oil PCA Isostearate	PEG-60 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-60 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-50 Hydrogenated Castor Oil Succinate	PEG-50 Hydrogenated Castor Oil Succinate is a polyethylene glycol derivative of the succinic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 50.
PEG-5 Hydrogenated Castor Oil Triisostearate [188734-82-9, generic to all PEG-X Hydrogenated Castor Oil Triisostearate]	PEG-5 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 5 moles of ethylene oxide.
PEG-10 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-10 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 10 moles of ethylene oxide.
PEG-15 Hydrogenated Castor Oil Triisostearate	PEG-15 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 15 moles of ethylene oxide.
PEG-20 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-20 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average ethoxylation value of 20.
PEG-30 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-30 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 30 moles of ethylene oxide.
PEG-40 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-40 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 40 moles of ethylene oxide.
PEG-50 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-50 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average of 50 moles of ethylene oxide.
PEG-60 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-60 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average of 60 moles of ethylene oxide.
Potassium PEG-50 Hydrogenated Castor Oil Succinate	Potassium PEG-50 Hydrogenated Castor Oil Succinate is the potassium salt of PEG-50 Hydrogenated Castor Oil Succinate.
Sodium PEG-50 Hydrogenated Castor Oil Succinate	Sodium PEG-50 Hydrogenated Castor Oil Succinate is the sodium salt of PEG-50 Hydrogenated Castor Oil Succinate.
Other PEG-X block added Oils	
Adansonia Digitata Seed Oil PEG-8 Esters	Adansonia Digitata Seed Oil PEG-8 Esters is the product obtained by the transesterification of Adansonia Digitata Seed Oil and PEG-8.
Almond Oil PEG-6 Esters	Almond Oil PEG-6 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Almond) Oil and PEG-6.
Almond Oil PEG-8 Esters	Almond Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Almond) Oil and PEG-8.
Apricot Kernel Oil PEG-6 Esters	Apricot Kernel Oil PEG-6 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-6.
Apricot Kernel Oil PEG-8 Esters	Apricot Kernel Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-8.
Apricot Kernel Oil PEG-40 Esters	Apricot Kernel Oil PEG-40 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-40.
Argan Oil PEG-8 Esters	Argan Oil PEG-8 Esters is the product obtained by the transesterification of Argania Spinosa Kernel Oil and PEG-8.
Astrocaryum Vulgare Oil PEG-8 Esters	Astrocaryum Vulgare Oil PEG-8 Esters is the product obtained by the transesterification of Astrocaryum Vulgare Kernel Oil and PEG-8.

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

Ingredient CAS No.	Definition
Avocado Oil PEG-8 Esters	Avocado Oil PEG-8 Esters is the product obtained by the transesterification of Persea Gratissima (Avocado) Oil and PEG-8.
Avocado Oil PEG-11 Esters	Avocado Oil PEG-11 Esters is the product obtained from the transesterification of Persea Gratissima (Avocado) Oil and PEG-11.
Bertholletia Excelsa Seed Oil PEG-8 Esters	Bertholletia Excelsa Seed Oil PEG-8 Esters is the product obtained from the transesterificaton of Bertholletia Excelsa Seed Oil and PEG-8.
Bitter Cherry Seed Oil PEG-8 Esters	Bitter Cherry Seed Oil PEG-8 Esters is a product obtained by the transesterification of Prunus Cerasus (Bitter Cherry) Seed Oil and PEG-8.
Borage Seed Oil PEG-8 Esters	Borage Seed Oil PEG-8 Esters is the product obtained by the transesterification of Borago Officinalis (Borage) Seed Oil and PEG-8.
Cannabis Sativa Seed Oil PEG-8 Esters	Cannabis Sativa Seed Oil PEG-8 Esters is a product obtained by the transesterification of PEG-8 and Cannabis Sativa Seed Oil.
Carapa Guaianensis Oil PEG-8 Esters	Carapa Guaianensis Oil PEG-8 Esters is the product obtained by the transesterification of Carapa Guaianensis Seed Oil and PEG-8.
Coconut Oil PEG-10 Esters	Coconut Oil PEG-10 Esters is a polyethylene glycol derivative of Cocos Nucifera (Coconut) Oil with an average of 10 moles of ethylene oxide.
Coffee Seed Oil PEG-8 Esters	Coffee Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 and Coffea Arabica (Coffee) Seed Oil.
Corn Oil PEG-6 Esters	Corn Oil PEG-6 Esters is a product obtained by the transesterification of Zea Mays (Corn) Oil and PEG-6.
Corn Oil PEG-8 Esters	Corn Oil PEG-8 Esters is a product obtained by the transesterification of Zea Mays (Corn) Oil and PEG-8.
Grape Seed Oil PEG-8 Esters	Grape Seed Oil PEG-8 Esters is the product obtained by the transesterification of Vitis Vinifera (Grape) Seed Oil and PEG-8.
Hazel Seed Oil PEG-8 Esters	Hazel Seed Oil PEG-8 Esters is the product obtained by the transesterification of Corylus Avellana (Hazel) Seed Oil and PEG-8.
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters is the product obtained by the transesterification of Hydrogenated Palm Kernel Oil, Hydrogenated Palm Oil and PEG-6.
Jojoba Oil PEG-8 Esters	Jojoba Oil PEG-8 Esters is the polyethylene glycol derivative of the acids and alcohols derived from Simmondsia Chinensis (Jojoba) Oil containing an average of 8 moles of ethylene oxide.
Jojoba Oil PEG-150 Esters	Jojoba Oil PEG-150 Esters is the polyethylene glycol derivative of the acids and alcohols derived from Simmondsia Chinensis (Jojoba) Oil containing an average of 150 moles of ethylene oxide.
Linseed Oil PEG-8 Esters	Linseed Oil PEG-8 Esters is the product obtained by the transesterification of Linum Usitatissimum (Linseed) Oil and PEG-8.
Macadamia Ternifolia Seed Oil PEG-8 Esters	Macadamia Ternifolia Seed Oil PEG-8 Esters is the product obtained by the transesterification of Macadamia Ternifolia Seed Oil and PEG-8.
Mango Seed Oil PEG-70 Esters	Mango Seed Oil PEG-70 Esters is the product obtained by the transesterification of Mangifera Indica (Mango) Seed Oil and PEG-70.
Mauritia Flexuosa Seed Oil PEG-8 Esters	Mauritia Flexuosa Seed Oil PEG-8 Esters is the product of the transesterification of PEG-8 and the oil obtained from the seeds of Mauritia flexuosa.
Mink Oil PEG-13 Esters	Mink Oil PEG-13 Esters is the product obtained by the transesterification of Mink Oil and PEG-13.
Olive Oil PEG-6 Esters	Olive Oil PEG-6 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-6.
Olive Oil PEG-7 Esters	Olive Oil PEG-7 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-7
Olive Oil PEG-8 Esters	Olive Oil PEG-8 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-8.
Olive Oil PEG-10 Esters	Olive Oil PEG-10 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-10.
Orbignya Oleifera Seed Oil PEG-8 Esters	Orbignya Oleifera Seed Oil PEG-8 Esters is the product obtained by the transesterification of Orbignya Oleifera Seed Oil and PEG-8.
Palm Oil PEG-8 Esters	Palm Oil PEG-8 Esters is the product obtained by the transesterification of Elaeis Guineensis (Palm) Oil and PEG-8.
Parinari Curatellifolia Oil PEG-8 Esters	Parinari Curatellifolia Oil PEG-8 Esters is the product obtained by the transesterification of the oil obtained from the seeds of Parinari curatellifolia with PEG-8.
Passiflora Edulis/Passiflora Incarnata Seed Oils PEG-8 Esters	Passiflora Edulis/Passiflora Incarnata Seed Oils PEG-8 Esters is a product obtained by the transesterification of a blend of Passiflora Edulis Seed Oil and Passiflora Incarnata Seed Oil with PEG-8.
Peanut Oil PEG-6 Esters	Peanut Oil PEG-6 Esters is the product obtained by the transesterification of Arachis Hypogaea (Peanut) Oil and PEG-6.
PEG-75 Crambe Abyssinica Seed Oil	PEG-75 Crambe Abyssinica Seed Oil is a polyethylene glycol derivative of Crambe Abyssinica Seed Oil with an average of 75 moles of ethylene oxide. PEG-75 Crambe Abyssinica Seed Oil is a mixture of the etherification and esterification products of crambe abyssinica seed oil glycerides and fatty acids from crambe abyssinica seed oil, with seventy-five equivalents of ethylene oxide.
PEG-75 Meadowfoam Oil	PEG-75 Meadowfoam Oil is a polyethylene glycol derivative of Limnanthes Alba (Meadowfoam) Seed Oil with an average of 75 moles of ethylene oxide. PEG-75 Meadowfoam Oil is a mixture of the etherification and esterification products of meadowfoam oil glycerides and fatty acids from meadowfoam oil, with seventy-five equivalents of ethylene oxide.
Pumpkin Seed Oil PEG-8 Esters	Pumpkin Seed Oil PEG-8 Esters is the product obtained by the transesterification of Cucurbita Pepo (Pumpkin) Seed Oil and PEG-8.
Rapeseed Oil PEG-3 Esters	Rapeseed Oil PEG-3 Esters is the product obtained by the transesterification of Brassica Campestris (Rapeseed) Oil and PEG-3.

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

Ingredient CAS No.	Definition
Rapeseed Oil PEG-20 Esters	Rapeseed Oil PEG-20 Esters is the product obtained by the transesterification of Brassica Campestris (Rapeseed) Oil and PEG-20.
Raspberry Seed Oil PEG-8 Esters	Raspberry Seed Oil PEG-8 Esters is the product obtained by the transesterification of Rubus Idaeus (Raspberry) Seed Oil and PEG-8.
Rosa Rubiginosa Seed Oil PEG-8 Esters	Rosa Rubiginosa Seed Oil PEG-8 Esters is the product obtained by the transesterification of Rosa Rubiginosa Seed Oiland PEG-8.
Safflower Seed Oil PEG-8 Esters	Safflower Seed Oil PEG-8 Esters is the product obtained by the transesterification of Carthamus Tinctorius (Safflower) Seed Oil and PEG-8.
Schinziophyton Rautanenii Kernel Oil PEG-8 Esters	Schinziophyton Rautanenii Kernel Oil PEG-8 Esters is the product obtained by the transesterification of Schinziophyton Rautanenii Kernel Oil and PEG-8.
Sclerocarya Birrea Seed Oil PEG-8 Esters	Sclerocarya Birrea Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Sclerocarya Birrea Seed Oil.
Sesame Seed Oil PEG-8 Esters	Sesame Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Sesamum Indicum Seed Oil.
Soybean Oil PEG-8 Esters	Soybean Oil PEG-8 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-8.
Soybean Oil PEG-20 Esters	Soybean Oil PEG-20 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-20
Soybean Oil PEG-36 Esters	Soybean Oil PEG-36 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-36.
Sunflower Seed Oil PEG-8 Esters	Sunflower Seed Oil PEG-8 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and PEG-8.
Sunflower Seed Oil PEG-32 Esters	Sunflower Seed Oil PEG-32 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and PEG-32.
Sweet Almond Oil PEG-8 Esters	Sweet Almond Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Amygdalus (Sweet Almond) Oil and PEG-6.
Trichilia Emetica Seed Oil PEG-8 Esters	Trichilia Emetica Seed Oil PEG-8 Esters is the product obtained by the transesterification of Trichilia Emetica Seed Butter and PEG-8.
Watermelon Seed Oil PEG-8 Esters	Watermelon Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Citrillus Lanatus (Watermelon) Seed Oil.
Wheat Germ Oil PEG-40 Butyloctanol Esters	Watermelon Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Citrillus Lanatus (Watermelon) Seed Oil.
Wheat Germ Oil PEG-8 Esters	Wheat Germ Oil PEG-8 Esters is the product obtained by the transesterificaton of Triticum Vulgare (Wheat) Germ Oil and PEG-8.
Ximenia Americana Seed Oil PEG-8 Esters	Ximenia Americana Seed Oil PEG-8 Esters is the product obtained by the transesterification of Ximenia Americana Seed Oil and PEG-8.

Table 4a. Historical and current use and concentration of use data for PEG-30, -33, -35, -36, -40 Castor Oil and PEG-30 and-40 Hydrogenated Castor Oil.[1,6]

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	PEG-30 Castor Oil				PEG-33 Castor Oil				PEG-35 Castor Oil			
Data Year	**1997**	**2011**	**1997**	**2012**	**1997**	**2011**	**1997**	**2012**	**1997**	**2011**	**1997**	**2012**
Totals*	**77[a]**	**1**	**≥ 50[b]**		**13**	**53**	**NR**		**4**	**33**	**NR**	
Duration of Use												
Leave-On	NR	NR	[b]		10	43	NR		4	18	NR	
Rinse-Off	73	1	[b]		3	10	NR		NR	14	NR	
Diluted for (Bath) Use	NR	NR	[b]		NR	NR	NR		NR	1	NR	
Exposure Type												
Eye Area	NR	NR	[b]		NR	2	NR		NR	2	NR	
Incidental Ingestion	NR	NR	[b]		NR	NR	NR		NR	NR	NR	
Incidental Inhalation-Spray	NR	NR	[b]		NR	NR	NR		1	1	NR	
Incidental Inhalation-Powder	NR	NR	[b]		NR	NR	NR		NR	NR	NR	
Dermal Contact	1	NR	[b]		8	47	NR		3	22	NR	
Deodorant (underarm)	NR	NR	[b]		NR	NR	NR		NR	NR	NR	
Hair - Non-Coloring	NR	1	[b]		5	6	NR		1	11	NR	
Hair-Coloring	72	NR	[b]		NR	NR	NR		NR	NR	NR	
Nail	NR	NR	[b]		NR	NR	NR		NR	NR	NR	
Mucous Membrane	NR	NR	[b]		NR	NR	NR		NR	2	NR	
Baby Products	NR	NR	[b]		NR	NR	NR		NR	NR	NR	

	PEG-36 Castor Oil				PEG-40 Castor Oil				PEG-30 Hydrogenated Castor Oil			
Data Year	**1997**	**2011**	**1997**	**2012**	**1997**	**2011**	**1997**	**2012**	**1997**	**2011**	**1997**	**2012**
Totals*	**3**	**4**	**NR**		**170[c]**	**87**	**≤ 10[b]**		**5**	**1**	**≤ 0.1[b]**	
Duration of Use												
Leave-On	3	4	NR		60	58	[b]		2	1	[b]	
Rinse Off	NR	NR	NR		46	29	[b]		3	NR	[b]	
Diluted for (Bath) Use	NR	NR	NR		1	NR	[b]		NR	NR	[b]	
Exposure Type												
Eye Area	NR	NR	NR		1	2	[b]		NR	NR	[b]	
Incidental Ingestion	NR	NR	NR		NR	NR	[b]		NR	NR	[b]	
Incidental Inhalation-Spray	NR	NR	NR		7	1	[b]		1	1	[b]	
Incidental Inhalation-Powder	NR	NR	NR		NR	NR	[b]		NR	NR	[b]	
Dermal Contact	3	4	NR		74	58	[b]		5	1	[b]	
Deodorant (underarm)	NR	NR	NR		NR	NR	[b]		1	NR	[b]	
Hair - Non-Coloring	NR	NR	NR		33	26	[b]		NR	NR	[b]	
Hair-Coloring	NR	NR	NR		NR	2	[b]		NR	NR	[b]	
Nail	NR	NR	NR		NR	1	[b]		NR	NR	[b]	
Mucous Membrane	NR	NR	NR		2	6	[b]		NR	NR	[b]	
Baby Products	NR	NR	NR		NR	NR	[b]		NR	NR	[b]	

	PEG-40 Hydrogenated Castor Oil			
	1997	**2011**	**1997**	**2012**
Totals*	**268[d]**	**1883**	**≤ 5[b]**	
Duration of Use				
Leave-On	186	1207	[b]	
Rinse-Off	50	644	[b]	
Diluted for (Bath) Use	20	32	[b]	
Exposure Type				
Eye Area	9	48	[b]	
Incidental Ingestion	NR	5	[b]	
Incidental Inhalation-Spray	31	262	[b]	
Incidental Inhalation-Powder	3	3	[b]	
Dermal Contact	197	1307	[b]	
Deodorant (underarm)	2	28	[b]	
Hair - Non-Coloring	54	480	[b]	
Hair-Coloring	2	78	[b]	
Nail	NR	3	[b]	
Mucous Membrane	30	319	[b]	
Baby Products	1	18	[b]	

NR = Not reported

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

b Breakdown not available.

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

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

Table 4b. Frequency and concentration of use according to duration and type of exposure for proposed expansion of PEGylated Oils.[6]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	PEG-9 Castor Oil		**PEG-50 Castor Oil**		**PEG-100 Castor Oil**	
Totals*	**1**		**2**		**1**	
Duration of Use						
Leave-On	1		2		1	
Rinse-Off	NR		NR		NR	
Diluted for (Bath) Use	NR		NR		NR	
Exposure Type						
Eye Area	NR		NR		NR	
Incidental Ingestion	NR		NR		NR	
Incidental Inhalation-Spray	1		NR		NR	
Incidental Inhalation-Powder	NR		NR		NR	
Dermal Contact	NR		2		1	
Deodorant (underarm)	NR		NR		NR	
Hair - Non-Coloring	1		NR		NR	
Hair-Coloring	NR		NR		NR	
Nail	NR		NR		NR	
Mucous Membrane	NR		NR		NR	
Baby Products	NR		NR		NR	

	PEG-2 Hydrogenated Castor Oil	**PEG-7 Hydrogenated Castor Oil**	**PEG-10 Hydrogenated Castor Oil**
Totals*	**5**	**13**	**4**
Duration of Use			
Leave-On	5	11	4
Rinse Off	NR	2	NR
Diluted for (Bath) Use	NR	NR	NR
Exposure Type			
Eye Area	5	NR	NR
Incidental Ingestion	NR	NR	NR
Incidental Inhalation-Spray	NR	4	NR
Incidental Inhalation-Powder	NR	NR	NR
Dermal Contact	NR	11	3
Deodorant (underarm)	NR	NR	NR
Hair - Non-Coloring	NR	2	1
Hair-Coloring	NR	NR	NR
Nail	NR	NR	NR
Mucous Membrane	NR	2	NR
Baby Products	NR	NR	NR

	PEG-20 Hydrogenated Castor Oil	**PEG-25 Hydrogenated Castor Oil**	**PEG-45 Hydrogenated Castor Oil**
Totals*	**11**	**35**	**1**
Duration of Use			
Leave-On	10	31	NR
Rinse-Off	1	4	1
Diluted for (Bath) Use	NR	NR	NR
Exposure Type			
Eye Area	NR	NR	NR
Incidental Ingestion	NR	NR	NR
Incidental Inhalation-Spray	NR	4	NR
Incidental Inhalation-Powder	NR	NR	NR
Dermal Contact	11	14	NR
Deodorant (underarm)	NR	NR	NR
Hair - Non-Coloring	NR	21	1
Hair-Coloring	NR	NR	NR
Nail	NR	NR	NR
Mucous Membrane	NR	3	NR
Baby Products	NR	NR	NR

Table 4b. Frequency and concentration of use according to duration and type of exposure for proposed expansion of PEGylated Oils.[6]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	PEG-60 Hydrogenated Castor Oil		**PEG-80 Hydrogenated Castor Oil**		**PEG-20 Hydrogenated Castor Oil Trisostearate**	
Totals	**362**		**3**		**3**	
Duration of Use						
Leave-On	263		3		3	
Rinse Off	95		NR		NR	
Diluted for (Bath) Use	4		NR		NR	
Exposure Type						
Eye Area	6		NR		3	
Incidental Ingestion	2		NR		NR	
Incidental Inhalation-Spray	13		NR		NR	
Incidental Inhalation-Aerosol	5		NR		NR	
Dermal Contact	314		3		NR	
Deodorant (underarm)	2		NR		NR	
Hair - Non-Coloring	45		NR		NR	
Hair-Coloring	NR		NR		NR	
Nail	NR		NR		NR	
Mucous Membrane	30		NR		NR	
Baby Products	1		NR		NR	

	PEG-40 Hydrogenated Castor Oil PCA Isostearate	**Apricot Kernel Oil PEG-6 Esters**	**Coconut Oil PEG-10 Esters**
Totals*	**2**	**23**	**8**
Duration of Use			
Leave-On	1	22	2
Rinse-Off	1	NR	6
Diluted for (Bath) Use	NR	1	NR
Exposure Type			
Eye Area	NR	3	NR
Incidental Ingestion	NR	4	NR
Incidental Inhalation-Spray	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR
Dermal Contact	1	19	2
Deodorant (underarm)	NR	NR	NR
Hair - Non-Coloring	1	NR	6
Hair-Coloring	NR	NR	NR
Nail	NR	NR	NR
Mucous Membrane	NR	5	NR
Baby Products	NR	NR	NR

	Grape Seed Oil PEG-8 Esters	**Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters**	**Jojoba Oil PEG-8 Esters**
Totals*	**16**	**5**	**40**
Duration of Use			
Leave-On	9	5	26
Rinse-Off	7	NR	7
Diluted for (Bath) Use	NR	NR	7
Exposure Type			
Eye Area	NR	1	NR
Incidental Ingestion	NR	NR	NR
Incidental Inhalation-Spray	1	NR	NR
Incidental Inhalation-Powder	NR	NR	1
Dermal Contact	16	5	34
Deodorant (underarm)	NR	NR	NR
Hair - Non-Coloring	NR	NR	6
Hair-Coloring	NR	NR	NR
Nail	NR	NR	NR
Mucous Membrane	5	NR	7
Baby Products	NR	NR	3

Table 4b. Frequency and concentration of use according to duration and type of exposure for proposed expansion of PEGylated Oils.[6]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Olive Oil PEG-7 Esters		**PEG-75 Meadowfoam Oil**			
Totals*	**85**		**1**			
Duration of Use						
Leave-On	39		1			
Rinse-Off	46		NR			
Diluted for (Bath) Use	NR		NR			
Exposure Type						
Eye Area	NR		NR			
Incidental Ingestion	NR		NR			
Incidental Inhalation-Spray	2		NR			
Incidental Inhalation-Powder	NR		NR			
Dermal Contact	65		NR			
Deodorant (underarm)	1		NR			
Hair - Non-Coloring	20		1			
Hair-Coloring	NR		NR			
Nail	NR		NR			
Mucous Membrane	22		NR			
Baby Products	1		NR			

NR = Not reported

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Data

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FINAL REPORT ON THE SAFETY ASSESSMENT OF PEG-30, -33, -35, -36, AND -40 CASTOR OIL AND PEG-30 AND -40 HYDROGENATED CASTOR OIL[1]

PEG Castor Oils and PEG Hydrogenated Castor Oils are a family of polyethylene glycol derivatives of castor oil and hydrogenated castor oil that are used in over 500 formulations representing a wide variety of cosmetic products. They are used as skin conditioning agents and as surfactants (emulsifying and/or solubilizing agents). The PEG Castor Oils and PEG Hydrogenated Castor Oils include various chain lengths, depending on the quantity of ethylene oxide used in synthesis. Although not all polymer lengths have been studied, it is considered acceptable to extrapolate the results of the few that have been studied to all ingredients in the family. Because a principal noncosmetic use of PEG Castor Oils is as solvents for intravenous drugs, clinical data are available that indicate intravenous exposure can result in cardiovascular changes. Results from animal studies indicate very high LD_{50} values, with some evidence of acute nephrotoxicity in rats but not in rabbits. Short-term studies with intravenous exposure produced some evidence of toxicity in dogs but not in rabbits. Intramusuclar injection produced no toxicity in several species, including dogs. Subchronic oral studies also were negative. No dermal or ocular irritation was observed in studies in rabbits. Irritation was seen during induction, but no sensitization was found on challenge in guinea-pig studies using up to 50% PEG-35 Castor Oil; however, this ingredient was found to be a potent adjuvant in guinea pigs and mice. No evidence of developmental toxicity was seen in mice and rat feeding studies. These ingredients, tested as vehicle controls, produced no mutagenic or carcinogenic effect. Clinical data are generally negative for irritation and sensitization, although some anaphylactoid reactions have been seen in studies of intravenous drugs in which PEG-35 Castor Oil was used as the vehicle. Because the maximum concentration used in animal sensitization studies was 50% for PEG Castor Oils and 100% for PEG Hydrogenated Castor Oils, it was concluded that PEG Castor Oils are safe for use in cosmetic formulations up to a concentration of 50% and that PEG Hydrogenated Castor Oils are safe as used in cosmetic formulations.

PEG-30, -33, -35, -36, and -40 Castor Oil and PEG-30 and -40 Hydrogenated Castor Oil are polyethylene glycol derivatives of castor

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel.

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oil (q.v.) and hydrogenated castor oil (q.v.) that are used in a variety of cosmetic products. This report reviews the safety data on these ingredients.

CHEMISTRY

Definition and Structure

PEG-30, -33, -35, -36, and -40 Castor Oil (generic CAS No. 61791-12-6) and PEG-30 and -40 Hydrogenated Castor Oil (generic CAS No. 61788-85-0) are polyethylene glycol derivatives of castor oil (q.v.) and hydrogenated castor oil (q.v.). The number associated with the name of the compound represents the average number of moles of ethylene oxide consumed in the reaction to form the compound. Other respective chemical names for the castor oil and hydrogenated castor oil compounds include (X = the number of moles of ethylene oxide) Polyethylene Glycol X Castor Oil; Polyethylene Glycol X Hydrogenated Castor Oil; Polyethylene Glycol X; and Polyethylene Glycol X Hydrogenated Castor Oil (Wenninger and McEwen, 1995a).

Chemical and Physical Properties

Because castor oil is a triglyceride containing approximately 87% ricinoleic acid, 7% oleic acid, 3% linoleic acid, 2% palmitic acid, 1% stearic acid, and a trace of dihydroxysteric acid (Budavari, 1989), PEG Castor Oils are predominantly glyceryl triricinoleyl polyethylene glycol and PEG Hydrogenated Castor Oils are predominantly tri-12-hydroxylstearyl polyethylene glycol.

PEG-36 Castor Oil is a light yellow and slightly viscous liquid with a mild fatty odor. It has a specific gravity of 1.05 to 1.06 at 25°/25°C and is soluble in water. A 1% aqueous (aq) solution of this ingredient has a pH range of 7.0 to 8.0 (Nikitakis and McEwen, 1990). PEG-40 Castor Oil is a nonionic amber colored liquid that is miscible in water and aqueous buffer solution. It has a density of 1057.0 kg^{-3}, a viscosity of 450 cps at 20°C, and a melting point of approximately 10°C. Over a concentration range of 0.0005% to 1.0% (w/v), the pH of PEG-40 Castor Oil aq is 5.0 to 6.0 (Yalabik-Kas et al., 1982).

Spectral Data

The ultraviolet spectra of PEG-40 Castor Oil has a maximum peak at 234 to 236 nm (Yalabik-Kas et al., 1982).

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Method of Manufacture

In general, PEG Castor Oils are made by reacting ethylene oxide with castor oil. The number (X) in the name of the compound refers to the molar ratio (X:1) of ethylene oxide to castor oil (Au et al., 1991).

USE

Cosmetic

The PEG Castor Oils and PEG Hydrogenated Castor Oils are used as skin-conditioning agents and as surfactants that function as emulsifying or solubilizing agents in cosmetic formulations (Wenninger and McEwen, 1995b). The product formulation data submitted to the Food and Drug Administration (FDA) in 1995 are listed in Tables 1 and 2 (FDA, 1995). Collectively, these ingredients are used in more than 500 cosmetic products. Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). Product formulation data submitted to the FDA in 1984 stated, however, that PEG-30 Castor Oil was used at concentrations of up to 50% and more and that PEG-40 Castor Oil was used at concentrations of up to 10%. PEG-30 Hydrogenated Castor Oil was used at concentrations of up to 0.1%, and PEG-40 Castor Oil was used at concentrations of up to 5% (FDA, 1984).

Noncosmetic

In the pharmaceutical industry, PEG-35 Castor Oil is used as an emulsifier and solubilizer in pharmaceuticals containing volatile oils, fat-soluble vitamins, diazepam, propanidid, alfaxolone/alfadolone acetate, miconazole, methotrimeprazine, thiopental, and glycerin suppositories (Smolinske, 1992).

BIOLOGY

Cell Function

Nässberger (1990) reported that PEG-35 Castor Oil (diluted 1:1) decreased the spontaneous production of adenosine triphosphate (ATP) in isolated rat kidney mitochondria by 4%. At greater dilutions no such effect was observed. During oxidative phosphorylation, PEG-35 Castor Oil inhibited ATP production by 9.0% to 36.9% at dilutions of 1:160 to 1:1. A dilution of 1:640 caused only minimal inhibition.

PEG-35 Castor Oil selectively inhibited the activation of protein kinase C (PKC) at submicromolar concentrations in vitro. In a study

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with PKC isolated from human leukemia ML-1 cells, PEG-35 Castor Oil interacted with the main enzyme activator of PKC, diacylglycerol, and prevented the enzyme from binding to and activating PKC. These inhibitory effects were not observed with studies of other polyoxyethylated nonionic solvents, which the investigators believed ruled out the possibility that PEG-35 Castor Oil acted by virtue of a detergent effect (Zhao et al., 1989).

The inhibitory effects of PEG-35 Castor Oil on PKC activity were tested further using 12-*o*-tetradecanolyphorbol-13-acetate (TPA), which mimicked the effects of intracellular diacylglycerol in activating PKC and inducing phosphorylation of cellular proteins. When added

Table 1. Cosmetic product formulation data on the PEG Castor Oil Family

Castor Oil	Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-30 Castor Oil	Hair dyes and colors (all types requiring caution statements and patch tests)	1437	72
	Cleansing	771	1
	Listing under		4
	1995 Total		***77***
PEG-33 Castor Oil	Hair conditioners	624	1
	Shampoos (noncoloring)	916	2
	Tonics, dressings, and other hair-grooming aids	624	1
	Other hair preparations	382	1
	Other skin-care preparations	782	8
	1995 Total		***13***
PEG-35 Castor Oil	Tonics, dressings, and other hair-grooming aids	624	1
	Face and neck (excluding shaving preparations	261	1
	Skin fresheners	228	1
	Indoor tanning preparations	62	1
	1995 Total		***4***
PEG-36 Castor Oil	Body and hand (excluding shaving)	987	1
	Other skin-care preparations	782	2
	1995 Total		***3***

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Table 1. Cosmetic product formulation data on the PEG Castor Oil Family (*continued*)

Castor Oil	Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-40 Castor Oil	Other bath preparations	144	1
	Eye makeup remover	89	1
	Other fragrance preparations	158	1
	Hair conditioners	693	8
	Hair sprays (aerosol fixatives)	348	2
	Permanent waves	423	10
	Tonics, dressings, and other hair-grooming aids	624	6
	Wave sets	104	3
	Other hair preparations	382	4
	Bath soaps and detergents	339	1
	Cleansing	771	15
	Face and neck (excluding shaving preparations)	261	3
	Body and hand (excluding shaving preparations	987	10
	Moisturizing	873	8
	Night	220	2
	Paste masks (mud packs)	276	8
	Skin fresheners	228	2
	Other skin-care preparations	782	18
	Suntan gels, creams, and liquids	196	2
	Indoor tanning preparations	62	2
	Listing under trade name of mixtures		63
	1995 Total		***170***

Source. FDA (1995).

extracellularly to human myeloblast ML-1 cells, PEG-35 Castor Oil greatly reduced the phosphorylation of proteins induced by TPA. It also inhibited the growth of ML-1 cells dose dependently but had no effect on TPA-induced cell differentiation. Because PKC is involved with cellular regulation, the researchers suggested that inhibition of PKC by PEG-35 Castor Oil may alter cellular functions (Chuang et al., 1991).

PEG-35 Castor Oil also affects the physiologic functioning of renal proximal tubule cells. Primary proximal tubule cells from the kidneys of New Zealand White rabbits were cultured to retain the functional polarity of the proximal tubule, and the effects of 156, 391, and 782

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Table 2. Cosmetic product formulation data on the PEG Hydrogenated Castor Oils

Castor oil	Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-30 Hydrogenated Castor Oil	Deodarants (underarm)	293	1
	Shaving cream	152	1
	Cleansing	771	2
	Moisturizing	873	1
	1995 Total		***5***
PEG-40 Hydrogenated Castor Oils	Other baby products	30	1
	Bubble baths	204	2
	Other bath preparations	144	18
	Eye shadow	597	3
	Eye makeup remover	89	1
	Mascara	211	3
	Other eye makeup preparations	130	2
	Colognes and toilet waters	776	18
	Other fragarance preparations	158	2
	Hair conditioners	693	1
	Hair sprays (aerosol fixatives)	348	3
	Shampoos (noncoloring)	916	2
	Tonics, dressings, and other hair-grooming aaids	624	31
	Wave sets	104	6
	Other hair preparations	382	11
	Hair bleaches	112	2
	Blushers (all types)	283	1
	Face powders	305	3
	Foundations	333	1
	Makeup bases	159	1
	Bath soaps and detergents	339	3
	Deodorants (underarm)	293	2
	Other personal cleanliness products	317	7
	Aftershave lotion	236	22
	Other shaving preparation products	60	4
	Cleansing	771	19
	Face and neck (excluding shaving preparations)	261	3

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Table 2. Cosmetic product formulation data on the PEG Hydrogenated Castor Oils (*continued*)

Castor oil	Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-40 Hydrogenated Castor oils	Body and hand (excluding shaving preparations)	987	32
	Moisturizing	873	9
	Paste masks (mud packs)	276	5
	Skin fresheners	228	11
	Other skin-care preparations	782	21
	Suntan gels, creams, and liquids	196	2
	Indoor tanning preparations	62	3
	Other suntan preparations	62	1
	Listing under trade name		11
	1995 Total		***268***

Source. FDA (1995).

μg/mL PEG-35 Castor Oil on the capacity of these cells to generate a pH gradient was determined. PEG-35 Castor Oil significantly inhibited the development of a pH gradient after 24 h and essentially eliminated it by 72 h. This effect was reversible. A decrease of 15% also occurred in cell viability following 72 h of exposure to 782 μg/mL PEG-35 Castor Oil. The investigators concluded that PEG-35 Castor Oil affected the capacity of rabbit primary proximal tubular cell cultures to carry out a characteristic physiologic function and proposed that the toxicity of the compound itself may contribute to nephrotoxicity observed with cyclosporine A, the drug for which it is a vehicle (Sokol et al., 1990).

PEG-35 Castor Oil also has been reported to affect neurites in vitro. In cultures of differentiating N1E.115 neuroblastoma cells treated with 0.005% PEG-35 Castor Oil, neurite outgrowth was inhibited 50% in serum-free medium. Surviving neurites were shorter in length and were disfigured. Deficits in rapid axonal transport also were detected. The investigators concluded that PEG-35 Castor Oil "impairs neurite outgrowth and disrupts organellar motility in a fashion that might account for neuropathologic effects *in vivo*" (Brat et al., 1992).

The effect of PEG-40 Hydrogenated Castor Oil on epithelial integrity was investigated using monolayers of human intestinal epithelial cells. Specifically, intracellular enzyme activity and morphology were studied, and cell monolayer permeability was determined by measuring the transport of marker molecules and by measuring transepithelial electrical resistance. At concentrations of 0.010

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to 7.1 mM, PEG-40 Hydrogenated Castor Oil had no effect on permeability; however, it caused a dose-dependent decrease in dehydrogenase activity, and, at a concentration of 7.1 mM, it caused alterations in a monolayer morphology (Anderberg et al., 1992).

Cytotoxicity

The toxicity of PEG-30 Castor Oil to hepatocytes was investigated by O'Hara et al. (1989). Hepatocytes isolated from male CD rats were treated with 0.063% to 1.0% PEG-30 Castor Oil for 5 h. Cell injury was measured by intracellular K^+, and cell death was measured by lactate dehydrogenase leakage. Cell injury and leakage were observed at concentrations between 0.25% and 1.0% after 5 h. The maximum no-effect concentration was 0.125%.

PEG-35 Castor Oil was cytotoxic to the porcine renal epithelial cell line LLC-PK_1. Using electron and fluorescence microscopy, a reduction in cell adherence at concentrations between 0.01% and 0.1% and alterations in intracellular morphology at lower concentrations were observed. The investigators stated, "This finding supports suggestions based on clinical experience that [PEG-35 Castor Oil] may be responsible for a part of the nephrotoxic effects associated with cyclosporin A treatment" (Nässberger et al., 1991).

Hemodynamic Effects

In Vitro

In a study by Board (1993), PEG-35 Castor Oil inhibited the transport of 2,4-dinitrophenyl glutathione (GSDNP) out of intact human erythrocytes. Approximately 20% of the total transport activity was not inhibited, which the investigators suggested was caused by the inhibitory effect differentiating between glutathione transporters. No hemolysis occurred at concentrations of up to 10% (v/v), the maximum concentration tested. Inhibition was not caused by a depletion of intracellular ATP because studies using a 1:1000 dilution of PEG-35 Castor Oil did not change the intracellular ATP concentrations.

Kongshaug et al. (1991) studied the interaction of PEG-35 Castor Oil with human plasma lipoproteins and nonlipoproteins using ultracentrifugation. They found that at concentrations of 1 to 3 mg/mL PEG-35 Castor Oil associates substantially with low-density lipoproteins; however, such an association was not observed at concentrations between 12 and 116 mg/mL. PEG-35 Castor Oil has a destructive effect on high-density lipoproteins, which was observable at all concentrations tested but was particularly severe at concentrations of 3.6 mg/mL or more PEG-35 Castor Oil. PEG-35 Castor Oil had no observable effect on human serum albumin or other heavy proteins.

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The effect of PEG-35 Castor Oil on endothelial function and vascular smooth muscle was investigated using isolated rat hearts. Hearts from AO/Olac rats were perfused using a modified Langendorf preparation (Langendorf, 1935). Groups of eight hearts were perfused with 50, 100, 500, and 1000 ng/mL PEG-35 Castor Oil, and basal coronary flow during perfusion was determined. Each heart was perfused separately with 5-hydroxytryptamine (5-HT) and nitroglycerine (GTN), and coronary flow was monitored to determine the effects of PEG-35 Castor Oil on changes induced by these vasodilators. A control group of hearts was perfused with buffer only, followed by perfusion with the two vasodilators.

At a dose of 50 ng/mL, PEG-35 Castor Oil caused a slight decrease in coronary flow, which was similar to that observed with the control experiment. At greater concentrations, however, PEG-35 Castor Oil caused dose-dependent coronary vasodilation. The greatest increase observed was a 24.8% increase in flow with 1000 ng/mL PEG-35 Castor Oil. No change occurred in the vasodilatory response to 5-HT and GTN in the control experiment; however, in the experiments with 500 and 1000 ng/mL PEG-35 Castor Oil, a significant reduction occurred in the 5-HT response, but no appreciable change occurred in the GTN response. The researchers concluded that PEG-35 Castor Oil caused endothelial dysfunction (Mankad et al., 1992).

In Vivo

The effect of PEG-35 Castor Oil on blood flow to various organs was studied using dogs. A group of five dogs was anesthetized and intravenously injected with 2 mL of a solution containing 1 g/mL PEG-35 Castor Oil over a 90-min period. Cardiac output; mean arterial pressure; and renal, hepatic, and pancreatic blood flow were monitored. A control group of five dogs also was anesthetized but received no infusions. Statistically significant changes were observed in the cardiac output, mean arterial pressure, and hepatic blood flow of the treated group compared with the control group. Curves for cardiac output and mean arterial blood pressure over the 90-min infusion period indicated a marked decrease immediately following the infusion of a few milliliters of PEG-35 Castor Oil, followed by a recovery toward baseline and then another rapid fall with time. A precipitous decline in hepatic blood flow occurred, which returned to baseline rate after approximately 60 min. In the control group, cardiac output, mean arterial blood pressure, and hepatic blood flow were relatively stable. The curve for pancreatic blood flow was similar to the bimodal pattern seen with cardiac output and mean arterial blood flow. The difference between this curve and that of the control group approached, but did not reach, statistical significance. A rapid linear decline occurred in renal blood flow over time in the PEG-35 Castor Oil–treated group, but this decline was not sta-

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tistically different from that observed with the control group (Bowers et al., 1991).

In a study with different types of species, PEG-35 Castor Oil depressed the blood pressure of dogs and cats, but not of rabbits, following intravenous administration at concentrations of 30 to 100 mg/kg and 100 mg/kg, respectively. The depressant effects observed with the dogs and cats was thought to be of allergic nature (BASF, no date, a).

Histamine Release

In in vitro studies with rat peritoneal mast cells, PEG-35 Castor Oil alone did not stimulate histamine release (Ennis et al., 1985). When administered in conjunction with histamine-releasing agents, however, PEG-35 Castor Oil potentiated the release of histamine with some agents but inhibited the release with others (Ennis et al., 1986).

PEG-30 Castor Oil (Constantine and Lebel, 1979) and PEG-35 Castor Oil (Lorenz et al., 1977; Lorenz et al., 1982; Ennis et al., 1985) caused histamine release and severe hypotension when administered intravenously to dogs. Oxethylated oleic acid was the most effective constituent of PEG-35 Castor Oil (Lorenz et al., 1977). In studies with miniature pigs, PEG-35 Castor Oil was also a histamine releaser, but only after a second exposure to the compound. In addition, hypertension, as opposed to hypotension, was observed (Glen et al., 1979). Although PEG-35 Castor Oil alone did not cause histamine release in studies with humans (Doenicke et al., 1973; Lorenz, 1975), this compound is believed to cause histamine release when administered in combination with certain anaesthetic drugs (Lorenz, 1975). This effect is thought to play a role in clinical anaphylactoid reactions caused by drugs dissolved in PEG-35 Castor Oil (Lorenz et al., 1982).

Pharmacologic Effects

In Vitro

Multidrug resistance was reversed in vitro by PEG-35 Castor Oil in studies with human myeloma cells (Schuurhuis et al., 1990), Ehrlich ascites tumor cells (Friche et al., 1990), and the R100 and K562 cell lines (Woodcock et al., 1990). PEG-35 Castor Oil is thought to modulate resistance by binding to the plasma membrane P-glycoproteins and preventing the efflux of drugs from cells (Friche et al., 1990; Woodcock et al., 1992).

In Vivo

Antidiuretic effects were observed when Sprague-Dawley rats were orally administered 2.5 mL/kg PEG-35 Castor Oil. The researchers

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attributed this observation to the laxative action induced by this compound (Coppi et al., 1971).

ANIMAL TOXICITY

Acute Toxicity

Oral

LD_{50} values of formulations containing 2.0% PEG-25 Hydrogenated Castor Oil and 0.25% PEG-40 Hydrogenated Castor Oil were reported to be more than 15.0 g/kg for rats (CTFA, 1982a; CTFA, 1982b). For a formulation containing 3.0% PEG-60 Hydrogenated Castor Oil, the LD_{50} for rats was more than 5.0 g/kg (CTFA, 1976a).

Intravenous

PEG-35 Castor Oil impaired renal function following intravenous administration in male Wistar rats. Five rats were injected with 0.7 mg/kg/min PEG-35 Castor Oil for 2 h, and a control group of five rats was injected with the same volume of 0.9% NaCl. Control measurements of blood pressure, renal blood flow, creatinine clearance, and urine output were determined prior to infusion. Then blood pressure and renal blood flow were determined five times during infusion and urine was collected at 30-min intervals for clearance determination. A slight decrease occurred in renal blood flow in some of the rats during the first 30 min of infusion, but no changes in arterial blood pressure or creatinine clearance were detected. Renal blood flow and creatinine clearance decreased at 45 min and decreased to 50% of their initial values at 90 min. Arterial blood pressure was only modestly reduced. Urine volume initially increased during the first 30 min of infusion but began to decrease after 45 min. It decreased to less than 50% of initial control values at 105 min, whereas in the control group urine flow doubled. The investigators concluded that PEG-35 Castor Oil caused vasoconstriction of renal arteries, which induced a more than 50% decrease in renal blood flow and glomerular filtration rate without affecting blood pressure (Thiel et al., 1986).

Short-Term Toxicity

Intravenous

Transient cholestasis occurred when PEG-35 Castor Oil was administered intravenously to rats. This condition was both dependent and independent of bile acid secretion and was accompanied by a marked

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reduction in bilirubin excretion with no significant changes in serum bilirubin concentrations (Roman et al., 1989).

PEG-30 and PEG-35 Castor Oil (0.5 mL/kg) each were administered intravenously to one male and one female beagle dog. A pair of control dogs was injected with 0.9% NaCl. Injections were performed daily for 30 days. The dogs were observed daily for signs of toxicity, and blood samples were taken after 9, 16, 23, and 31 days. All of the dogs were killed on day 31 for necropsy. Clinical signs of toxicity were observed in both treatment groups and included edematous wrinkling of the skin above the eyes, flushing of the skin of the external ears, and shaking or rubbing of the head. These signs were more pronounced in the dogs treated with PEG-35 Castor Oil. Salivation and rhinorrhea also were observed in both treatment groups but only for the first 10 days. Thrombocytopenia occurred in the dogs treated with PEG-30 Castor Oil and increased platelet counts were observed in the dogs administered PEG-35 Castor Oil. Clinical chemistry changes included increases in serum concentrations of total cholesterol, triglycerides, total lipids, and percentage of chylomicrons. Electrophoretic patterns indicated a decrease in the percentage of α-lipoproteins and demonstrated the appearance of a new peak near the origin. Changes in the lipid and lipoprotein values were more marked in the PEG-35 Castor Oil–treated dogs. Excessive amounts of lipid were present in the spleen, lymph nodes, liver, and kidneys at histopathologic examination (Hacker et al., 1981).

Six male and six female rabbits were intravenously injected in the ear vein with 4.0 mL/kg of 25% aq PEG-35 Castor Oil (= 1.0 g/kg) for 5 consecutive days. A control group of two male and two female rabbits was injected with the same volume of saline solution following the same protocol. The animals were weighed daily, and hematologic evaluations were performed prior to the study and on day 5. Two rabbits, one male and one female, were killed on day 5, three male and three female rabbits were killed on day 8, and the remaining rabbits were killed on day 12. There were no clinical signs of toxicity in any of the rabbits. The only significant changes was a decrease in hemoglobin content compared with both initial values and that of the controls. At necropsy, no evidence of lipid accumulation or any other adverse macroscopic changes was present (BASF, no date, b).

A different batch of PEG-35 Castor Oil was tested using similar procedures. A group of two male and two female rabbits was injected in the ear vein with 4.0 mL/kg of 25% PEG-35 Castor Oil (= 1.0 g/kg) on 5 consecutive days. The animals were observed for signs of toxicity during the study and were killed on day 7 for necropsy. No clinical signs of

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toxicity were observed. At necropsy, one rabbit had an enlarged spleen, but no significant pathologic changes were observed during macroscopic or microscopic examination (BASF, no date, b).

PEG-40 Hydrogenated Castor Oil was also tested for short-term toxicity. Groups of 60 Sprague-Dawley rats were administered daily injections of 300, 900, and 2700 mg/kg PEG-40 Hydrogenated Castor Oil via the tail vein for 4 wk. A control group of 60 rats was administered saline. At the end of 4 wk, all except 10 animals from each group were killed for necropsy. The remaining animals were maintained for an additional 6 wk without treatment. At doses of 300 and 900 mg/kg PEG-40 Hydrogenated Castor Oil, no systemic toxicity was observed; however, at a dose of 2700 mg/kg, slight ataxia was observed and body weight was reduced significantly in the males and slightly in the females. Feed intake also was reduced accordingly. At the end of 4 wk, the number of reticulocytes was increased but was not significantly different from control values. Microscopic evaluation produced evidence of a storage process in the splenic reticulum, but these effects apparently did not cause functional disturbance. At necropsy, heart weight was increased and ovary weight was reduced in the females. Hemorrhages and thrombosis were observed at the injection sites of both experimental and control animals, and thrombophlebitis was found during microscopic evaluation. These effects were found to be reversible in the animals that were maintained for an additional 6 wk without treatment. Body weights, feed intake, and reticulocyte numbers normalized, and damage at the injection sites healed. Microscopically, the injection sites had no changes, and only slight accumulation in the splenic reticulum was observed (BASF, 1976).

Intramuscular

Dogs (number not specified) were alternately injected intramuscularly in the right and left flank with 1.0 mL of 50% PEG-35 Castor Oil. Each dog was given a total of 11 injections. Spotty reddening of the skin was observed at the injection sites, but no resorptive toxicity or macroscopic lesions were observed (BASF, no date, c).

In another study, rabbits and guinea pigs (numbers not specified) were alternately injected intramuscularly in the right and left flank with 0.5 mL and 0.1 mL PEG-35 Castor Oil, respectively. Both species were given a total of 10 injections. No irritation of the skin or resorptive poisoning was observed. At microscopic examination of the muscle tissue, nonspecific foreign body reaction of resorptive character was found at the injection sites; however, this lesion was transient (BASF, no date, c).

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Subchronic Toxicity

Oral

In a 90-day feeding study, groups of 15 Sherman-Wistar rats were fed diets containing 0.01%, 0.04%, 0.16%, 0.64%, 2.5%, and 5.0% (initially 10.0%) PEG-40 Castor Oil. A control group of 30 rats was fed untreated feed. The animals were weighed at weekly intervals and feed intake was measured. Blood samples were taken from two male and two female rats prior to the study and then periodically during the study. After 8 wk on the diet, the lightest two male and two female rats were killed for necropsy and tissues were removed for microscopic examination. At the end of the study, the lightest two male and two female rats also were killed for necropsy. After 1 wk on the diet, the animals of the 10.0% treatment group stopped eating the feed, so the concentration was reduced to 5.0% PEG-40 Castor Oil. Weight gain, feed intake, and hematology results were comparable between the experimental groups and the control group. No significant gross or microscopic lesions were found at either 8 wk or 90 days (Industrial Biology Research and Testing Laboratories, no date, a).

Dogs also were used in a 90-day feeding study with PEG-40 Castor Oil. One beagle each was fed a diet containing 0.04%, 0.64%, or 5.0% PEG-40 Castor Oil. A control group of three dogs was fed untreated feed. The animals were weighed at weekly intervals and feed intake was measured. Blood samples were taken prior to the study and then periodically during the study. At the end of the 90 days, the dogs were killed and necropsy was performed. No significant difference was observed in weight gain, feed intake, or hematologic values between the dogs fed the PEG-40 Castor Oil diet and the untreated control dogs. At necropsy, perilobular cellular infiltration and parasitic granulomas were observed, but these conditions also were present in the control animals and were attributed to parasitic infection and migration rather than a treatment-related effect (Industrial Biology Research and Testing Laboratories, no date, b).

The subchronic toxicity of PEG-40 Hydrogenated Castor Oil also was investigated. Groups of 20 male and 20 female Sprague-Dawley rats were given feed containing 32,000-ppm or 64,000-ppm PEG-40 Hydrogenated Castor Oil. A group of 25 male and 25 female rats was fed a diet containing 100,000-ppm PEG-40 Hydrogenated Castor Oil and a control group of 20 male and 20 female rats was fed untreated feed. All of the animals survived the study period. During the study, no significant changes in feed intake, body weight gain, or hematologic evaluations were observed. When 20 male and 20 female rats from each group were killed for necropsy after 6 mo, body and organ weights were within the parameters of those of the control group and no significant

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changes in gross or microscopic lesions were found. The remaining five male and five female rats fed the 100,000-ppm diet were fed untreated feed for an additional 21 days. No signs of toxicity were observed clinically and no lesions were observed at necropsy in these rats (BASF, no date, d).

A summary of a 6-mo feeding study with dogs reported that groups of three male and three female beagle were fed diets containing 1.0%, 2.5%, and 5.0% PEG-40 Hydrogenated Castor Oil. A control group of dogs was given untreated feed. During the study, no significant changes in behavior, feed intake, or body weight gain were observed. Hematologic and biochemical parameters and urine analyses were similar to those of the control group. One male dog of the low-dose group died before termination of the study, but its death was considered unrelated to treatment. When the remaining animals were killed for necropsy at the end of the study, body and organ weights were within normal limits and no gross changes were observed. No lesions were observed in tissues examined microscopically (BASF, no date, e).

A PEG Castor Oil (number of moles of ethylene oxide was not specified) was tested as a vehicle control in a study with CD-1 mice. Forty mice (20 of each sex) were given 10% PEG Castor Oil in their drinking water for 90 days. A nontreated control group was given deionized water. The animals were observed for signs of toxicity twice a day and body weights were taken at weekly intervals. Necropsy was performed on the animals either when they died during the study or when they were killed at the end of the study. Hematology and clinical chemistry determinations also were performed. All of the mice survived until the end of the study. PEG Castor Oil seemed to make the drinking water less palatable, because the mean fluid consumption was significantly less for the treated animals compared with the untreated control mice. Terminal body weights of the PEG Castor Oil–treated group did not differ significantly from the those of the untreated group. The absolute and relative weights of the kidneys and liver were significantly greater, and the weight of the brain was significantly less in the treated group than in the control group. Significant differences in hematology included greater hematocrit and lower polymorphonuclear values in the male mice. Among the clinical chemistry parameters studied, the percentage of calcium and creatinine was greater and the BUN–creatinine ratio was lower in experimental mice of both sexes. Female mice also had greater cholesterol and albumin values, and male mice had greater plasma alkaline phosphatase values. No significant differences between the PEG Castor Oil group and the groups administered a drug dissolved in PEG Castor Oil were observed (Borzelleca et al., 1985).

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In a similar study in which PEG Castor Oil (number of moles of ethylene oxide was not specified) was tested as a vehicle control, 10 male and 10 female Sprague-Dawley rats were administered 0.5% PEG Castor Oil in drinking water for 13 wk. All of the rats survived the study. The PEG Castor Oil–treated rats had slightly lower water consumption than did untreated control animals, but no significant differences in body weight gain were observed. The only change in organ weights occurred with the brain weight, expressed as a percentage of body weight, which was lower than that of the untreated group. No significant changes were observed in the biochemical, hematologic, and histologic parameters investigated (Villeneuve et al., 1985).

Dermal

A formulation containing 0.25% PEG-40 Hydrogenated Castor Oil was applied by gentle inunction to the shaved skin on the backs of 10 male and 10 female Sprague-Dawley rats. Applications were made once daily for 5 days-wk over a 13-wk period. The daily dose, 1640 mg/kg/day of the formulation, was considered to be 100 times the average daily use level of the product by consumers. Behavioral observations were made daily, body weight was measured weekly, and blood and urine samples were evaluated during weeks 7 and 13. Clinical chemistry parameters also were monitored. At the end of the study, all of the rats were killed and necropsy performed. No deaths occurred during the study and no treatment-related changes in body weight gain, behavior, hematology, urinalysis, or clinical chemistry parameters were observed. After five doses, minimal irritation and desquamation were observed and persisted until the end of the study. The mean relative hepatic weight for male rats was significantly greater compared with the untreated controls; however, this finding was not considered toxicologically significant because no significant lesions were observed at microscopic examination (CTFA, 1984).

In a similar study, two groups of 10 female ChR-CD rats were given topical applications of 284 or 2840 mg/kg of a formulation containing 3.0% PEG-60 Hydrogenated Castor Oil. Applications were made five times a week for 13 consecutive weeks. As seen in the previous study, the only treatment-related lesions occurred on the skin. Slight erythema and drying of the skin was observed; however, control animals also exhibited these effects. At necropsy, no gross lesions were observed. The hepatic weights of the rats treated with 2840 mg/kg of the formulation and the renal-to-body weight ratio of the rats treated with 284 mg/kg of the formulation were significant. It was noted, however, that these changes were within the normal accepted range for the laboratory and that no significant lesions were observed during histopathologic examination (CTFA, 1977a).

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Nephrotoxicity

The isolated perfused rat kidney model was used to assess the acute nephrotoxic effects of cyclosporine and its vehicle, PEG-35 Castor Oil. In this model, the right kidney from male Sprague-Dawley rats was perfused with 100 mL of a perfusate solution at normothermic temperature. After 50 min of perfusion, cyclosporine dissolved in PEG-35 Castor Oil or 200 µL PEG-35 Castor Oil was added to the perfusate, and perfusion was continued for an additional 130 min. Control experiments were conducted with the perfusate alone. Serial determination of renal hemodynamics and tubular function was made over the 3-h period. Marked vasoconstriction occurred following perfusion with PEG-35 Castor Oil, and renal blood flow and glomerular filtration rate were reduced by 45% and 28%, respectively, after 3 h. A statistically significant increase occurred in renal vascular resistance. The investigators concluded that PEG-35 Castor Oil had a direct toxic effect on the tubular cells. Because similar results were observed in tests with cyclosporine dissolved in PEG-35 Castor Oil, the investigators suggested that PEG-35 Castor Oil is a contributing factor in severe acute nephrotoxicity sometimes observed in patients following prolonged treatment with intravenous cyclosporine (Hirsch et al., 1987; Besarab et al., 1987).

Cyclosporine in PEG-35 Castor Oil, diluted in NaCl, was evaluated for nephrotoxicity in a study using male Fisher rats. Three control rats were administered intravenous PEG-35 Castor Oil in NaCl, and six control rats were administered NaCl alone for 15 days (volume of intravenous administration not reported). The rats were killed on day 15, and functional studies (inulin clearance) were performed and microscopic examination of the kidneys conducted. No evidence showed that PEG-35 Castor Oil caused alterations in the glomerular filtration rate. Numerous cytoplasmic dark crystals were observed in the proximal tubules of both groups receiving cyclosporine in PEG-35 Castor Oil and the control group receiving PEG-35 Castor Oil and NaCl. Unlike the rats treated with cyclosporine, the rats administered PEG-35 Castor Oil and NaCl had no vacuolization of the proximal tubules. Because no crystals were observed in the tubules of the rats treated with NaCl alone, the investigators concluded that PEG-35 Castor Oil caused the crystal structures in the proximal tubules (Verani, 1986).

No evidence of nephrotoxic effects were observed with PEG-35 Castor Oil in a study using New Zealand White rabbits. In this study, groups of five rabbits were given daily intravenous injections (1.0 mL) of cyclosporine in PEG-35 Castor Oil diluted in saline for 30 days. One control group of rabbits was administered saline, and another received only PEG-35 Castor Oil. The rabbits were placed in metabolic cages for

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24-h urine collections. Serum and whole blood also were collected and analyzed regularly during the study. At the end of the study, cardiac puncture was performed to obtain both heparinized whole blood and serum for creatinine and cyclosporine determinations. Tissue samples were taken from different regions of each kidney and microscopic and ultrastructural evaluations were performed. Reductions in creatinine clearance and the development of leukocyte infiltrates, tubular atrophy, and interstitial fibrosis of the kidneys were observed in rabbits treated with cyclosporine. Structural changes also were observed in specimens examined by light and electron microscopy; however no morphologic or functional changes were observed in the rabbits treated with PEG-35 Castor Oil alone. The investigators concluded that PEG-35 Castor Oil did not contribute to the compromise in renal structure and function observed with cyclosporine administration (Thliveris et al., 1991).

Anaphylactoid Reactions

Twenty-percent PEG-35 Castor Oil was administered intravenously to dogs at a constant 30 mL/h; the infusion was stopped when the systolic arterial pressure decreased by more than 50% of the control. This treatment induced a significant decrease in blood pressure and cardiac output associated with massive increases in plasma histamine and catecholamine. The investigators suggested that the large increase in histamine release was indicative of acute mast cell degranulation. Thoracopulmonary compliance decreased rapidly and was reduced markedly by the end of infusion. A significant reduction in blood volume, which was caused by a decrease in plasma volume, was observed. Hematocrit increased significantly by the end of infusion, whereas platelet and leukocyte counts sharply decreased. It was also noted that 6 of 13 dogs had cutaneous erythema and edema of their paws and muzzle. The investigators concluded that 20% PEG-35 Castor Oil induced cardiovascular collapse, and that PEG-35 Castor Oil–induced shock "is of the anaphylactoid type, and includes cutaneous erythema and edema, hypotension, venous pooling, plasma extravasation, histamine and catecholamine release, and decreases in dynamic thoracopulmonary compliance and leucocyte and platelet counts" (Gaudy et al., 1987).

Dermal Irritation

When undiluted PEG-35 Castor Oil was applied to the shaved backs or to the external ears of albino rabbits for more than 20 h (experimental details not provided), slight transient irritation was reported (BASF, no date, c).

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Undiluted PEG-40 Hydrogenated Castor Oil reportedly caused reddening and scaling of the skin when applied to the backs of albino rabbits for 20 h (experimental details not provided). Only slight transient reddening was reported when applications were made to the external ears of rabbits for 20 h (BASF, no date, c).

The primary skin irritation potential of a formulation containing 2.0% PEG-25 Hydrogenated Castor Oil was minimal. Only one of nine rabbits had evidence of erythema 24 h after a single application of the formulation under an occlusive patch (amount not stated). The overall primary irritation index (PII) was 0.11/8 (CTFA, 1982c). For formulations containing either 0.25% PEG-40 Hydrogenated Castor Oil or 3.0% PEG-60 Hydrogenated Castor Oil, the PIIs were 0.22/8 and 0.67/8, respectively (CTFA, 1982d; CTFA, 1976b).

Dermal Sensitization

The flanks of 10 guinea pigs were shaved, degreased with ether, and 50% PEG-35 Castor Oil in acetone was applied to the left flank of each animal (painted three times sequentially with a saturated cotton swab) for 10 consecutive days. The right flanks were left untreated. After a 12-day nontreatment period, 5% PEG-35 Castor Oil in acetone was applied to the right flank (as above, after degreasing with ether). The skin was observed for signs of irritation after 12 h. A control group of three guinea pigs was untreated during the induction phase of the experiment but was given a single application of 5% PEG-35 Castor Oil. Slight reddening of the skin was observed during induction with PEG-35 Castor Oil, but no signs of irritation were observed after the challenge application. When this study was duplicated, the same results were obtained (BASF, no date, f).

In a subcutaneous sensitization study, 10 daily injections with 0.1% PEG-35 Castor Oil (1 $\times$ 0.05 mL; 9 $\times$ 0.1 mL) were administered to guinea pigs (number not specified) in their backs. After a 13-day nontreatment period, a challenge injection of 0.1% PEG-35 Castor Oil (1 $\times$ 0.05 mL) was administered into the neck. Reddening occurred around the injection sites during induction, but no sign of sensitization was present (BASF, no date, f).

Tachon et al. (1983) also assessed the allergenic potential of PEG-35 Castor Oil. Ten consecutive intradermal injections of 0.5 mL PEG-35 Castor Oil were performed to the backs of 10 male and 10 female Dunkin-Hartley guinea pigs, and an occlusive patch was applied for 48 h. After a 12-day nontreatment period, the animals were challenged with 0.5 mL PEG-35 Castor Oil on their abdomens. When macroscopic evaluations were performed 48 h following challenge, 60% of the male and 50% of the female guinea pigs had doubtful reactions; however, no

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evidence of sensitization was observed at microscopic examination. The investigators concluded that PEG-35 Castor Oil was not a sensitizing agent.

Adjuvancy

Descotes et al. (1983) conducted three studies to determine the adjuvancy of PEG-35 Castor Oil. In the first study, groups of six female Dunkin-Harley guinea pigs were injected with 100 μg bovine serum albumin (BSA) in 0.05 mL PEG-35 Castor Oil. A positive control groups of animals was injected with BSA in Freund's complete adjuvant (FCA), and a negative control group of animals was treated with BSA in saline. Three weeks later the animals were intradermally injected in the right flank with BSA in saline. Skin evaluations were made at 2, 24, and 48 h. PEG-35 Castor Oil caused erythema and skin induration that was of the same severity as seen with FCA.

In the second study, groups of 10 Swiss mice were injected subcutaneously in the back with 10^8 sheep erythrocytes in either 0.005 or 0.01 mL PEG-35 Castor Oil in saline. A control group of mice was injected with sheep erythrocytes in saline. Five days later, the mice were administered an eliciting dose of 10^8 sheep erythrocytes in the hind footpad. The percent increase in footpad swelling was taken as a measure of delayed hypersensitivity. Both doses of PEG-35 Castor Oil caused significant increases in footpad thickness.

In the third study, 10^9 sheep erythrocytes in 0.01 and 0.05 mL PEG-35 Castor Oil in saline was administered intraperitoneally to 10 Swiss mice. A control group of mice was treated with erythrocytes in saline only. Eight days later, blood samples were taken from the mice to measure hemagglutinin concentrations. PEG-35 Castor Oil had no effect on antibody concentrations. Based on the three studies, the investigators concluded that PEG-35 Castor Oil is "a potent adjuvant of cellular immune response."

Ocular Irritation

A 5% active solution (pH = 6–8) of PEG-5 Hydrogenated Castor Oil (w/w) (0.1 mL) was instilled into the left conjunctival sac of six New Zealand white rabbits. Three of the eyes were rinsed after 30 sec. The rights eyes left untreated served as controls. Scoring according to the method of Draize (1944) was made at 24, 48, and 72 h postinstillation. Slight to mild corneal opacity was observed in two unrinsed eyes at 24 h and persisted until 72 h. None of the other treated eyes had evidence of corneal damage. Slight iridial damage was observed in one unrinsed eye at 24 and 48 h, and in another unrinsed eye at 48 and 72 h. Iridial

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damage also was observed in one rinsed eye at 24 h, but it cleared by 72 h. At 24 h, all of the treated eyes had mild to moderate conjunctival irritation manifest as hyperemia, chemosis, and discharge. One rinsed eye and one unrinsed eye cleared by 72 h, whereas the remaining eyes were irritated through 72 h. The 24-h maximum mean total score was 36.3/110 for the unrinsed eyes and 13.7/110 for the rinsed eyes. The investigators concluded that PEG-5 Hydrogenated Castor Oil was severely irritating to unrinsed eyes and mildly irritating to rinsed eyes (Product Safety Labs, 1988).

When 50 mm^3 of 50% aq PEG-35 Castor Oil in acetone was instilled into the conjunctival sac of rabbits (number not specified), lacrimation and mild irritation of the conjunctiva were observed. A 30% aq solution did not cause any signs of irritation (BASF, no date, c).

Undiluted and 50% aq PEG-40 Hydrogenated Castor Oil was instilled (0.05 mL) into the conjunctival sacs of rabbits (number not specified), and observations were made at 24 and 48 h. Slight transient reddening of the conjunctiva was observed with both concentrations (BASF, no date, c).

No irritation was observed when the eyes of six rabbits were instilled (volume not given) with a formulation containing 2.0% PEG-25 Hydrogenated Castor Oil (CTFA, 1982e). In a similar study, a formulation containing 0.25% PEG-40 Hydrogenated Castor Oil caused mild transient irritation. The total irritation scores on days 1 to 3 postinstillation were 1/110. All eyes were clear by day 4 (CTFA, 1982f).

A formulation containing 3.0% PEG-60 Hydrogenated Castor Oil (volume not given) caused minimal irritation to the eyes of 2 of 6 rabbits. The irritation score for both rabbits was 2/110 24 h after instillation. All signs of irritation disappeared by 48 h (CTFA, 1976c).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

PEG-40 Hydrogenated Castor Oil was tested for teratogenic effects in a feeding study with Sprague-Dawley rats. Two groups of pregnant rats, 30 in one group and 27 in the other, were fed diets containing 50,000 ppm or 100,000 ppm PEG-40 Hydrogenated Castor Oil, respectively, on days 0 to 20 of gestation. Two control groups of 26 and 29 rats were fed untreated feed. All of the animals were observed for signs of toxicity during gestation and were killed on day 20 for evaluation of the uteri. No evidence of either maternal or fetal toxicity was present. A slight but not statistically significant increase occurred in the number of resorptions in the group treated with 100,000 ppm. The type and number of malformations and anomalies found in the fetuses of the experimental groups were similar to those found among the fetuses from the control groups. The investigators concluded

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that PEG-40 Hydrogenated Castor Oil was not teratogenic (BASF, no date, g).

Negative results were also obtained in a teratogenicity study with NMRI mice. Two groups of pregnant mice, 25 in one group and 31 in the other, were fed diets containing either 5000 ppm or 10,000 ppm PEG-40 Hydrogenated Castor Oil on days 6 to 15 of gestation. Two groups of 26 and 28 mice were given untreated feed. There was no statistically significant evidence of either maternal or fetal toxicity. The few malformations observed among the fetuses of the treated dams were similar to type and number to those found in the control groups (BASF, no date, h).

Lane et al. (1982) tested PEG-30 Castor Oil as a vehicle control in a multigeneration study that was modified to include a screening for dominant lethal and teratogenic effects. Ten male and 30 female ICR Swiss mice (F/0) were administered 1% PEG-30 Castor Oil in their drinking water continuously throughout the study. After 35 days on the test solution, the mice were randomly mated to produced F/1A litters. Two weeks following the weaning of the F/1A litters, the F/0 mice were rerandomized and mated to produce F/1B litters. Then the F/0 mice were mated randomly again 2 weeks after the weaning of the F/1B litters to produce F/1C litters.

Ten male and 30 female weanling mice from the F/1B litters also were administered 1% solutions of PEG-30 Castor Oil in their drinking water and were mated in nonsibling matches to produce F/2A litters. Body weight and fluid consumption, as well as fertility and gestational indices, were determined regularly for the parental mice. Twenty-one day survival studies were conducted on the litters from the F/1A, F/1B, and F/2A matings.

F/1C and F/2B matings also were produced to screen for dominant lethal and teratology effects. In these studies, female mice were killed during gestation and the number of fetal implants, early and late resorptions, viable fetuses, and dominant lethal factors were determined. Fetuses were removed and individually evaluated for gross defects, and one third of them were examined for skeletal and visceral malformations.

No significant changes in reproductive performance were observed in any of the matings. Mean litter size, postnatal body weights, and survival indices also were unaffected. The only significant change observed in both the dominant lethal and teratology screenings was an increase in the ratio of dead fetuses to live fetuses.

PEG-35 Castor Oil also was tested as a solvent control in a teratogenicity study. Groups of pregnant ICR and C57B1/10Dg mice (numbers not specified) were orally given 0.05 mL/10 g body weight 8% PEG-35 Castor Oil and 10% propylene glycol in water on either day 9, 10, or

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11 of gestation. An untreated control group of pregnant mice was used for comparison. All of the mice were killed on day 18 of gestation, and the fetuses and placentas were removed for examination. PEG-35 Castor Oil did not have any significant effects on growth or development in any of the treatment groups (Cusic and Dagg, 1984, 1985).

In the following studies, PEG-30 Castor Oil and PEG-35 Castor Oil were tested as negative vehicle control substances. No untreated control animals were used for comparison.

Burkhalter and Balster (1979) used PEG-30 Castor Oil as a vehicle control in a behavioral development evaluation. Male and female albino ICR mice were given daily oral doses of 10 mL/kg of a solution containing one part PEG-30 Castor Oil and eight parts saline. The mice were mated after 3 wk of treatment with PEG-30 Castor Oil, and the dams continued to receive daily doses of PEG-30 Castor Oil through gestation and lactation. A total of five litters was used. Each of these litters was randomly reduced to eight pups, and oral administration of PEG-30 Castor Oil to the pups was initiated 7 d following birth and continued for the remainder of the study. On days 7 to 21, the pups were weighed, and a battery of tests to determine neurobehavioral development was conducted. These tests included measurement of righting reflex, forepaw grasp, rooting reflex, cliff-drop aversion, auditory startle response, bar-holding ability, eye opening, motor performance and learning measures, and placing and grasping responses. In general, the pups experienced gradual weight gain and progressive neurobehavioral development.

PEG-35 Castor Oil was used as the vehicle control in a study using embryo cultures. Embryos from pregnant Swiss Webster mice were removed on day 8.5 of gestation and grown in culture containing 130 μg/mL PEG-35 Castor Oil for 24 h. At the end of culture, the embryos were evaluated for viability and only viable embryos were examined for malformations. Of the 44 embryos examined, only three had abnormalities, including defect of the neural tube, facial arch, and cranial rotation. The mean somite number was 24.2, mean crown-rump length was 2.25, and mean protein content was 86.5 μg per embryo (Uhing et al., 1993).

MUTAGENICITY

Au et al. (1991) investigated the clastogenic and coclastogenic activity of PEG-35 Castor Oil using male ICR mice. Cytogenetic and metabolite analyses were conducted with groups of five mice given 0.1 mL/g of 0.03%, 0.3%, or 3.0% PEG-35 Castor Oil orally. Other groups of mice were treated with benzene in olive oil or benzene in combination with the various doses of PEG-35 Castor Oil. An untreated control group and

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a vehicle control (olive oil) group also were used. The mice in the single-treatment groups were killed at 30 h, and the mice receiving the combined treatment were killed after the first treatment. Bone-marrow samples were harvested at the end of the study and evaluated for micronuclei (MN) frequencies in polychromatic erythrocytes (PCE).

The investigators also tested the effect of PEG-35 Castor Oil in hepatic cytochrome P450 isoenzyme expression in liver. Male Swiss albino CD1 mice were given 0.01 mL/g body weight 3% PEG-35 Castor Oil in water orally. Another group of mice was given benzene followed by 3% PEG-35 Castor Oil 1, 3, and 5 h later. The mice given PEG-35 Castor Oil only were killed 1, 3, 5, 15, or 30 h after treatment, whereas the mice treated with both PEG-35 Castor Oil and benzene were killed after 30 h. The livers were removed from all of the mice for evaluation.

PEG-35 Castor Oil did not cause any significant or dose-dependent increses in MN but did enhance significantly the clastogenicity of benzene. When PEG-35 Castor Oil was administered 1, 3, and 5 h after benzene treatment, an inverse time-dependent change occurred in MN frequencies. The enhancement effects of PEG-35 Castor Oil were attributed to its ability to induce the cytochrome P450I family when it was administered 1 h after benzene treatment. No positive synergistic effect was observed when PEG-35 Castor Oil was administered at later intervals. The investigators also noted an increase in *trans,trans* muconic acid (a genotoxic metabolite of benzene) in the urine following combined treatment.

PEG-30 Castor Oil and PEG-35 Castor Oil also were used as negative vehicle controls in several studies. PEG-30 Castor Oil was used in a chromosomal aberration assay using Chinese hamster ovary (CHO) cells and micronucleus and spermhead abnormality assays with mice (Blazak et al., 1988). Machemer and Lorke (1978) used PEG-35 Castor Oil in dominant lethal tests on male and female mice, micronucleus tests on male and female mice, and a spermatogonial test using Chinese hamsters. PEG-35 Castor Oil also was used in a study to detect sex-linked recessive lethals in *Drosophila* spermatozoa (Kortselius, 1978). In all of these studies, known mutagens were used as positive controls and had significant evidence of mutagenicity compared with the PEG-30 Castor Oil and PEG-35 Castor Oil vehicle controls.

CARCINOGENICITY

In the following studies, the PEG Castor Oils were used as vehicle control substances, and no untreated control groups were used.

In an oral carcinogenicity study of several agents, PEG-30 Castor Oil was used as a vehicle control. Male Sprague-Dawley rats were given 1

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mL of 10% PEG-30 Castor Oil by gavage three times a week for 16 wk and then once per week for an additional 10 wk. All of the rats were killed during week 77 and necropsy was performed. No untreated control group of animals was used. Of the 29 rats examined, the following neoplasms (and number of neoplasms) were found: benign liver tumor (1), keratoacanthoma (1), pituitary adenomas (4), prostate carcinoma in situ (1), Leydig cell tumor of the testis (1), ear spindle cell sarcoma (1), pancreatic islet cell adenoma (1), spleen lymphomas (2), mammary fibroma (1), subcutaneous myxolipoma (1), subcutaneous fibromas (2), and adrenal adenoma (1). No comment was made by the investigators regarding the normal range of occurrence of these tumors in their historical data base (Fiala et al., 1987).

In another study, a PEG Castor Oil (number of moles of ethylene oxide was unspecified) was used as a vehicle control in a lung adenoma assay using A/J mice. Two groups of 20 female mice were given either 0.2 mL of 2% PEG Castor Oil three times a week for 8 wk or 0.2 mL of 2% PEG Castor Oil twice each dosing day following the same dosing schedule. A positive control group of 40 mice was given benzo[*a*]pyrene (BaP) in PEG Castor Oil following the first dosing schedule. No untreated control group was used. All of the animals were killed 8 mo after the first dose and were examined for neoplasms. The neoplastic response was not significantly different between the two PEG Castor Oil groups, so the data were pooled. Only two of the mice died during the study. Twenty-nine percent of the mice had lung neoplasms, and the average number of neoplasms per mouse was 0.32. None of the mice had squamous cell papillomas or carcinomas of the nonglandular stomach. Of the BaP-treated group, four mice died, 61% of the mice had lung neoplasms, the average number of neoplasms per mouse was 1.42, and 92% of the mice had squamous cell neoplasms of the nonglandular stomach (Robinson et al., 1987).

In a tumor-promotion study, a 2% solution of PEG Castor Oil (unspecified number of moles of ethylene oxide) was used as a vehicle control. PEG Castor Oil (0.2 mL) was orally administered to 110 female SENCAR mice three times a week for 2 wk. After a nontreatment period of 2 wk, 1.0 µg of TPA in acetone was topically applied to the mice three times per week for 20 wk. No untreated control group of animals was used. At the end of the study, 15% of the mice had neoplasms. A total of 20 neoplasms was present, and the neoplasms–animal ratio was 0.18. The investigators also reported the result of 90 mice treated with dimethylsulfoxide followed by TPA treatment: 6% of the mice had neoplasms, there were a total of 5 neoplasms, and the neoplasm–animal ratio was 0.06 (Robinson et al., 1989).

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CLINICAL STUDIES

Hemodynamics

Eight men who were previously tested intravenously with a drug dissolved in 20% PEG-35 Castor Oil were given 0.15 mL/kg PEG-35 Castor Oil intravenously over a 10-sec infusion period. Blood samples were taken 1, 5, 10, 20, and 30 min postinjection for histamine analysis, and blood pressure and heart rate was monitored. No increase in plasma histamine concentrations or effects on blood pressure and heart rate were detected (Doenicke et al., 1973).

Dermal Irritation

Twenty subjects were patch tested with 30% PEG-35 Castor Oil in water and 100% PEG-40 Hydrogenated Castor Oil on the skin of their backs. Observations were made after 24 and 48 h. No signs of irritation were observed (University Clinic Eppendorf, 1951–1954).

A 24-h single insult patch test of a formulation containing 2% PEG-25 Hydrogenated Castor Oil was conducted using 20 subjects. One subject developed mild erythema and two subjects had barely perceptible reactions (CTFA, 1982g). In a similar study, a formulation containing 0.25% PEG-40 Hydrogenated Castor Oil caused 1 of 20 subjects to develop a mild reaction to the formulation (CTFA, 1981).

The cumulative irritation potential of a formulation containing 3% PEG-60 Hydrogenated Castor Oil was conducted using 12 volunteers. Occlusive patches of 0.2 mL of the formulation were applied to the backs of each subject for 23 h for 21 consecutive days. Test sites were scored 24 h after each application. The composite total score was 22/756. The investigators concluded that this formulation was essentially nonirritating (Hill Top Research, 1976).

Dermal Irritation and Sensitization

A formulation containing 0.05% PEG-40 Hydrogenated Castor Oil was tested in a repeated insult patch test using 120 volunteers. The formulation (0.10 mL) was applied under occlusive patches to the backs of each subject for 24 h on Mondays, Wednesdays, and Fridays for 3 wk. After a 2-wk nontreatment period, challenge patches of the formulation were applied to previously untreated sites.

Five subjects had one incidence each of barely perceptible erythema during the induction phase of the study. One of these subjects also had a mild reaction to the challenge application at both the 24-h and 48-h readings. One subject, who showed no reaction during the induction phase, had a barely perceptible reaction at the 48-h challenge reading.

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Follow-up testing of these two subjects was conducted using the formulation "as is" and at a 1:3 dilution in water. Reactivity was not confirmed in one subject, but the other subject had a very weak reaction to the "as-is" formulation at the 24-h grading period. The investigators noted that this reactivity was much less than at challenge and was of questionable clinical significance. They concluded that this formulation was not an allergic sensitizer (CTFA, 1977b).

Using the same procedures, a formulation containing 0.25% PEG-40 Hydrogenated Castor Oil was tested for allergic contact sensitization potential on 86 subjects. Two subjects had minimal irritation during the induction phase of the study, but neither reacted to the challenge patch. One subject, who had no signs of irritation during induction, had faint erythema at the 24-h grading period only. The investigators concluded that this formulation was not a sensitizer (CTFA, 1982h).

A formulation containing 3.0% PEG-60 Hydrogenated Castor Oil also was tested using the same repeated insult patch procedures with 102 subjects. No signs of irritation were observed in any of the subjects durng induction. Only one doubtful reaction was observed at the 48-h reading after challenge. Follow-up testing of this subject with the formulation and a 1:3 dilution of the formulation was negative (CTFA, 1976d).

Jones and Kennedy (1988) reported two cases of eczema from a topical medicament used to treat leg ulcers. Patch tests with the constituents of this cream implicated PEG-40 Castor Oil (0.1% and 1% pet.) as the sensitizing agent. This ingredient induced severe grade-3 reactions at 48 and 96 h in both patients. The allergenicity of these reactions was supported by tests with 10 control patients, who had negative reactions to 0.1% and 1% PEG-40 Castor Oil.

Anaphylactoid Reactions

Several case studies of anaphylactoid reactions associated with intravenous administration of drugs dissolved in PEG-35 Castor Oil have been reported. In all of these cases, PEG-35 Castor Oil could not be diretly implicated as the cause for the adverse reaction; however, such factors as tolerance of the drugs alone when administered orally, treatment with drugs from the same family not dissolved in PEG-35 Castor Oil, and similar in several types of drugs in which PEG-35 Castor Oil was the solvent strongly suggest that PEG-35 Castor Oil was the cause of the anaphylaxis.

Most of the case reports are of intravenous treatment with cyclosporine dissolved in PEG-35 Castor Oil (Van Hooff et al., 1987; Magalini et al., 1986; Ptachcinski et al., 1985; Howrie et al., 1985; Chapuis et al., 1985; Leunissen et al., 1985; Friedman et al., 1985;

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Kahan et al., 1984). In general, subjects experienced flushing, bronchospasm, dyspnea, chest pains, pruritus, urticaria, and hypotension within minutes of injection. Reactions were documented occurring both after the first dose and after multiple doses. In some instances, the researchers were able to determine that the subjects had previous exposure to other drugs dissolved in PEG-35 Castor Oil.

Intravenous treatment with vitamin K_1 (phytonadione) also has been linked with anaphylactoid reactions (de la Rubia et al., 1989; Lefrere and Girot, 1987; Rich and Drage, 1982; Barash et al., 1976). Within minutes of a bolus injection, patients developed facial flushing, hypotension, chest pain, dyspnea, and abdominal pain. In the five cases reported, four subjects were administered the drug an undiluted and one was administered a diluted form. In one case, anaphylactoid reactions were prevented in a subsequent injection by using a diluted form of the drug and administering it at a slower infusion rate. Three of the cases occurred on the first injection, and two occurred after a second injection, which resulted in one death.

The anesthetic drug, Althesin, which was a combination of alphaxalone and alphadolone, was withdrawn from the market in 1983 because of the high incidence of anaphylactic reactions to the solvent, PEG-35 Castor Oil (Smolinske, 1992).

Anaphylactic reaction also have been associated with intravenous treatments with diazepam (Hüttel et al., 1980), teniposide (Siddal et al., 1989), and disoprofol (Briggs et al., 1982).

The mechanism behind these types of reactions is not clear. Doenicke et al. (1973) reported that although histamine release occurs in patients treated with drugs dissolved in PEG-35 Castor Oil, this vehicle alone did not induce histamine release. It is believed that this compound causes histamine release when administered in combination with certain anaesthetic drugs (Lorenz, 1975). Watkins et al. (1976) also proposed that the surfactant properties of PEG-35 Castor Oil enhance the immunogenicity of concurrently administered drugs.

In a study by Radford et al. (1982), activation of the alternative complement pathway was associated with subjects reacting to first exposure to Althesin, whereas the activation of the classic complement pathway was associated with reactions to a repeat exposure to the drug. In general, patients reacting to a repeat exposure to the drug have more severe clinical reactions, which are immunologically related.

In a 10-year survey of 118 patients with Althesin-related hypersensitivity, 1% of the cases were classified as immunoglobin E–mediated type I hypersensitivity, 36% to immune complement-mediated reactions involving other antibodies, 40% to alternate pathway complement C3 activation, and 23% to mixed reactions (Watkins, 1986).

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SUMMARY

PEG-30, -33, -35, -36, and -40 Castor Oil and PEG-30 and -40 Hydrogenated Castor Oil are polyethylene glycol derivatives of castor oil and hydrogenated castor oil that are used in a variety of cosmetic products as emulsifiers or solubilizing agents. Formulation data submitted to the FDA in 1995 reported a total of 540 cosmetic formulations containing these ingredients.

At the cellular level, PEG-35 Castor Oil affects a variety of cellular functions, including ATP production, PKC activation, renal proximal tubule cell function, and neurite outgrowth. PEG-40 Hydrogenated Castor Oil affected the integrity of human epithelial cells.

In the pharmaceutical industry, PEG-35 Castor Oil and PEG-40 Castor Oil are commonly used as solvents for intravenous drugs. Therefore, much of the toxicity data available on this family of ingredients are specifically on intravenous use.

Hemodynamic studies indicate that intravenous exposure to PEG-35 Castor Oil causes alterations in cardiac output, blood pressure, blood flow to various organs, and histamine release. Endothelial dysfunction of isolated rat hearts also was altered by exposure to PEG-35 Castor Oil.

The oral LD_{50} of two cosmetic formulations containing either 2.0% PEG-25 Hydrogenated Castor Oil or 0.25% PEG-40 Hydrogenated Castor Oil was reported to be more than 15.0 g/kg for rats. For a formulation containing 3.0% PEG-60 Hydrogenated Castor Oil, the LD_{50} for rats was more than 5.0 g/kg.

PEG-35 Castor Oil causes acute nephrotoxicity in rats. In the isolated perfused rat kidney model, this ingredient induced vasoconstriction and reduced renal blood flow and glomerular filtration rate in rats. Another study reported that PEG-35 Castor Oil caused the development of crystals in the proximal tubules of rats; however, no nephrotoxic effects were observed in a study using rabbits.

Impairment of renal function also was observed in acute intravenous studies of PEG-35 Castor Oil using rats.

In short-term studies, the toxicity of PEG-35 Castor Oil to dogs following intravenous exposure was greater than that of PEG-30 Castor Oil. Changes in lipid and lipoprotein values and accumulation of lipid in the spleen, lymph nodes, liver, and kidneys were observed; however, no toxicity or any adverse macroscopic or microscopic changes were observed in two studies using rabbits. A study of PEG-40 Hydrogenated Castor Oil produced some evidence of toxicity as well as a storage process in the splenic reticulum, but no functional disturbance occurred.

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Following repeated intramuscular injections with 50% PEG-35 Castor Oil, no significant signs of toxicity were observed in dogs. Negative results also were obtained in studies with rabbits and guinea pigs.

No significant signs of toxicity were observed in subchronic oral studies of 5% PEG-40 Castor Oil using rats and dogs, 100,000-ppm PEG-40 Hydrogenated Castor Oil using rats, and 5% PEG-40 Hydrogenated Castor Oil using dogs. Results were also negative in subchronic dermal studies using rats for formulations containing 0.25% PEG-40 Hydrogenated Castor Oil or 3.0% PEG-60 Hydrogenated Castor Oil.

Undiluted PEG-35 Castor Oil and PEG-40 Hydrogenated Castor Oil caused mild transient dermal irritation when applied to the skin of rabbits. Primary irritation studies of formulations containing either 2.0% PEG-25 Hydrogenated Castor Oil or 0.25% PEG-40 Hydrogenated Castor Oil produced minimal signs of irritation.

In a sensitization study with guinea pigs, 50% PEG-35 Castor Oil caused irritation during the induction phase of the experiment, but no sensitization was observed following a challenge application of 5% PEG-35 Castor Oil. Similar results were obtained in intradermal studies.

Some evidence showed that PEG-35 Castor Oil was a potent adjuvant of cellular immune response in studies using guinea pigs and mice.

No ocular irritation was observed in rabbits with either 30% aq PEG-35 Castor Oil or a formulation containing 2.0% PEG-25 Hydrogenated Castor Oil. Slight, transient ocular irritation was observed with undiluted and 50% aq PEG-40 Hydrogenated Castor Oil and with formulations containing either 0.25% PEG-40 Hydrogenated Castor Oil or 3% PEG-60 Hydrogenated Castor Oil.

A diet of 100,000-ppm PEG-40 Hydrogenated Castor Oil fed to pregnant rats through 20 days of gestation did not cause teratogenic effects to the fetuses. Similarly, no teratogenic effects were observed when pregnant mice were fed 10,000-ppm PEG-40 Hydrogenated Castor Oil.

In reproductive and developmental toxicity studies in which 1% PEG-30 and 8% PEG-35 Castor Oil were used as vehicle controls, adverse effects on fertility or development following oral administration were not observed.

PEG-35 Castor Oil did not cause any significant clastogenic effects in mice but did produce coclastogenic effects when administered in combination with benzene. PEG-30 and PEG-35 Castor Oil were used as negative vehicle controls in a variety of mutagenicity assays. In these studies, known mutagens had significant evidence of mutagenicity compared with these vehicles.

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The only available data on the carcinogenic potential of the PEG Castor Oils were from studies in which these ingredients were used as vehicle controls. In clinical studies, PEG-35 Castor Oil had no effect on the plasma histamine concentration of men following intravenous administration.

A 30% solution of PEG-35 Castor Oil and 100% PEG-40 Hydrogenated Castor Oil were not irritating to the skin of 20 subjects. Negative results also were obtained in single 24-h insult patch tests with formulations containing either 2.0% PEG-25 Hydrogenated Castor Oil or 0.25% PEG-40 Hydrogenated Castor Oil. In a cumulative irritation study, a formulation containing 3% PEG-60 Hydrogenated Castor Oil was nonirritating.

No evidence of sensitization was shown in clinical studies with formulations containing either 0.05% or 0.25% PEG-40 Hydrogenated Castor Oil, or 3.0% PEG-60 Hydrogenated Castor Oil.

PEG-35 Castor Oil has been associated with case reports of anaphylactoid reactions following intravenous administration of drugs dissolved in this vehicle. Although PEG-35 Castor Oil has not been directly implicated as the cause for these types of reactions, factors such as tolerance of the drugs alone when administered orally, treatment with drugs from the same family not dissolved in PEG-35 Castor Oil, and similar reactions observed in several types of drugs in which PEG-35 Castor Oil was the solvent strongly suggest that PEG-35 Castor Oil was the cause of the anaphylactic reactions.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel reviewed the available safety data on the PEG Castor Oils and the PEG Hydrogenated Castor Oils and agreed that these ingredients seem to have little toxicity. The only adverse reactions observed were anaphylactoid reactions in intravenous studies. Because this route of exposure does not occur from cosmetic use, the Panel was not concerned about this type of risk. The Panel did express concern over the lack of current concentration of use data. It was agreed that concentration limits should be based on the available test data on irritation and sensitization. The highest concentration tested yielding negative results for the PEG Castor Oil family was 50% PEG-35 Castor Oil in a sensitization study with guinea pigs. For the PEG Hydrogenated Castor Oil family, undiluted PEG-40 Hydrogenated Castor Oil was negative in animal and clinical irritation studies. The Panel agreed that the chemical similarity of these two ingredients to the other ingredients in their respective families allows for extrapolation of the concentration limits to these other ingredients.

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CONCLUSION

Based on the irritation and sensitization data presented in this report, the CIR Expert Panel concludes that PEG-30, -33, -35, -36, and -40 Castor Oil are safe for use in cosmetics at concentrations up to 50% and that PEG-30 and -40 Hydrogenated Castor Oil are safe for use at concentrations of up to 100%.

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Final Report

Plant-Derived Fatty Acid Oils as Used in Cosmetics

March 4, 2011

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ABSTRACT

The CIR Expert Panel assessed the safety of 244 Plant-Derived Fatty Acid Oils as used in cosmetics. Oils are used in a wide variety of cosmetic products for their skin conditioning, occlusive, emollient, and moisturizing properties. Since many of these oils are edible, and their systemic toxicity potential low, the review of the Panel focused on their potential dermal effects. The Expert Panel concluded that the 244 Plant-Derived Fatty Acid Oils are safe as used in cosmetics.

INTRODUCTION

Oils derived from edible vegetables, fruits, seeds, and tree and ground nuts have been safely consumed by humans for millennia. While nuts and some fruits and vegetables themselves may cause allergic reactions in certain individuals, the refined oils derived from these plants generally pose no significant safety concern following oral exposure, and their general biology is well characterized due to extensive use in food materials. Most of the ingredients in this report are mixtures of triglycerides containing fatty acids and fatty acid derivatives, the safety of which in cosmetics has been established. This safety assessment focused solely on the basic chemistry, manufacturing/production, uses, and irritation and sensitization data available on these oils as they are used in cosmetic ingredients.

Various oils have been used on the skin since antiquity. Initially used for anointing in religious ceremonies, oils and their components have also been long used on the skin for cosmetic purposes. They are used in a wide variety of cosmetic products for their skin conditioning, occlusive, emollient, moisturizing and other properties. The full list of ingredients in this report, which includes oils, hydrogenated oils, unsaponifiables, oil fatty acids, and salts of the fatty acids, is found in Table 1. While a large number of oils derived from plants are included in this literature review, there is a commonality in that they all are mixtures of triglycerides containing fatty acids and fatty acid derivatives, the safety of which in cosmetics have been established.

In preparing this report, numerous inconsistencies were noted with both taxonomic and INCI naming conventions. For example, this report includes the macadamia nut ingredients, Macadamia Integrifolia Seed Oil and Macadamia Ternifolia Seed Oil, which are described in the International Cosmetic Ingredient Dictionary and Handbook.[1] The species *M. integrifolia* is currently the only species of macadamia nut that is used for oil production. The name *M. ternifolia* is an old naming convention for the edible nut that is currently used to describe a non-cultivated, inedible species.[2,3] Macadamia Integrifolia Seed Oil and Macadamia Ternifolia Seed Oil are the same ingredient. Similar naming conflicts have been discovered with Triticum Vulgare (Wheat) Germ Oil and Triticum Aestivum (Wheat) Germ Oil, Orbignya Oleifera Seed Oil and Orbignya Speciosa Kernel Oil, and Moringa Pterygosperma Seed Oil and Moringa Oleifera Seed Oil, with these pairs being synonyms for each other. The shea plant also has two species names, *Butyrospermum parkii* and *Vitellaria paradoxa*. Only *B. parkii* (as Butyrospermum Parkii [Shea] Oil or Butter) is the current naming convention described by the cosmetics industry.

This report includes cosmetic ingredients that have been previously reviewed by the Cosmetic Ingredient Review Expert Panel. The ingredients, their conclusions, and published citations are found in Table 2. Previously reviewed fatty acids and glyceryl triesters are also found in Table 2.

CHEMISTRY

The group of ingredients characterized as fats and oils are the glyceryl esters of fatty acids (triglycerides) normally found in plants, including those which have been hydrogenated to reduce or eliminate unsaturation.[4] Figure 1 represents the general structure of fats and oils. The raw oil may include diglycerides, monoglycerides, free fatty acids, plant sterols, pigments, glucosides, proteins, natural antioxidants, vitamins and impurities.[5,6] The extent to which these components are removed during processing varies. The available information on chemical properties of oils in this report, including Food

Chemicals Codex specifications when provided, are found in Table 3.[7] The available fatty acid compositions for the oils in this report are found in Table 4.

The percentage of chemical constituents in individual oil types is dependent on the region where the oilseed plant is grown, individual cultivars, and plant genetics.[6] This is especially true with rapeseed, where the erucic acid content varies from 1% to 58.6%. Low erucic acid rapeseed oil is also known as canola oil.

The nutritional content of these oils varies with oil type. For example, sunflower oil contains high levels of vitamins A, D, and K, while palm oil is a rich source of vitamins A and E. Crude sunflower oil also has the highest content of vitamin E in the form of α-tocopherol amongst vegetable oils.[6]

Vegetable Oil and Hydrogenated Vegetable Oil are cosmetic labeling names for blends of plant-derived oils.[8] The composition of a blend is determined by the desired physical properties. Vegetable Oil and Hydrogenated Vegetable Oil may include, but are not limited to: Canola Oil, Brassica Campestris (Rapeseed) Oil, Carthamus Tinctorius (Safflower) Seed Oil, Helianthus Annuus (Sunflower) Seed Oil, Sesamum Indicum (Sesame) Seed Oil, Elaeis Guineensis (Palm) Oil, Elaeis Guineensis (Palm Kernel) Oil, Cocos Nucifera (Coconut) Oil, Gossypium Herbaceum (Cottonseed) Oil, Glycine Soja (Soybean) Oil, Zea Mays (Corn) Oil, Olea Europaea (Olive) Oil, Prunus Amygdalus Dulcis (Sweet Almond) Oil, and hydrogenated products of these oils.

Processing

The oil may be directly expressed from the source (seed or pulp) followed by solvent extraction. *Bailey's Industrial Oil and Fat Products* states that the removal of pigments and polar materials is mandatory for most cosmetic applications.[9] The process used for oil refining for foods may be adequate for this purpose, or additional steps may be required. Special refining methods to yield colorless and odorless oils are used by the cosmetic industry and include proprietary adsorption chromatography and supercritical fluid extractions.

The majority of the oils presented in this report are produced either from mechanical extraction or solvent extraction or a hybrid of both methods, known as prepress solvent extraction.[6] In solvent extraction, hexane is the most commonly used solvent, as it is economical and easily removed from the extracted oil. Seeds that are rich in oil can be cold pressed to extract oil without the use of solvents.[10]

After the initial extraction by methods such as solvent extraction, the crude (degummed) oil is often refined.[6] The first step is treating the oil with caustic soda to neutralize free fatty acids, hydrolyze phosphatides, and remove some colored pigments and unsaponifiable materials. Soap stock is usually a by-product of this step. The next step involves treating the neutralized oil with activated earth to further adsorb pigments. The last major step in refining oil is deodorizing, usually by a type of steam distillation, which is intended to remove all oxidative cleavage products that impart odor or flavor to the oil. Deodorization also removes tocopherols, sterols, and other minor constituents of free fatty acids and undesirable foreign materials. Figure 2 is a flowchart of the basic refinement process.

After deodorization, oils can be further processed by hydrogenation, which makes oil more resistant to oxidative and thermal damage, and by winterization, where oil is slowly cooled to promote formation of crystals that cause cloudiness, and then filtered to remove the crystals.

Cosmetic grade fatty acid plant oils may include a physical refining step that involves heating crude oil under vacuum.[10] This step allows for the removal of volatile components such as color compounds, odor compounds, and free fatty acids, which gives the refined oil a lighter color, less odor, and lower acid values.

Analytical Methods

Near infrared spectroscopy and gas chromatography have been used, respectively, to phenotype and analyze fatty acid profiles in shea fat (described as *Vitellaria paradoxa*, not *Butyrospermum parkii*).[11] The fatty acid composition of hazel seed oil (*Corylus avellana*, in crude form) has also been analyzed by gas chromatography.[12] The triacylglycerol and diacylglycerol composition oils from hazelnut, pistachio, almond, Brazil nut, and macadamia nuts have been characterized with high-performance liquid chromatography with atmospheric pressure chemical ionization and UV detection.[13] The triacylglycerol profile of Brazil nut oil has also been quantified using dry matrix-assisted laser desorption/ionization time-of flight mass spectrometry.[14]

Impurities

Proteins

Many edible fatty acid oils are derived from foods that are recognized as potent food allergens. It has been shown that an individual that is allergic to a food will generally not react to the refined oil, especially if the oil has been "hot-pressed" or has undergone more processing.[15,16] A prime example is Arachis Hypogaea (Peanut) Oil. Peanuts are extremely allergenic to a large population, but reaction to the oil is rare. In its safety assessment on Arachis Hypogaea (Peanut) Oil, the Expert Panel noted that the major concern associated with allergic reactions to peanuts is the protein.[17] The protein does not partition into the refined oil, and therefore the oil is safe for use in cosmetics. However, researchers have reported protein levels in processed oils. Halsey et al. reported that Lowry protein determinations of cold-pressed and refined sunflower oil found 2-8 µg/ml protein,[18] while Zitouni et al. reported trace amounts of protein in the refined oil.[19] Olszewski et al. found 0.1-0.2 µg protein per g of peanut oil,[20] while Ramazzotti et al. reported finding IgE responsive residual proteins in peanut oil extracts.[21] Porras et al. found soy protein in some samples of soy oil, but not others.[22] Awazuhara et al. reported 1.4-4.0 µg protein per 100 g of soy oil.[23] Although Paschke et al. found approximately 35 µg/l protein content in refined soybean oil, no IgE-binding activity was detectable.[24]

While the Panel has found a general lack of clinical effects for fatty acid oils already reviewed,[17,25-33] other groups have raised concerns. The European Medicines Agency (EMEA) Working Party on Herbal Medicinal Products concluded that soy and peanut products "should be treated as allergenic unless they have an analytically-monitored non-allergenic specification and a safe maximum daily dose."[34] The EMEA found that threshold concentrations for induction of a protein contact dermatitis were not available and recommended, "all medications for topical use containing soya or peanut products should be treated as allergenic."

Aflatoxin

Aflatoxins are metabolic products of the molds *Aspergillus flavus* and *Aspergillus parasiticus*. They are most often produced in stored agricultural crops (such as peanuts and other nut crops) when growth conditions and genetic requirements are favorable.[35-37] The International Agency for Research on Cancer (IARC) categorized aflatoxins as group 1 agents, "carcinogenic to humans".[38,39]

The United States government places the following limitations on peanuts to be considered "negative" for aflatoxin: $\leq$ 15 ppb for "peanuts which have been certified as meeting edible quality grade requirements" and $\leq$ 25 ppb for "non-edible quality categories" (7 CFR Sections 997.30 and 998.200).[40]

> A study reported that crude peanut oil (obtained by solvent extraction or hydraulic pressing) has reduced aflatoxin concentration compared to peanut kernels, and that subsequent processing (alkali refining and bleaching) reduces the concentration still further.[17] In one example, processed peanut oil from moldy peanuts (contaminated with 5500 ppb aflatoxin) had an aflatoxin concentration of < 1ppb. [From CIR assessment on Arachis Hypogaea (Peanut) Oil, 2001.][17]

In 50 samples of hazel nuts from Spain, all samples showed fungal contamination, but no aflatoxin contamination.[41] Of the 50 fungal strains identified, 25 were aflatoxigenic strains. In 20 hazel nut samples collected in Egypt, however, aflatoxin (25-175 µg/kg) was reported as a contaminant in 90% of samples. [From CIR assessment on Hazel Seed Oil, 2001.][42]

Aflatoxin contamination of raw and dried coconut copra has been reported.[33] Improper drying, handling, and storage greatly increase the possibility of contamination by aflatoxins growing on copra. Smoke drying of copra inhibited aflatoxin formation. [From CIR assessment on Cocos Nucifera (Coconut) Oil, 2008.][43]

Glycidol

Glycidol and glycidol fatty acid esters have been detected in refined fatty acid oils.[44-47]

USE

Cosmetic

There are 244 oil ingredients included in this safety assessment, 146 of which are reported to be used; 118 of the in-use ingredients have never been reviewed by CIR, while 28 have been reviewed previously. For the ingredients being reviewed for the first time, the frequency of use, as supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP),[48] and/or concentration of use, as supplied by industry in response to a Personal Care Products Council (Council) survey,[49-51] can be found in Table 5a. (Also included in Table 5a are three ingredients, Citrullus Vulgaris (Watermelon) Seed Oil, Macadamia Nut Oil, and Vaccinium Oxycoccos (Cranberry) Seed Oil, that do not have identifiable International Nomenclature Cosmetic Ingredient (INCI) names. While these ingredients are not part of this assessment, they are very similar to the oils that are identified and information on them is included in this report for completeness.) For the ingredients that have been reviewed previously, the current and historical[26-28,32,52-55] frequency and concentration of use is given in Table 5b. The 97 ingredients not currently reported to be used are listed in Table 5c. [48-51,56,57]

It should be noted that the names vegetable oil and hydrogenated vegetable oil, are used in cosmetic formulations, refer to a blend of plant-derived oils, and the composition of the blend varies.[8]

Of the oils included in this report, Butyrospermum Parkii (Shea) Butter has the most reported uses in cosmetic and personal care products, with a total of 1950; 1680 of those uses are in leave-on formulations. A recent survey of use concentrations for Butyrospermum Parkii (Shea) Butter reports a maximum use concentration of 60% in leave-on products as a cuticle softener, a manicuring application.[58] Helianthus Annuus (Sunflower) Seed Oil has the second greatest number of overall uses reported, with a total of 1414; 1054 of those uses are in leave-on formulations, having use concentrations up to 96%. Many other ingredients are used in an extensive number of formulations. For example, Prunus Amygdalus Dulcis (Sweet Almond) Oil, Olea Europaea (Olive) Fruit Oil, and Glycine Soja (Soybean) Oil have 1127, 915, and 912 uses, respectively. Most of the in-use ingredients have uses in both leave-on and rinse-off product types, many are used in products that are applied around the eye and some are used in a way they can possibly be ingested. Some are used in products that involve mucous membrane exposure, and a few are used in underarm deodorant formulations. Many of the products are used in formulations at relatively high concentrations. Olea Europaea (Olive) Fruit Oil is used at up to 100%, Persea Gratissima (Avocado) Oil is used at up to 98%, Helianthus Annuus (Sunflower) Seed Oil at up to 96%, and Glycine Soja (Soybean) Oil at 95%.

Oils are used in a wide variety of cosmetic products for their skin conditioning, occlusive, emollient, moisturizing and other properties.

Some of the oils included in this report are used in products that can be inhaled, and effects on the lungs that may be induced by aerosolized products containing these ingredients are of concern. The particle size of aerosol hair sprays and of

pump hair sprays is 38 μm and >80 μm, respectively, and is relatively large compared to respirable particle sizes (≤10 μm). Therefore, because of their size, most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

None of the oils, hydrogenated oils, unsaponifiables, oil fatty acids, and salts of the fatty acids described in this report were restricted from use in any way under the rules governing cosmetic products in the European Union.[59]

Non-Cosmetic

The primary uses for plant-derived fatty acid oils are for cooking. Palm oil is the world's most widely consumed edible oil (41.7 million metric tons), followed by soybean oil, rapeseed oil, sunflower seed oil, cottonseed oil, peanut oil, palm kernel oil, coconut oil, ,and olive oil.[6,60] Non-food, non-cosmetic uses for edible fatty acid oils are found in Table 6.

ANIMAL TOXICOLOGY

Many of the fatty acid oils in this assessment are edible, and exposure to the oils from food use would result in a much larger systemic dose than that resulting from use in cosmetic products. Consequently, their systemic toxicity potential is not addressed in this report. The safety focus of use of these oils as cosmetic ingredients is on the potential for irritation and sensitization.

CARCINOGENICITY

The safety of glycidol fatty acid esters in refined vegetable oils was assessed by IARC. Glycidol was determined to be a Group2A (probably carcinogenic to humans) chemical while glycidol fatty acid esters was determined to be a Group 3 (not classifiable as to carcinogenicity to humans) chemical.[46,47]

The Federal Institute for Risk Assessment in Germany released a summary of their initial evaluation of the assessment of levels of glycidol fatty acid esters detected in refined vegetable fats.[45] While acknowledging that the levels of glycidol that may be released from glycidol fatty acid esters are not known, the evaluation noted that glycidol is classified as probably carcinogenic to humans. The evaluation was based on findings of the German Chemical and Veterinary Test Agency (CVUA) that noted that glycidol is converted to 3-chloropropanediol and it appeared to be the 3-chloropropanediol that was detected in the vegetable fat.[44] The levels of 3-chloropropanediol were negligible at the crude oil, degummed, neutralized, and bleached stages, but levels were significant at the deodorized stage.

Anacardium Occidentale (Cashew) Seed Oil

The modulatory effect of Anacardium Occidentale (Cashew) Seed Oil on antioxidant potential was investigated in female Swiss albino mice in a 120 day skin papillomagenesis study.[61] The mice were divided into 4 groups of 15 and 1 group of 10 (vehicle control). Test groups were as follows: Group I was the vehicle control, receiving 0.1 ml acetone; Group II was the positive control, receiving a single dose of 7,12-dimethylbenz(a)anthracene (DMBA) (0.005 mg/0.05 ml acetone) followed by applications of 2% croton oil 3 times a week until study termination; Group III received a single dose of DMBA followed by applications of 2.5% cashew nut kernel oil 3 times a week until study termination; Group IV received a single dose of DMBA followed by applications of 5% cashew nut kernel oil 3 times a week until study termination; and Group V was 5% cashew nut kernel oil applied until study termination. The oil was applied to the clipped dorsal scapular region that was 2 cm in diameter. Body weights were recorded at regular intervals. Skin papillomas greater than 1 mm in diameter at the application sites were recorded weekly and included in the data analysis if they persisted for more than 2 weeks. The positive control group yielded expected results (86% tumor incidence). No tumors were observed in the vehicle control or the other test groups. The authors concluded that cashew nut kernel oil did not exhibit any solitary carcinogenic activity.

IRRITATION AND SENSITIZATION

Dermal Effects

Non-Human

Dermal irritation and sensitization studies were performed in animals on a number of the plant-derived fatty acid oils, and the results were mostly negative in all of the studies. These studies are summarized in Table 7a. Photosensitization data, when available, are also included in Table 7a. None of the tested oils were phototoxic. Summary statements of non-human dermal studies from previous CIR reports on oils are provided in Table 7b.

Human

Plant-derived fatty acid oils are commonly believed to be safe for use on the skin.[9] de Groot notes that no documentation exists to show that high quality edible lipids cause adverse reactions in normal individuals (except for potential comedogenicity).[62] Very few reports of adverse reactions to cosmetic use of edible fatty acid oils have been reported.

Many plant-derived fatty acid oils are derived from foods that are recognized as potent food allergens. The allergic reactions are thought to be caused by the proteins present in the food. It has been shown that an individual that is allergic to a food will generally not react to the refined oil, especially if the oil has been "hot-pressed" or has undergone more processing.[15,16] In its safety assessment on Arachis Hypogaea (Peanut) Oil, the CIR Expert Panel noted that while peanuts are extremely allergenic to a large population, reaction to the oil is rare. Because the major concern associated with allergic reactions to peanuts is the protein[17] which does not partition into the refined oil; therefore the oil is safe for use in cosmetics. Crevel et al. also concluded that chemically refined peanut oil is safe for the majority of peanut allergic individuals.[16] They stated that "as peanut is acknowledged to be one of the most potent food allergens, it is reasonable to extrapolate the conclusions drawn up for peanut oil to other edible oils." However, they concede that validated analytical methodology for establishing the protein content of oil is needed.

In support of the conclusions stated earlier, Crevel et al. also examined the allergenicity of some other oils. Very few instances of allergic reactions to other major edible fatty acid oils have been reported. Even sesame oil, which differs from the other oils in that it is used as a flavorant and, therefore, is not as refined and is expected to contain significantly more protein that the other edible fatty acid oils, has had very few reports of allergic reaction. Additional studies demonstrating safety are summarized later in this section.[18,63]

A large number of clinical irritation and sensitization studies were made available on many of the oils, primarily in formulation, and these studies are summarized in Table 8a. All of the data indicated that the oils were not irritants or sensitizers. Summary statements of human dermal studies, including phototoxicity/photosensitization data, from previous CIR reports on oils are provided in Table 8b.

Mucosal Irritation

Non-Human

Ocular irritation studies were performed using animals on a number of plant-derived fatty acid oils. While the majority of the oils were non-irritating to mildly irritating, Crambe Abyssinica Seed Oil was an ocular irritant and Linum Usitatissimum (Linseed) Seed Oil was moderately irritating. Available ocular irritation studies are summarized in Table 9a. Summary statements of ocular irritation studies from previous CIR reports on oils are provided in Table 9b.

Human

In clinical ocular irritation studies, formulations containing Linum Usitatissimum (Linseed) Oil and Ribes Nigrum (Black Currant) Seed Oil did not produce adverse reactions, and were considered safe for contact lens wearers. These studies are also summarized in Table 9a.

CLINICAL USE

Clinical Trials/Case Studies

Case studies reporting various results have been summarized in Table 10 for a number of the oils included in this report.

SUMMARY

The report addresses the safety of Plant-Derived Fatty Acid Oils. These oils, which are derived from vegetable and fruit plants, are composed of mono-, di-, and, primarily, triglycerides, free fatty acids and other minor components, including natural antioxidants and fat-soluble vitamins. The percentage of chemical constituents and nutritional content of individual oil types is dependent on region where the oil plant is grown, individual cultivars, and plant genetics. Oils used in cosmetics are likely produced in the same manner as those used in the food industry. Oils may be expressed through mechanical or solvent extraction. The oils may undergo further refining, such as neutralizing, bleaching, and deodorizing, to remove pigments, odors, unsaponifiable materials, and other undesirables.

Individuals who have food allergies to a plant protein rarely exhibit allergic reactions when exposed to refined oils of the same plant. Data evaluation by the CIR Expert Panel regarding method of manufacture indicates that protein constituents do not partition into the refined oils. The CIR Expert Panel also has found a general lack of clinical effects for fatty acid oils that they have already reviewed; however, other researchers have raised concerns about the presence of residual proteins in oils, such as peanut and soy.

Glycidol fatty acid esters are possible impurities in refined vegetable oils. While the amount of glycidol that may be present with glycidol fatty acid esters is not known, the IARC has noted that glycidol is probably carcinogenic to humans and that glycidol fatty acid esters are not classifiable as to carcinogenicity in humans. Peanuts and soy may contain aflatoxins, metabolic products of certain molds that are carcinogenic to humans.

Of the oils described in this report, Butyrospermum Parkii (Shea) Butter has the most reported uses in cosmetic and personal care products with a total of 1950 and is used at a maximum concentration of 60%. Oils are used in a wide variety of cosmetic products, including use in hair spray and other aerosolized products. None of the oils, or the related counterparts, described in this report are restricted from use in the European Union.

Anacardium Occidentale (Cashew) Seed Oil was not a tumor promoter in a DMBA skin test system.

The safety focus of use of these oils as cosmetic ingredients is on the potential for irritation and sensitization. Undiluted, technical grade, Arachis Hypogaea (Peanut) Oil was moderately irritating to rabbits and guinea pig skin, and 5% aq. solutions of a bar soap containing 13% sodium cocoate had irritation scores of 1.6-4.0/8 in animal studies. However, the remaining animal and clinical irritation and/or sensitization studies conducted on a large number of the oils included in this report, primarily in formulation, did not report any significant irritation or sensitization reactions, indicating that refined oils derived from plants are not dermal irritants or sensitizers.

The phototoxic potential of formulations containing Butyrospermum Parkii (Shea) Butter and Elaeis Guineensis (Palm) Oil and of Oryza Sativa (Rice) Bran and (Rice) Germ Oil, neat, was evaluated in animal studies, and the phototoxic

potential of Cocos Nucifera (Coconut) Oil, Sodium Cocoate, Prunus Amygdalus Dulcis (Sweet) Almond Oil, and Oryza Sativa (Rice) Bran Oil was examined clinically. None of these ingredients were phototoxic.

The comedogenicity of Corylus Avellana (Hazel) Seed Oil was evaluated using rabbits, and a slight difference in the number and size of the pilosebaceous follicles and a slight excess of sebum and a dilation of the follicles was observed. In clinical testing with an eye mask containing 0.2% Ribes Nigrum (Black Currant) Seed Oil (undiluted), the formulation was non-comedogenic.

The ocular irritation potential of a number of the oils, mostly in formulation, was evaluated in testing using animals or alternative assays. The majority of the test results did not report significant ocular irritation. A lotion containing 1.5% Elaeis Guineensis (Palm) Oil was moderately irritating to rabbit eyes, and a mascara containing 9.4% Linum Usitatissimum (Linseed) Seed Oil was moderately irritating in an alternative assay.

In human testing, a mascara containing 9.4% Linum Usitatissimum (Linseed) Seed Oil did not produce ocular irritation or adverse effects in contact lenses wearers or subjects with sensitive eyes. An eye mask containing 0.2% Ribes Nigrum (Black Currant) Seed Oil (undiluted) was tested and considered safe for contact lens wearers.

DISCUSSION

Plant-derived fatty acid oils, oils which have been hydrogenated to reduce or eliminate unsaturation, fatty acid salts, and oil unsaponifiables were reviewed by the CIR Expert Panel. Most of theses ingredients in this report are mixtures of triglycerides containing fatty acids and fatty acid derivatives, the safety of which in cosmetics has been established. Upon review of these ingredients, the Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulations.

Additionally, the Panel considered the safety of glycidol and glycidol fatty acid esters in refined vegetable oils. While the Panel recognizes that these impurities may be carcinogenic, absorption through the skin would be very low and likely does not pose a significant hazard. Nonetheless, suppliers should take steps to eliminate or reduce the presence of glycidol and glycidol fatty acid esters in plant-based fatty acid oils that are used in cosmetic products. Aflatoxins, which are potent carcinogens, may be present in moldy nuts and coconut copra, but are not found in oils expressed from these nuts and copra. The Panel adopted the U.S. Department of Agriculture designation of $\leq$15 ppb as corresponding to “negative” aflatoxin content.

Certain of the plant-derived oils are used in cosmetic products that may be inhaled during their use. In practice, however, the particle sizes produced by the cosmetic aerosols are not respirable.

The Panel discussed the relationship between food allergies and exposure to refined oils. Individuals who have food allergies to a plant protein rarely exhibit allergic reactions when exposed to refined oils of the same plant. The Panel has found a general lack of clinical effects for plant-derived fatty acid oils already reviewed.

Fatty acid composition data were available for the majority of the oils included in this review and the Panel agreed that the composition data, in combination with the available data on method of manufacture, impurities, safety test data, a long history of safe use in foods, and an absence of adverse reactions in clinical experience, was a sufficient basis for determining safety. The Expert Panel did note that vegetable oil is a blend of a number of different oils, and that a specific composition of vegetable oil was not available. The Expert Panel determined that the safety of vegetable oil as used in cosmetic formulations has been established, providing that the blend contains oils for which the fatty acid composition is known.

Addtionally, while data on the fatty acid composition of Fragaria Vesca (Strawberry) Seed Oil and Fragaria Virginiana (Strawberry) Seed Oil were not available, data were available for Fragaria Ananassa (Strawberry) Seed Oil and Fragaria Chiloensis (Strawberry) Seed Oil. In that the fatty acid compositions of Fragaria Ananassa and Fragaria Chiloensis (Strawberry) Seed Oil were similar to each other, it was assumed that Fragaria Vesca and Fragaria Virginiana (Strawberry) Seed Oils would also have similar fatty acid compositions.

The Expert Panel also noted that arachidonic acid is a fatty acid constituent of Lycium Barbarum Seed Oil, Oryza Sativa (Rice) Germ Oil, and Sclerocarya Birrea Seed Oil. Although a previously published CIR evaluation concluded that insufficient data exist to support the safety of arachidonic acid in cosmetic products, the Panel was of the opinion that the concentration of use of these ingredients was sufficiently low that the amount of free arachidonic acid from these oils would not warrant concern.

Finally, the conclusion reached by the Panel on the safety of the plant-derived fatty acid oils supersedes the 2001 conclusion of insufficient data for Corylus Americana and Corylus Avellana (Hazel) Seed Oil.

CONCLUSION

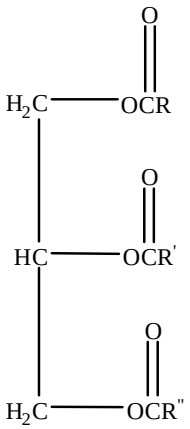
The CIR Expert Panel concluded that the 244 plant-derived fatty acid oils included in this review are safe in the present practices of use and concentration described in this safety assessment. Were the ingredients not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and concentrations comparable to others in these groups. The ingredients found safe are:

Actinidia Chinensis (Kiwi) Seed Oil
Adansonia Digitata Oil
Adansonia Digitata Seed Oil*
Aleurites Moluccanus Bakoly Seed Oil*
Aleurities Moluccana Seed Oil
Amaranthus Hypochondriacus Seed Oil*
Anacardium Occidentale (Cashew) Seed Oil
Arachis Hypogaea (Peanut) Oil
Arctium Lappa Seed Oil*
Argania Spinosa Kernel Oil
Astrocaryum Murumuru Seed Butter
Avena Sativa (Oat) Kernel Oil
Babassu Acid*
Bassia Butyracea Seed Butter*
Bassia Latifolia Seed Butter
Bertholletia Excelsa Seed Oil
Borago Officinalis Seed Oil
Brassica Campestris (Rapeseed) Oil Unsaponifiables*
Brassica Campestris (Rapeseed) Seed Oil
Brassica Napus Seed Oil*
Brassica Oleracea Acephala Seed Oil*
Brassica Oleracea Italica (Broccoli) Seed Oil
Butyrospermum Parkii (Shea) Butter
Butyrospermum Parkii (Shea) Butter Unsaponifiables
Butyrospermum Parkii (Shea) Oil
Camelina Sativa Seed Oil
Camellia Japonica Seed Oil
Camellia Kissi Seed Oil
Camellia Oleifera Seed Oil
Camellia Sinensis Seed Oil
Canarium Indicum Seed Oil*
Canola Oil
Canola Oil Unsaponifiables
Carica Papaya Seed Oil
Carthamus Tinctorius (Safflower) Seed Oil
Carya Illinoensis (Pecan) Seed Oil*
Caryocar Brasiliense Fruit Oil
Chenopodium Quinoa Seed Oil
Citrullus Lanatus (Watermelon) Seed Oil
Citrus Aurantifolia (Lime) Seed Oil*
Citrus Aurantifolia (Lime) Seed Oil Unsaponifiables*
Citrus Aurantium Dulcis (Orange) Seed Oil*
Citrus Aurantium Dulcis (Orange) Seed Oil Unsaponifiables*
Citrus Grandis (Grapefruit) Seed Oil*
Citrus Grandis (Grapefruit) Seed Oil Unsaponifiables*
Citrus Limon (Lemon) Seed Oil*
Citrus Paradisi (Grapefruit) Seed Oil
Coconut Acid
Cocos Nucifera (Coconut) Oil
Cocos Nucifera (Coconut) Seed Butter*
Coix Lacryma-Jobi (Job's Tears) Seed Oil*
Corn Acid*
Corylus Americana (Hazel) Seed Oil
Corylus Avellana (Hazel) Seed Oil
Cottonseed Acid*
Crambe Abyssinica Seed Oil
Cucumis Sativus (Cucumber) Seed Oil
Cucurbita Pepo (Pumpkin) Seed Oil
Cynara Cardunculus Seed Oil*
Elaeis (Palm) Fruit Oil*
Elaeis Guineensis (Palm) Butter*
Elaeis Guineensis (Palm) Kernel Oil
Elaeis Guineensis (Palm) Oil
Elaeis Oleifera Kernel Oil
Euterpe Oleracea Fruit Oil
Fragaria Ananassa (Strawberry) Seed Oil*
Fragaria Chiloensis (Strawberry) Seed Oil*
Fragaria Vesca (Strawberry) Seed Oil*
Fragaria Virginiana (Strawberry) Seed Oil*
Garcinia Indica Seed Butter
Gevuina Avellana Seed Oil
Gevuina Avellana Oil

Glycine Soja (Soybean) Oil
Glycine Soja (Soybean) Oil Unsaponifiables
Gossypium Herbaceum (Cotton) Seed Oil
Guizotia Abyssinica Seed Oil*
Helianthus Annuus (Sunflower) Seed Oil
Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables
Hippophae Rhamnoides Fruit Oil
Hippophae Rhamnoides Oil
Hippophae Rhamnoides Seed Oil*
Hydrogenated Adansonia Digitata Seed Oil*
Hydrogenated Apricot Kernel Oil
Hydrogenated Apricot Kernel Oil Unsaponifiables*
Hydrogenated Argania Spinosa Kernel Oil*
Hydrogenated Avocado Oil
Hydrogenated Black Currant Seed Oil*
Hydrogenated Camelina Sativa Seed Oil*
Hydrogenated Camellia Oleifera Seed Oil
Hydrogenated Canola Oil
Hydrogenated Coconut Acid
Hydrogenated Coconut Oil
Hydrogenated Cottonseed Oil
Hydrogenated Cranberry Seed Oil*
Hydrogenated Evening Primrose Oil
Hydrogenated Grapefruit Seed Oil*
Hydrogenated Grapefruit Seed Oil Unsaponifiables*
Hydrogenated Grapeseed Oil
Hydrogenated Hazelnut Oil*
Hydrogenated Kukui Nut Oil*
Hydrogenated Lime Seed Oil*
Hydrogenated Lime Seed Oil Unsaponifiables*
Hydrogenated Macadamia Seed Oil*
Hydrogenated Meadowfoam Seed Oil*
Hydrogenated Olive Oil
Hydrogenated Olive Oil Unsaponifiables
Hydrogenated Orange Seed Oil*
Hydrogenated Orange Seed Oil Unsaponifiables*
Hydrogenated Palm Acid*
Hydrogenated Palm Kernel Oil
Hydrogenated Palm Oil
Hydrogenated Passiflora Edulis Seed Oil*
Hydrogenated Peach Kernel Oil*
Hydrogenated Peanut Oil
Hydrogenated Pistachio Seed Oil*
Hydrogenated Pumpkin Seed Oil*
Hydrogenated Punica Granatum Seed Oil*
Hydrogenated Rapeseed Oil*
Hydrogenated Raspberry Seed Oil
Hydrogenated Rice Bran Oil*
Hydrogenated Rosa Canina Fruit Oil*
Hydrogenated Safflower Seed Oil*
Hydrogenated Sesame Seed Oil*
Hydrogenated Shea Butter
Hydrogenated Soybean Oil
Hydrogenated Sunflower Seed Oil
Hydrogenated Sweet Almond Oil
Hydrogenated Sweet Almond Oil Unsaponifiables*
Hydrogenated Vegetable Oil
Hydrogenated Wheat Germ Oil*
Hydrogenated Wheat Germ Oil Unsaponifiables*
Irvingia Gabonensis Kernel Butter
Juglans Regia (Walnut) Seed Oil
Limnanthes Alba (Meadowfoam) Seed Oil
Linseed Acid
Linum Usitatissimum (Linseed) Seed Oil
Luffa Cylindrica Seed Oil
Lupinus Albus Oil Unsaponifiables*
Lupinus Albus Seed Oil
Lycium Barbarum Seed Oil
Macadamia Integrifolia Seed Oil
Macadamia Ternifolia Seed Oil
Magnesium Cocoate
Mangifera Indica (Mango) Seed Butter
Mangifera Indica (Mango) Seed Oil
Morinda Citrifolia Seed Oil*
Moringa Oleifera Seed Oil
Moringa Pterygosperma Seed Oil
Oenothera Biennis (Evening Primrose) Oil
Olea Europaea (Olive) Husk Oil*
Olea Europaea (Olive) Oil Unsaponifiables
Olea Europaea (Olive) Fruit Oil
Olive Acid*
Orbignya Cohune Seed Oil
Orbignya Oleifera Seed Oil
Orbignya Speciosa Kernel Oil
Oryza Sativa (Rice) Bran Oil
Oryza Sativa (Rice) Germ Oil
Oryza Sativa (Rice) Seed Oil*
Palm Acid
Palm Kernel Acid
Passiflora Edulis Seed Oil
Peanut Acid*
Perilla Ocymoides Seed Oil
Persea Gratissima (Avocado) Butter
Persea Gratissima (Avocado) Oil
Persea Gratissima (Avocado) Oil Unsaponifiables
Pistacia Vera Seed Oil
Plukenetia Volubilis Seed Oil
Potassium Babassuate*
Potassium Cocoate
Potassium Cornate*
Potassium Hydrogenated Cocoate*
Potassium Hydrogenated Palmate*
Potassium Olivate
Potassium Palm Kernelate
Potassium Palmate
Potassium Peanutate
Potassium Rapeseedate*
Potassium Safflowerate*
Potassium Soyate*
Prunus Amygdalus Dulcis (Sweet Almond) Oil
Prunus Amygdalus Dulcis (Sweet Almond) Oil Unsaponifiables*
Prunus Armeniaca (Apricot) Kernel Oil
Prunus Armeniaca (Apricot) Kernel Oil Unsaponifiables*
Prunus Avium (Sweet Cherry) Seed Oil
Prunus Domestica Seed Oil
Prunus Persica (Peach) Kernel Oil
Punica Granatum Seed Oil
Pyrus Malus (Apple) Seed Oil
Rapeseed Acid*
Ribes Nigrum (Black Currant) Seed Oil
Ribes Rubrum (Currant) Seed Oil*
Rice Bran Acid*
Rosa Canina Fruit Oil
Rubus Chamaemorus Seed Oil
Rubus Idaeus (Raspberry) Seed Oil
Safflower Acid*
Schinziophyton Rautanenii Kernel Oil
Sclerocarya Birrea Seed Oil
Sesamum Indicum (Sesame) Oil Unsaponifiables
Sesamum Indicum (Sesame) Seed Butter*
Sesamum Indicum (Sesame) Seed Oil
Silybum Marianum Seed Oil [Thistle]

Sodium Astrocaryum Murumuruate
Sodium Avocadoate
Sodium Babassuate
Sodium Cocoa Butterate*
Sodium Cocoate
Sodium Grapeseedate
Sodium Hydrogenated Cocoate*
Sodium Hydrogenated Palmate*
Sodium Macadamiaseedate*
Sodium Mangoseedate
Sodium Olivate
Sodium Palm Kernelate
Sodium Palmate
Sodium Peanutate*
Sodium Rapeseedate*
Sodium Safflowerate*
Sodium Sesameseedate
Sodium Soyate*
Sodium Sweet Almondate
Sodium Theobroma Grandiflorum Seedate*
Solanum Lycopersicum (Tomato) Fruit Oil
Solanum Lycopersicum (Tomato) Seed Oil
Soy Acid*
Sunflower Seed Acid*
Theobroma Cacao (Cocoa) Seed Butter
Theobroma Grandiflorum Seed Butter
Torreya Nucifera Seed Oil*
Triticum Aestivum (Wheat) Germ Oil*
Triticum Vulgare (Wheat) Germ Oil
Triticum Vulgare (Wheat) Germ Oil Unsaponifiables*
Vaccinium Corymbosum (Blueberry) Seed Oil*
Vaccinium Macrocarpon (Cranberry) Seed Oil
Vaccinium Myrtillus Seed Oil
Vaccinium Vitis-Idaea Seed Oil
Vegetable (Olus) Oil
Vitis Vinifera (Grape) Seed Oil
Wheat Germ Acid
Zea Mays (Corn) Germ Oil
Zea Mays (Corn) Oil
Zea Mays (Corn) Oil Unsaponifiables

FIGURES AND TABLES



-OCR, -OCR', and -OCR" may be the same or different fatty acid radicals.

Figure 1. **General structure of fats and oils**
(Reference[4])

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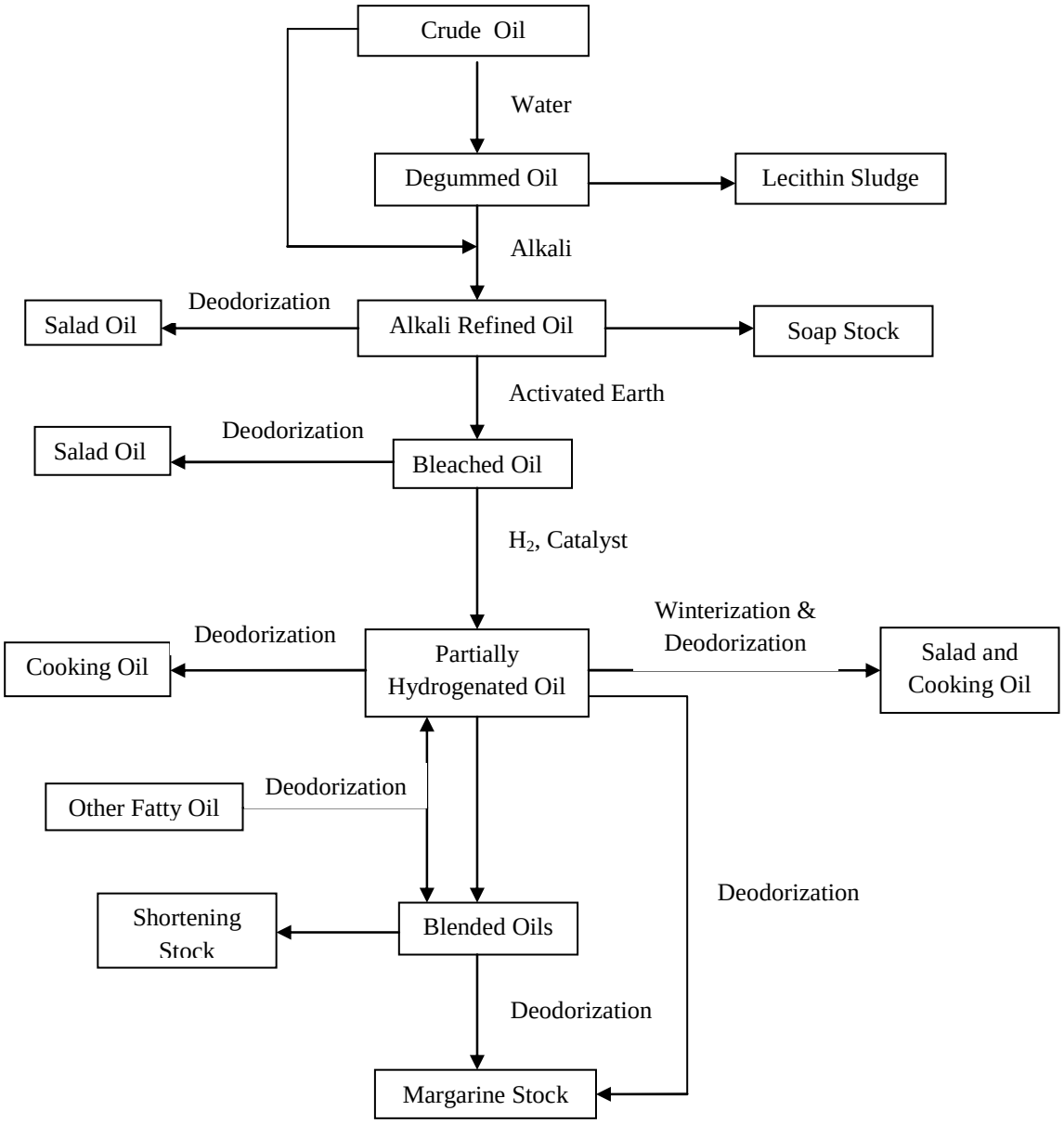

Figure 2. **Basic oil refinement flowchart**
(Reference.[6])

Table 1. **Plant-derived fatty acid oils**.

Actinidia Chinensis (Kiwi) Seed Oil
Adansonia Digitata Oil [Baobab]
  Adansonia Digitata Seed Oil
  Hydrogenated Adansonia Digitata Seed Oil
Aleurities Moluccana Seed Oil [Kukui] (CAS No. 8015-80-3)
  Hydrogenated Kukui Nut Oil
  Aleurites Moluccanus Bakoly Seed Oil
Amaranthus Hypochondriacus Seed Oil [Amaranth]
Anacardium Occidentale (Cashew) Seed Oil (CAS No. 8007-24-7)
Arachis Hypogaea (Peanut) Oil (CAS No. 8002-03-7)[a]
  Hydrogenated Peanut Oil (CAS No. 68425-36-5)
  Potassium Peanutate
  Sodium Peanutate
  Peanut Acid (CAS No. 91051-35-3)
Arctium Lappa Seed Oil [Burdock]
Argania Spinosa Kernel Oil [Argan]
  Hydrogenated Argania Spinosa Kernel Oil
Astrocaryum Murumuru Seed Butter [Murumuru]
  Sodium Astrocaryum Murumuruate
Avena Sativa (Oat) Kernel Oil
Bassia Butyracea Seed Butter
Bassia Latifolia Seed Butter [Mahwa]
Bertholletia Excelsa Seed Oil [Brazil]
Borago Officinalis Seed Oil [Borage] (CAS No. 225234-12-8)
Brassica Campestris (Rapeseed) Seed Oil
  Brassica Campestris (Rapeseed) Oil Unsaponifiables
  Hydrogenated Rapeseed Oil
  Rapeseed Acid
  Potassium Rapeseedate
  Sodium Rapeseedate
Brassica Napus Seed Oil [Rapeseed]
Brassica Oleracea Acephala Seed Oil [Kale]
Brassica Oleracea Italica (Broccoli) Seed Oil
Butyrospermum Parkii (Shea) Oil
  Butyrospermum Parkii (Shea) Butter (CAS No. 68920-03-6;194043-92-0)
  Butyrospermum Parkii (Shea) Butter Unsaponifiables
    (CAS No. 194043-92-0; 225234-14-0)
  Hydrogenated Shea Butter
Camelina Sativa Seed Oil [False Flax]
  Hydrogenated Camelina Sativa Seed Oil
Camellia Japonica Seed Oil
Camellia Kissi Seed Oil [Tea]
Camellia Oleifera Seed Oil [Tea Seed]
  Hydrogenated Camellia Oleifera Seed Oil
Camellia Sinensis Seed Oil
Canarium Indicum Seed Oil [Galip]
Canola Oil
  Canola Oil Unsaponifiables
  Hydrogenated Canola Oil
Carica Papaya Seed Oil [Papaya]
Carthamus Tinctorius (Safflower) Seed Oil
  Hydrogenated Safflower Seed Oil
  Potassium Safflowerate
  Sodium Safflowerate
  Safflower Acid
Carya Illinoensis (Pecan) Seed Oil
Caryocar Brasiliense Fruit Oil [Pequi]
Chenopodium Quinoa Seed Oil [Quinoa]
Citrullus Lanatus (Watermelon) Seed Oil
Citrus Aurantifolia (Lime) Seed Oil
  Citrus Aurantifolia (Lime) Seed Oil Unsaponifiables
  Hydrogenated Lime Seed Oil
  Hydrogenated Lime Seed Oil Unsaponifiables
Citrus Aurantium Dulcis (Orange) Seed Oil
  Citrus Aurantium Dulcis (Orange) Seed Oil Unsaponifiables
  Hydrogenated Orange Seed Oil
  Hydrogenated Orange Seed Oil Unsaponifiables
Citrus Grandis (Grapefruit) Seed Oil
  Citrus Grandis (Grapefruit) Seed Oil Unsaponifiables
  Hydrogenated Grapefruit Seed Oil
  Hydrogenated Grapefruit Seed Oil Unsaponifiables
Citrus Paradisi (Grapefruit) Seed Oil
Citrus Limon (Lemon) Seed Oil (CAS No. 85085-28-5)
Cocos Nucifera (Coconut) Oil (CAS No. 8001-31-8)
  Hydrogenated Coconut Oil (CAS No. 84836-98-6)
  Cocos Nucifera (Coconut) Seed Butter
  Magnesium Cocoate
  Potassium Cocoate (CAS No. 61789-30-8)
  Potassium Hydrogenated Cocoate
  Sodium Cocoate (CAS No. 61789-31-9)
  Sodium Hydrogenated Cocoate
  Coconut Acid (CAS No. 61788-47-4)
  Hydrogenated Coconut Acid (CAS No. 68938-15-8)
Coix Lacryma-Jobi (Job's Tears) Seed Oil
Corylus Americana (Hazel) Seed Oil
  Hydrogenated Hazelnut Oil
Corylus Avellana (Hazel) Seed Oil
Crambe Abyssinica Seed Oil [Abyssinian Mustard]
Cucumis Sativus (Cucumber) Seed Oil (CAS No. 70955-25-8)
Cucurbita Pepo (Pumpkin) Seed Oil (CAS No. 8016-49-7)
  Hydrogenated Pumpkin Seed Oil
Cynara Cardunculus Seed Oil [Artichoke] (CAS No. 923029-60-1)
Elaeis Guineensis (Palm) Oil (CAS No. 8002-75-3)
  Elaeis Guineensis (Palm) Kernel Oil (CAS No. 8023-79-8)

Table 1. Plant-derived Fatty Acid Oils

Hydrogenated Palm Kernel Oil (CAS No. 68990-82-9; 84540-04-5)
Elaeis (Palm) Fruit Oil
Hydrogenated Palm Oil (CAS No. 8033-29-2; 68514-74-9)
Elaeis Guineensis (Palm) Butter (CAS No. 8002-75-3)
Palm Kernel Acid
Potassium Palm Kernelate
Potassium Palmate
Potassium Hydrogenated Palmate
Sodium Palm Kernelate (CAS No. 61789-89-7)
Sodium Palmate (CAS No. 61790-79-2)
Sodium Hydrogenated Palmate
Palm Acid
Hydrogenated Palm Acid
Elaeis Oleifera Kernel Oil
Euterpe Oleracea Fruit Oil [Acai]
Fragaria Ananassa (Strawberry) Seed Oil
Fragaria Chiloensis (Strawberry) Seed Oil
Fragaria Vesca (Strawberry) Seed Oil
Fragaria Virginiana (Strawberry) Seed Oil
Garcinia Indica Seed Butter [Kokum]
Juglans Regia (Walnut) Seed Oil (CAS No. 8024-09-7)
Limnanthes Alba (Meadowfoam) Seed Oil (CAS No. 153065-40-8)
Hydrogenated Meadowfoam Seed Oil
Linum Usitatissimum (Linseed) Seed Oil (CAS No. 8001-26-1)
Linseed Acid (CAS No. 68424-45-3)
Luffa Cylindrica Seed Oil [Luffa]
Lupinus Albus Seed Oil [White Lupine]
Lupinus Albus Oil Unsaponifiables
Lycium Barbarum Seed Oil [Goji Berry]
Macadamia Integrifolia Seed Oil
Hydrogenated Macadamia Seed Oil
Macadamia Ternifolia Seed Oil (CAS No. 128497-20-1 or 129811-19-4)
Sodium Macadamiaseedate
Mangifera Indica (Mango) Seed Oil
Mangifera Indica (Mango) Seed Butter
Sodium Mangoseedate
Morinda Citrifolia Seed Oil [Noni]
Moringa Oleifera Seed Oil [Ben/Moringa]
Moringa Pterygosperma Seed Oil
Oenothera Biennis (Evening Primrose) Oil
Hydrogenated Evening Primrose Oil
Olea Europaea (Olive) Fruit Oil (CAS No. 8001-25-0)
Olea Europaea (Olive) Oil Unsaponifiables (CAS No. 156798-12-8)
Hydrogenated Olive Oil
Hydrogenated Olive Oil Unsaponifiables
Potassium Olivate (CAS No. 68154-77-8)
Sodium Olivate (CAS No. 64789-88-6)
Olea Europaea (Olive) Husk Oil
Olive Acid (CAS No. 92044-96-7)
Gevuina Avellana Oil [Chilean Hazel]
Gevuina Avellana Seed Oil
Glycine Soja (Soybean) Oil (CAS No. 8001-22-7)
Glycine Soja (Soybean) Oil Unsaponifiables (CAS No. 91770-67-1)
Hydrogenated Soybean Oil (CAS No. 8016-70-4)
Soy Acid (CAS No. 68308-53-2)
Potassium Soyate
Sodium Soyate
Gossypium Herbaceum (Cotton) Seed Oil (CAS No. 8001-29-4)
Hydrogenated Cottonseed Oil (CAS No. 68334-00-9)
Cottonseed Acid (CAS No. 68308-51-0)
Guizotia Abyssinica Seed Oil [Ramtil/Niger]
Helianthus Annuus (Sunflower) Seed Oil (CAS No. 8001-21-6)
Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables
Hydrogenated Sunflower Seed Oil
Sunflower Seed Acid (CAS No. 84625-38-7)
Hippophae Rhamnoides Oil [Sea-Buckthorn]
Hippophae Rhamnoides Fruit Oil [Sea-Buckthorn]
Hippophae Rhamnoides Seed Oil [Sea-Buckthorn]
Irvingia Gabonensis Kernel Butter [Dika] (CAS No. 192230-28-7)
Orbignya Cohune Seed Oil [Cohune]
Orbignya Oleifera Seed Oil [Babassu] (CAS No. 91078-92-1)
Potassium Babassuate
Sodium Babassuate
Babassu Acid
Orbignya Speciosa Kernel Oil
Oryza Sativa (Rice) Bran Oil (CAS No. 68553-81-1; 84696-37-7)
Hydrogenated Rice Bran Oil
Oryza Sativa (Rice) Germ Oil
Oryza Sativa (Rice) Seed Oil
Rice Bran Acid (CAS No. 93165-33-4)
Passiflora Edulis Seed Oil [Passion Fruit] (CAS No. 87676-26-1)
Hydrogenated Passiflora Edulis Seed Oil
Perilla Ocymoides Seed Oil [Perilla]
Persea Gratissima (Avocado) Oil (CAS No. 8024-32-6)
Persea Gratissima (Avocado) Oil Unsaponifiables (CAS No. 91770-40-0)
Hydrogenated Avocado Oil
Persea Gratissima (Avocado) Butter
Sodium Avocadoate
Pistacia Vera Seed Oil [Pistachio] (CAS No. 90082-81-8; 129871-01-8)
Hydrogenated Pistachio Seed Oil
Plukenetia Volubilis Seed Oil [Sacha Inchi]
Prunus Amygdalus Dulcis (Sweet Almond) Oil
(CAS No. 8007-69-0; 90320-37-9)
Prunus Amygdalus Dulcis (Sweet Almond) Oil Unsaponifiables
Hydrogenated Sweet Almond Oil
Hydrogenated Sweet Almond Oil Unsaponifiables
Sodium Sweet Almondate
Prunus Armeniaca (Apricot) Kernel Oil (CAS No. 72869-69-3)

Table 1. Plant-derived Fatty Acid Oils

Prunus Armeniaca (Apricot) Kernel Oil Unsaponifiables
Hydrogenated Apricot Kernel Oil
Hydrogenated Apricot Kernel Oil Unsaponifiables
Prunus Avium (Sweet Cherry) Seed Oil
Prunus Domestica Seed Oil [Prune/Plum]
Prunus Persica (Peach) Kernel Oil (CAS No. 8002-78-6; 8023-98-1)
Hydrogenated Peach Kernel Oil
Punica Granatum Seed Oil [Pomegranate]
Hydrogenated Punica Granatum Seed Oil
Pyrus Malus (Apple) Seed Oil
Ribes Nigrum (Black Currant) Seed Oil (CAS No. 97676-19-2)
Hydrogenated Black Currant Seed Oil
Ribes Rubrum (Currant) Seed Oil
Rosa Canina Fruit Oil [Dog Rose]
Hydrogenated Rosa Canina Fruit Oil
Rubus Chamaemorus Seed Oil [Cloudberry]
Rubus Idaeus (Raspberry) Seed Oil
Hydrogenated Raspberry Seed Oil
Schinziophyton Rautanenii Kernel Oil [Mongongo]
Sclerocarya Birrea Seed Oil [Marula]
Sesamum Indicum (Sesame) Seed Oil (CAS No. 8008-74-0)
Sesamum Indicum (Sesame) Oil Unsaponifiables
Hydrogenated Sesame Seed Oil
Sesamum Indicum (Sesame) Seed Butter
Sodium Sesameseedate
Silybum Marianum Seed Oil [Thistle]
Solanum Lycopersicum (Tomato) Fruit Oil
Solanum Lycopersicum (Tomato) Seed Oil
Theobroma Cacao (Cocoa) Seed Butter (CAS No. 8002-31-1)
Sodium Cocoa Butterate
Theobroma Grandiflorum Seed Butter [Cupuacu] (CAS No. 394236-97-6)
Sodium Theobroma Grandiflorum Seedate
Torreya Nucifera Seed Oil [Kaya]
Triticum Vulgare (Wheat) Germ Oil (CAS No. 8006-95-9; 68917-73-7)
Triticum Aestivum (Wheat) Germ Oil
Triticum Vulgare (Wheat) Germ Oil Unsaponifiables
Hydrogenated Wheat Germ Oil Unsaponifiables
Hydrogenated Wheat Germ Oil
Wheat Germ Acid (CAS No. 68938-32-9)
Vaccinium Corymbosum (Blueberry) Seed Oil
Vaccinium Macrocarpon (Cranberry) Seed Oil
Hydrogenated Cranberry Seed Oil
Vaccinium Myrtillus Seed Oil [Bilberry] (CAS No. 1161921-09-0)
Vaccinium Vitis-Idaea Seed Oil [Ligonberry],
Vegetable (Olus) Oil
Hydrogenated Vegetable Oil
Vitis Vinifera (Grape) Seed Oil (CAS No. 8024-22-4)
Hydrogenated Grapeseed Oil
Sodium Grapeseedate
Zea Mays (Corn) Oil (CAS No. 8001-30-7)
Zea Mays (Corn) Oil Unsaponifiables
Zea Mays (Corn) Germ Oil
Potassium Cornate (CAS No. 61789-23-9)
Corn Acid (CAS No. 68308-50-9)

[a] Previously reviewed ingredients are in ***bold and italics***.

Table 2. **Previously reviewed oil and fatty acid ingredients.**

Ingredients	Publication Date	Conclusion
Oil Ingredients		
Arachis Hypogaea (Peanut) Oil (CAS No. 8002-03-7) Hydrogenated Peanut Oil (CAS No. 68425-36-5) Peanut Acid (CAS No. 91051-35-3)	IJT 20(S2):65-77, 2001	Safe
Carthamus Tinctorius (Safflower) Seed Oil (CAS No. 8001-23-8)	JACT 4(5):171-197, 1985; Re-reviewed, not reopened IJT 25(2):1-89, 2006	Safe
Cocos Nucifera (Coconut) Oil (CAS No. 8001-31-8) Coconut Acid (CAS No. 61788-47-4) Hydrogenated Coconut Acid (CAS No. 68938-15-8) Hydrogenated Coconut Oil (CAS No. 84836-98-6) Magnesium Cocoate Potassium Cocoate (CAS No. 61789-30-8) Potassium Hydrogenated Cocoate Sodium Cocoate (CAS No. 61789-31-9) Sodium Hydrogenated Cocoate	JACT 5(3):103-121, 1986; CIR Final Report, 2008	Safe
Corylus Americana (Hazel) Seed Oil Corylus Avellana (Hazel) Seed Oil	IJT 20 (S1):15-20, 2001	Insufficient data
Elaeis Guineensis (Palm) Oil (CAS No. 8002-75-3) Elaeis Guineensis (Palm) Kernel Oil (CAS No. 8023-79-8) Hydrogenated Palm Oil (CAS No. 8033-29-2; 68514-74-9) Hydrogenated Palm Kernel Oil (CAS No. 68990-82-9; 84540-04-5)	IJT 19(S2):7-28, 2000	Safe
Gossypium Herbaceum (Cotton) Seed Oil (CAS No. 8001-29-4) Cottonseed Acid (CAS No. 68308-51-0) Hydrogenated Cottonseed Oil (CAS No. 68334-00-9)	IJT 20(S2):21-29, 2001	Safe
Oryza Sativa (Rice) Bran Oil (CAS No. 68553-81-1; 84696-37-7) Oryza Sativa (Rice) Germ Oil Rice Bran Acid (CAS No. 93165-33-4)	IJT 25(S2):91-120, 2006	Safe
Prunus Amygdalus Dulcis (Sweet Almond) Oil (CAS No. 8007-69-0)	JACT 2(5):85-99, 1983; Re-reviewed, not reopened IJT 24 (S1):1-102, 2005	Safe
Sesamum Indicum (Sesame) Seed Oil (CAS No. 8008-74-0) Hydrogenated Sesame Seed Oil Sesamum Indicum (Sesame) Oil Unsaponifiables Sodium Sesameseedate	JACT 12(3):261-277, 1993; Amended Final Report, 2009	Safe
Zea Mays (Corn) Oil (CAS No. 8001-30-7) Zea Mays (Corn) Germ Oil Zea Mays (Corn) Oil Unsaponifiables Corn Acid (CAS No. 68308-50-9) Potassium Cornate (CAS No. 61789-23-9)	Final Report, 2008	Safe
Persea Gratissima (Avocado) Oil (CAS No. 8024-32-6)	JEPT 4(4):93-103, 1980; Re-reviewed, not reopened IJT 22(1):1-35, 2003	Safe
Triticum Vulgare (Wheat) Germ Oil (CAS No. 8006-95-9; 68917-73-7)	JEPT 4(4):33-45, 1980; Re-reviewed, not reopened IJT 22(1):1-35, 2003	Safe
Fatty Acids		
Arachidonic Acid (CAS No. 506-32-1)	JACT 12 (5):481-559, 1993	Insufficient data
Hydroxystearic Acid (CAS No. 106-14-9)	IJT 18(S1):1-10, 1999	Safe
Lauric Acid (CAS No. 143-07-7) Myristic Acid (CAS No. 544-63-8) Oleic Acid (CAS No. 112-80-1) Palmitic Acid (CAS No. 57-10-3) Stearic Acid (CAS No. 57-11-4)	JACT 6(3):321-401, 1987; Re-reviewed, not reopened IJT 25(2):1-89, 2006	Safe

Table 2. **Previously reviewed oil and fatty acid ingredients.**

Ingredients	Publication Date	Conclusion
Glyceryl Triesters		
Trilaurin		
Triarachidin		
Tribehenin		
Tricaprin		
Tricaprylin		
Trierucin		
Triheptanoin		
Triheptylundecanoin		
Triisononanoin		
Triisopalmitin		
Triisostearin		
Trilinolein	IJT 20 (S4):61-94, 2001	Safe
Trimyristin		
Trioctanoin		
Triolein		
Tripalmitin		
Tripalmitolein		
Triricinolein		
Tristearin		
Triundecanoin		
Glyceryl Triacetyl Hydroxystearate		
Glyceryl Triacetyl Ricinoleate		
Glyceryl Stearate Diacetate		

Table 3. **Chemical properties for plant-derived fatty acid oils.**

Properties and Constituents [a]	Actinidia Chinensis (Kiwi) Seed Oil[64]	Adansonia Digitata Oil [65,66]	Aleurites Moluccana Seed Oil [Kukui][67-70]	Anacardium Occidentale (Cashew) Seed Oil[71]	Arachis Hypogaea (Peanut) Oil[6,67,72-75]	Argania Spinosa Kernel Oil[76,77]	Astrocaryum Murumuru Seed Butter[6,78]
Appearance		Pale yellow	Clear yellow liquid		Light yellow	Yellow	Pale brown waxy solid at room temperature
Specific gravity			0.920-0.930 (20◦C)		0.912-0.920 (20◦C)	0.908-0.918 (20◦C)	0.890-0.910 (25◦C)
Refractive index			1.470-1.480 (20◦C)		1.46-1.475 (20◦C)		
Iodine value		65-95	130-175		74-107	95	15 max
Saponification value		190-210	185-210		180-208		270-350
Peroxide value (meq/kg)	44.37	5.0-10	5.0 max	0.22	0.39, 5.0 max	10.0 max	20.0 max
Melting point (◦C)							25-37
Unsaponifiable matter (%)			0.3 - 1		≤1.0		
Free fatty acids (%)	1.2	2.0 max as oleic acid	0.1-4		0.2-2.08		12.56 as oleic acid
Titer (◦C)					26-32		
Acid value					0.5	3-4	

Properties and Constituents	Avena Sativa (Oat) Kernel Oil[79]	Bertholletia Excelsa Seed Oil[71,80]	Borago Officinalis Seed Oil[81,82]	Brassica Campestris (Rapeseed) Seed Oil[6]	Hydrogenated Rapeseed Oil[7]	Rapeseed Acid[83]	Canola Oil[7]
Appearance	Yellow		Clear, pale yellow-golden		White waxy solid		Light yellow oil
Specific gravity	0.914-0.932 (25◦C)	1.473	0.918-0.928 (20◦C)				
Refractive index	1.469-1.471 (25◦C)	0.914 (20◦C)	1.474-1.479 (20◦C)				1.465-1.467 (40°C)
Iodine value		74.2	130-155	81-112	4 max	119-120 g/100 g	110-126
Saponification value	176-186	192.4	184-194	168-192			
Peroxide value (meq/kg)	0.6-1.1	0.16	10.0 max		2.0 max		10 max
Melting point (◦C)							
Unsaponifiable matter (%)	3.7-4.3			0.5 - 2			1.5 max
Free fatty acids (%)	0.1-0.3			1	2.0 max as oleic acid		0.1% max as oleic acid
Titer (◦C)							
Acid value			1.0 max			197-200 mg KOH/g	

Table 3. Chemical properties for plant-derived fatty acid oils (continued).

Properties and Constituents [a]	Brassica Oleracea Acephala Seed Oil[84]	Brassica Oleracea Italica (Broccoli) Seed Oil[85]	Butyrospermum Parkii (Shea) Butter[6,67,86-89]	Butyrospermum Parkii (Shea) Oil[7]	Camellia Oleifera Seed Oil[90,91]	Canarium Indicum Oil[92,93]	Carica Papaya Seed Oil[94,95]
Appearance	Yellow	Golden	Grey, tallow-like	Pale yellow	Clear, pale yellow or "water white"	Cream to golden	Pale yellow
Specific gravity	0.9010 (20◦C)	0.910-0.918 (20◦C)	0.918 (15◦C)				
Refractive index	1.4741 (23◦C)	1.465-1.475 (20◦C)	1.468 (25◦C)			1.45-1.47	
Iodine value	61.2	90-120	45-77	28 - 43	80-94		65-100
Saponification value	123.06		165-190	185-195	188-196		
Peroxide value (meq/kg)			5.0 max	≤ 10	10.0 max	≤ 20	10.0 max
Melting point (◦C)			32-46; 28-42 (slip)				
Unsaponifiable matter (%)	1.6		3-13	≤ 1.5	1.5 max	≤ 1	
Free fatty acids (%)			1.0 max as oleic acid	≤ 0.1 as oleic acid		0.2	0.8-3
Titer (◦C)			49-54				
Acid value	2.1	1.5	1.5		1.0 max	≤ 10	

Properties and Constituents	Carthamus Tinctorius (Safflower) Seed Oil[7]	Carya Illinoensis (Pecan) Seed Oil[67,71,80]	Caryocar Brasiliense Fruit Oil [Pequi][83,96]	Citrullus Lanatus (Watermelon) Seed Oil[6,97]	Citrus Aurantifolia (Lime) Seed Oil[98,99]	Citrus Aurantium Dulcis (Orange) Seed Oil[100,101]	Citrus Paradisi (Grapefruit) Seed Oil[102,103]
Appearance	Light yellow oil		Yellow[96]	Pale to golden yellow liquid	Clear yellow	Clear, light yellow	Clear yellow
Specific gravity		0.924 (25◦C)		0.8930-0.9166		0.910-0.920 (20◦C)	
Refractive index		1.472		1.4668		1.466-1.475 (20◦C)	
Iodine value	135-150	100 - 105	48.65-74.80[96] 50-70 g/100 g[83]	113-123		90-110	80-125
Saponification value		190	160.15-202[96] 190-210 mg KOH/g	193-195		185-200	
Peroxide value (meq/kg)	10 max	0.15	0.99-5.22[96] ≤20[83]	≤ 5.0	5.0 max	5-10	5-10
Melting point (◦C)							
Unsaponifiable matter (%)	1.5 max	0.35-40					
Free fatty acids (%)	0.1 max as oleic acid		0.98-2.85 (mg KOH/g) [96]	< 5.0 as oleic acid		0.5 as oleic acid	
Titer (◦C)							
Acid value			10 mg KOH/g max[83]		1.0 max	0.8 max	1.0 max

Table 3. Chemical properties for plant-derived fatty acid oils (continued).

Properties and Constituents [a]	Cocos Nucifera (Coconut) Oil[6,7,104]	Cucurbita Pepo (Pumpkin) Seed Oil[105,106]	Elaeis Guineensis (Palm) Oil[6,7]	Elaeis Guineensis (Palm) Kernel Oil[6,7]	Fragaria Ananassa (Strawberry) Seed Oil[6,107,108]	Fragaria Chiloensis (Strawberry) Seed Oil[109,110]	Garcinia Indica Seed Butter [Kokum][111-113]
Appearance	White to light yellow-tan	Dark green	Pale yellow to deep orange in color	Nearly colorless	Light golden/yellow to yellow	Light yellow with some green	
Specific gravity	0.917 - 0.919 (25◦/15.5◦C)		0.921-0.925 (40◦C)		0.93-0.95	0.912-0.930	
Refractive index	1.448 - 1.450 (40◦C)		1.453-1.458 (40◦C)			1.465-1.485	1.4565-1.4575 (40◦C)
Iodine value	6-11	110-330	44-58	14-33		170-190	30-50
Saponification value	248-265	174-197	195-205	245-255		180-195	185-195
Peroxide value (meq/kg)	≤ 10	5.0 max	10 max	10 max	< 15	10 max	
Melting point (◦C)	22 - 26		25-50	25-30			37-43; 27 (slip)
Unsaponifiable matter (%)	≤ 0.5	1.5	0.2-0.8	1.5 max			1.5 max; 18-20; 32-40
Free fatty acids (%)	≤ 0.1% as oleic acid; ≤ 0.07% as lauric acid	1.5 as oleic acid	0.1 max as oleic acid; 0.09 as palmitic acid	0.1 max as oleic acid; 0.07 max as lauric acid		3	0.1-1
Titer (◦C)	20 - 24						
Acid value					18 max		

Properties and Constituents	Glycine Soja (Soybean) Oil[6,7]	Gossypium Herbaceum (Cotton) Seed Oil[6,7]	Guizotia Abyssinica Seed Oil[6]	Hazel Seed Oil*[72,114-116]	Helianthus Annuus (Sunflower) Seed Oil[6,7]	Sunflower Seed Acid[83]	Hippophae Rhamnoides Fruit Oil[117]
Appearance	Light amber oil	Dark red-brown oil	Pale yellow with a bluish tint		Light amber oil		Orange-red
Specific gravity			0.910-0.928	0.912-0.917 (15.5◦C); 0.905-0.925 (20◦C)	0.894-0.899 (60◦C)		0.90
Refractive index			1.467-1.471	1.467-1.474 (20◦C)	1.4597-1.4745 (25◦C)		
Iodine value	120.9-151.4	90-113	126-139	83-100	128-144	125-140 g/100 g	
Saponification value		180-198	180-195	180-200	188-194		
Peroxide value (meq/kg)	10 max	10 max		0.43; 10.0 max	10 max		10 max
Melting point (◦C)					0		
Unsaponifiable matter (%)	0.3-0.6	1.5 max	0.5-1	≤ 1.0	0.3-0.5		
Free fatty acids (%)	0.05-0.7	0.1 max as oleic acid	0.4-3	0.2 max as oleic acid	0.1 max as oleic acid		
Titer (◦C)							
Acid value				≤ 0.5		125-140 mg KOH/g	18 max

*Information mainly on Corylus Avellena.

Table 3. Chemical properties for plant-derived fatty acid oils (continued).

Properties and Constituents [a]	Hippophae Rhamnoides Seed Oil[118-120]	Irvingia Gabonenesis Kernel Butter[121]	Juglans Regia (Walnut) Seed Oil[67,72,80]	Linum Usitatissimum (Linseed) Seed Oil[6]	Macadamia Nut Oil[72,80,122-124]	Mangifera Indica (Mango) Seed Oil[6]	Moringa Oleifera Seed Oil[125-127]
Appearance	Orange				Pale to golden yellow	Pale yellow to ivory cream color	
Specific gravity	0.890-0.955 (20◦C)		0.917 (25◦C)	0.927-0.931 (20◦C)	0.911-0.918 (20◦C)	0.91	0.908 (20◦C); 0.8933 (24◦C)
Refractive index	1.4650-1.4825 (20◦C)		1.475 (25◦C)	1.4786-1.4815	1.466-1.470 (20◦C)	1.456	1.4566 (40◦C)
Iodine value	130-200		150 - 162	170-204	62-82	32-93	66.47
Saponification value	184-210		190 - 197	189-196	190-200	190-195	164.27; 192
Peroxide value (meq/kg)	5-10 max		0.37		0.36; 10.0 max		0.45; 10.0
Melting point (◦C)				0		34-43	18.93
Unsaponifiable matter (%)	1.0	0.13	0.5	0.5-1.5	1.5	0.8-2.9	0.58
Free fatty acids (%)	2.0 max; 18 max	0.30	0.2 - 2.5	5	0.5 max; 1.0 max as oleic acid		2.55 as oleic acid
Titer (◦C)							
Acid value	15				1		

Properties and Constituents	Oenothera Biennis (Evening Primrose) Oil[128,129]	Olea Europaea (Olive) Fruit Oil[6]	Olea Europaea(Olive) Husk Oil[130]	Olive Acid[83]	Oryza Sativa (Rice) Bran Oil[131,132]	Oryza Sativa (Rice) Bran Oil[131,132]	Passiflora Edulis Seed Oil [Passion Fruit]
Appearance	Light yellow	Almost colorless to yellow, greenish, or brown in color			Light golden yellow	Light golden yellow	Golden-orange
Specific gravity	0.920-0.930 (20◦C)	0.914-0.918			0.916-0.922 (15.5◦C)	0.916-0.922 (15.5◦C)	0.917 (20◦C)
Refractive index	1.475-1.480 (20◦C)	1.469-1.484			1.470-1.473 (20◦C)	1.470-1.473 (20◦C)	1.468-1.473 (20◦C)
Iodine value	145-165	64-88; refined 75-94		85-91 g/100 g	92-115	92-115	119.9-129.29[133]
Saponification value	180-195	185-212; refined 184-186			180-195	180-195	176-187.4
Peroxide value (meq/kg)	10.0 max	20 max (refined)	14.33		10.0 max	10.0 max	1.37-2.23
Melting point (◦C)							
Unsaponifiable matter (%)		0.6-1.2; 1.5 max refined					0.9-2.86
Free fatty acids (%)		0.6-1.4; 0.3 max refined			1.0 as oleic acid	1.0 as oleic acid	
Titer (◦C)							
Acid value	1-2			190-201 mg KOG/g			2.11-2.36

Table 3. Chemical properties for plant-derived fatty acid oils (continued).

Properties and Constituents [a]	Persea Gratissima (Avocado) Oil[6]	Pistacia Vera Seed Oil [71]	Plukenetia Volubilis Seed Oil[134]	Prunus Amygdalus (Sweet Almond) Oil[6,67,72,135-137]	Prunus Armeniaca (Apricot) Kernel Oil	Prunus Avium (Sweet Cherry) Seed Oil[138,139]
Appearance			Yellow-amber	Colorless to pale yellow liquid		Clear light yellow
Specific gravity	0.910-0.916		0.90-0.93 (20◦C)	0.911-0.920 (20◦C)	0.923[6]	0.905-0.925 (20◦C)
Refractive index	1.461-1.465		1.478-1.481 (20◦C)	1.467-1.473 (20◦C)	1.4672-1.4722[6]	1.463-1.480 (20◦C)
Iodine value	71-95		180-200	93 - 106	81-123[6]	90-115
Saponification value	177-198		180-210	183 - 197	191[6]	105-135
Peroxide value (meq/kg)		0.22	0-15	0.19		10.0 max
Melting point (◦C)						
Unsaponifiable matter (%)				0.4-1.0	0.4-1.4	
Free fatty acids (%)				1.0 max		0.5% max
Titer (◦C)					0-6[140]	
Acid value			0-2	0.5		1.0 max

Properties and Constituents	Prunus Domestica Seed Oil[141,142]	Prunus Persica (Peach) Kernel Oil[6,143]	Punica Granatum Seed Oil[144,145]	Pyrus Malus (Apple) Seed Oil[146]	Ribes Nigrum (Black Currant) Seed Oil[147-149]	Ribes Rubrum (Currant) Seed Oil[150]
Appearance		Pale yellow (refined)	Golden to dark yellow		Pale yellow or slightly greenish	Pale yellow or slightly greenish
Specific gravity		0.910-0.920 (20◦C) refined	0.935 (15.5◦C)	0.902-0.903 (25◦C)	0.92	0.92
Refractive index				1.465-1.466 (40◦C)		
Iodine value	90-108	90-115 (refined)	190-230	94.14-101.15	145-185	
Saponification value				179.01-197.25		
Peroxide value (meq/kg)	10.0 max	5.0 max (refined)	10.0 max	2.43-2.52	1-10	10 max
Melting point (◦C)						
Unsaponifiable matter (%)						
Free fatty acids (%)	2.0 max as oleic acid		1.4; 5.0 max as oleic acid		0.2	
Titer (◦C)						
Acid value				4.036-4.323	3; 18 max	18 max

Table 3. Chemical properties for plant-derived fatty acid oils (continued).

Properties and Constituents [a]	Rubus Chamaemorus Seed Oil[151]	Rubus Idaeus (Raspberry) Seed Oil[152-154]	Schinziophyton Rautanenii Kernel Oil[155]	Sclerocarya Birrea Seed Oil [Marula][156]	Solanum Lycopersicum (Tomato) Seed Oil[157]	Theobroma Cacao (Cocoa) Seed Butter[6]
Appearance	Yellow-red	Yellow or yellow-red	Light yellow		Clear golden yellow to darker red	
Specific gravity	0.92	0.92			0.9135-0.9357	0.950-0.998
Refractive index			1.4830	1.46	1.4577-1.4771	1.453-1.458
Iodine value		175-195		100.25	105-130.5	35-40
Saponification value		180-200		162.70	156-194.9	190-200
Peroxide value (meq/kg)	10 max	5.0 max; 10 max	10 mg/kg	4.58		
Melting point (◦C)				26-28		33.5
Unsaponifiable matter (%)				3.06		
Free fatty acids (%)		1.5 max as oleic acid				
Titer (◦C)						
Acid value	18 max	18 max		33.70		

Properties and Constituents	Vaccinium Corymbosum (Blueberry) Seed Oil[64,158,159]	Vaccinium Macrocarpon (Cranberry) Seed Oil[6,64,160-163]	Vaccinium Myrtillus Seed Oil[164]	Vaccinium Vitis-Idaea Seed Oil[165]	Vitis Vinifera (Grape) Seed Oil[6]	Zea Mays (Corn) Oil[166,167]
Appearance	Green with yellow tint or dark green /brown	Pale yellow to greenish; light green	Pale yellow to greenish	Pale yellow		Clear, bright golden yellow
Specific gravity		0.923	0.93	0.92	0.91-0.93	0.920-0.928 (15.5◦C)
Refractive index					1.470-1.476	1.472-1.476 (20◦C)
Iodine value	155-175	140-180			125-143	103-128
Saponification value		170-200			176-206	185-195
Peroxide value (meq/kg)	20-24.62	< 15; 10 max	10 max	10 max		10.0 max
Melting point (◦C)						
Unsaponifiable matter (%)						
Free fatty acids (%)	0.67; 2.0 as oleic acid	0.7; 1.0 as oleic acid				
Titer (◦C)						
Acid value		2.0 max; 18 max	18 max	18 max		0.2 max

Table 4. **Total fatty acid composition of plant-derived fatty acid oils (%).**

Fatty Acids	Actinidia Chinensis (Kiwi) Seed Oil[64]	Adansonia Digitata Oil [Baobab] [65,66]	Aleurites Moluccana Seed Oil [Kukui][67,69,70]	Amaranthus Hypochondriacus Seed Oil [Amaranth][168]	Anacardium Occidentale (Cashew) Seed Oil[71]	Arachis Hypogaea (Peanut) Oil[6,73,74]	Arctium Lappa Seed Oil[169]	Argania Spinosa Kernel Oil [Argan][76,77]	Astrocaryum Murumuru Seed Butter [Murumuru][78]	Avena Sativa (Oat) Kernel Oil[79,170]
Caproic (C6)										
Caprylic (C8)									1.85	
Capric (C10)									1.85	
Lauric (C12)*	0.02								47.46	
Myristic (C14)	0.03				0.07		0.01		26	0.2-0.3
Myristoleic (C14:1)										
Palmitic (C16)	5.96	18-30	5-8	19 - 20	9.9	5-16	7.27	10-15	6.28	13.9-18.82
Palmitoleic (C16:1)		1	0.5		0.4		0.01			0.1-0.4
Heptadecanoic (C17:0)					0.1					
Stearic (C18)	3.09	2-8	0.1-6.7	3	8.7	1-6.5	32.56	5-6.5	2.65	0.8-2.79
Oleic (C18:1)	14.6	30-40	10-35	22 - 26	57.2	33.3-76	50.21	45-55	12.56	31.4-51.26
Linoleic (C18:2)	17.55	24-34	35-50	46 - 50	20.8	8-47.5	3.18	28-36	2.87	22.8-43.1
Linolenic (C18:3)	57.4	1-3	24-40		0.2	0-0.6				0.64-2.1
Arachidic (C20)	0.34		1.5		1	0.17-3	0.22			
Eicosenoic (C20:1)			1		0.3	0.33-3	0.33			0.5-1
Eicosadienoic (C20:2)										
Arachidonic (C20:4)										
Behenic (C22)					0.4	1-5				
Erucic (C22:1)					0.3	0.5				
Docosadienoic (C22:2)										
Docosahexaenoic (C22:6)										
Lignoceric (C24)						0.2-3	0.49			
Others						<C16:0 = 0.4	heptadecenoic=0.02; nonadecadienoic acid=2.99; heneicosanoic acid =1.07; dicosanoic acid=0.43			Arachidic (C20) + Eicosadienoic (C20:2)=0.1-0.3; C18:1, n-11=0.9-1.3

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Bassia Butyracea Seed Butter[a,111]	Bassia Latifolia Seed Butter [Mahwa][b,111]	Bertholletia Excelsa Seed Oil [Brazil][71]	Borago Officinalis Seed Oil [Borage] [81,82]	Brassica Campestris (Rapeseed) Seed Oil[6]	Rapeseed Acid[83]	Brassica Napus Seed Oil [Rapeseed][171]	Hydrogenated Rapeseed Oil[7]	Canola Oil[7]
Caproic (C6)									
Caprylic (C8)									
Capric (C10)									
Lauric (C12)									
Myristic (C14)			0.06			≤0.5		< 1.0	<0.2
Myristoleic (C14:1)									
Palmitic (C16)	60.8	23.7-24.7	13.5	9-13	1.5 - 3	≤8	2	3-5.0	<6.0
Palmitoleic (C16:1)			0.3			≤2			<1.0
Heptadecanoic (C17:0)			0.2						
Stearic (C18)	3.2	19.3-29.9	11.8	3-5	0.7 - 1.3	≤3	1	38-42	<2.5
Oleic (C18:1)	30.9	36.3-43.3	29.1	10-22	12.1 - 57.4	54-70	21	1	>50
Linoleic (C18:2)	4.9	11.6-15.8	42.8	33-46	11.4 - 22.1	18-24	20	< 1.0	<40.0
Linolenic (C18:3)			0.2	18-25	8.3 - 12.5	5-10	2		<14
Arachidic (C20)			0.5			≤6	1	8-10.0	<1.0
Eicosenoic (C20:1)			0.2	2-6	5.6 - 3.1			< 1.0	<2.0
Eicosadienoic (C20:2)									
Arachidonic (C20:4)									
Behenic (C22)			0.1					42-50	<0.5
Erucic (C22:1)			0.3	1-3.5	1 - 58.6		53	< 1.0	<2.0
Docosadienoic (C22:2)									
Docosahexaenoic (C22:6)									
Lignoceric (C24)							2	1-2.0	<0.2
Others				α-Linolenic (C18:3) = 0.4%; γ-Linolenic = 1-3.5%		<C14 = ≤0.5; >C18:3 = ≤5; >C20 = ≤6			<C14 = <0.1; C24:1 = <0.2

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Brassica Oleracea Acephala Seed Oil [Kale][84]	Brassica Oleracea Italica (Broccoli) Seed Oil[85]	Butyrospermum Parkii (Shea) Oil[7]	Butyrospermum Parkii (Shea) Butter[6,86-88]	Camelina Sativa Seed Oil [False Flax][172]	Camellia Japonica Seed Oil[173]	Camellia Kissi Seed Oil[173]	Camellia Oleifera Seed Oil [Tea Seed][90,91]	Camellia Sinensis Seed Oil[173]
Caproic (C6)									
Caprylic (C8)									
Capric (C10)									
Lauric (C12)									
Myristic (C14)				0.5					
Myristoleic (C14:1)									
Palmitic (C16)	4.4	0-5	3.8-4.1	3-9	7.8	7.9		6.1-15	8-10
Palmitoleic (C16:1)						0.16			
Heptadecanoic (C17:0)									
Stearic (C18)	0.7	0-5	41.2-56.8	30-50	2.96	2.46		0.8-2	1.5-3.5
Oleic (C18:1)	11.3	10-20	34.0-46.9	38-50	16.77	84.99	80	72-87	78-86
Linoleic (C18:2)	12.6	10-20	3.7-6.5	3-8	23.08	3.76		5.3-14.3	7-10
Linolenic (C18:3)	10.2	5-10		0.5 max	31.2				0.2-0.8
Arachidic (C20)	8.2		1-2	2.5-3		0.49			
Eicosenoic (C20:1)	0.4	5-10			11.99				
Eicosadienoic (C20:2)									
Arachidonic (C20:4)									
Behenic (C22)									
Erucic (C22:1)	51.8	40-50			2.8				
Docosadienoic (C22:2)									
Docosahexaenoic (C22:6)									
Lignoceric (C24)									
Others					3.4				

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Canarium Indicum Oil [Galip][92,93]	Carica Papaya Seed Oil [Papaya][94,95]	Carthamus Tinctorius (Safflower) Seed Oil[32,174]	Carya Illinoensis (Pecan) Seed Oil[67,71]	Caryocar Brasiliense Fruit Oil [Pequi][c,83,96]	Chenopodium Quinoa Seed Oil [Quinoa][175]	Citrullus Lanatus (Watermelon) Seed Oil[97]	Citrus Aurantifolia (Lime) Seed Oil[98,99]	Citrus Aurantium Dulcis (Orange) Seed Oil[100,101]
Caproic (C6)									
Caprylic (C8)									
Capric (C10)									
Lauric (C12)	≤ 2								
Myristic (C14)	≤ 2			Trace	0.5	0.2		1	
Myristoleic (C14:1)									
Palmitic (C16)	28-38	8-18	2	3-4.3	34.4-44.3	9.9 - 11	8.0 - 13.0	20-30	14-22
Palmitoleic (C16:1)	≤ 2	2		0.1	1.3	0.1	< 1.0		
Heptadecanoic (C17:0)	≤ 2			0.1					
Stearic (C18)	10-20	2-6		1.8-2	0.66-1.8	0.7 - 0.8	8.0 - 12.0	3-8	2-6
Oleic (C18:1)	30-40	60-77	26	40.6-79	54.55-57.4	22 – 50.2	15.0 - 30.0	20-38	26-35
Linoleic (C18:2)	12-22	3-25	68	16-50.3	0.84-2.8	1.2 – 56	55.0 - 65.0	30-45	35-45
Linolenic (C18:3)		0.8	Trace	0.7	0.18-1.0	0.7 – 7	< 1.0	5-15	2-6
Arachidic (C20)			Trace	Trace		0.7	< 1.0	2	0.5
Eicosenoic (C20:1)		2		1.2			< 1.0		
Eicosadienoic (C20:2)									
Arachidonic (C20:4)									
Behenic (C22)				0.2			< 1.0		
Erucic (C22:1)				0.3					
Docosadienoic (C22:2)									
Docosahexaenoic (C22:6)							< 2.0		
Lignoceric (C24)									
Others	Others = ≤ 2	α-Linolenic (C18:3) = 2%;					< 1.0		

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Citrus Grandis (Grapefruit) Seed Oil[102,103]	Citrus Limon (Lemon) Seed Oil[176]	Citrus Paradisi (Seed) Oil[177]	Cocos Nucifera (Coconut) Oil[33]	Coix Lacryma-Jobi (Job's Tears) Seed Oil[178]	Corylus Americana (Hazel) Seed Oil[171]	Corylus Avellana (Hazel) Seed Oil[12,114-116]	Crambe Abyssinica Seed Oil [Abyssinian Mustard][171,179]	Cucumis Sativus (Cucumber) Seed Oil[180]	Cucurbita Pepo (Pumpkin) Seed Oil[105,106]
Caproic (C6)				0-1						
Caprylic (C8)				5-9						
Capric (C10)				6-10				<0.01-0.11		
Lauric (C12)	1.5		2.95	44-52				<0.01-0.14		
Myristic (C14)	1		1.01	13-19			≤0.2	<0.01-0.43		
Myristoleic (C14:1)								<0.01-0.09		
Palmitic (C16)	18-30	18.8	36.25	8-11	16.0	6	4-9	0.81-5.55	9-13	10-16
Palmitoleic (C16:1)				0-1			0.2-1	<0.01-0.77		
Heptadecanoic (C17:0)		0.08					≤0.1			
Stearic (C18)	2-8	3.5	5.95	1-3	trace	3	1-6	0.6-10.42	6-9	3-7
Oleic (C18:1)	20-38	30.1	18.34	5-8	53	76	66-85	12.8-23.13	14-20	18-38
Linoleic (C18:2)	30-48	33.4	29.26	Trace-2.5	30.5	15	7-25	9.08-15.86	60-68	40-62
Linolenic (C18:3)	2-6	13.5	3.58		trace		≤0.6	3.27-9.43	<1	1
Arachidic (C20)		0.3	0.38				≤0.5	<0.01-1.19		
Eicosenoic (C20:1)		0.03	0.84				≤0.5	<0.01-6		
Eicosadienoic (C20:2)								<0.01-0.21		
Arachidonic (C20:4)								<0.01		
Behenic (C22)		0.08					≤0.3	<0.01-2.59		
Erucic (C22:1)							Trace-0.01	48.86-60		
Docosadienoic (C22:2)										
Docosahexaenoic (C22:6)								<0.01-1.34		
Lignoceric (C24)		0.2					0.01	<0.01-1.85		
Others		C23:0 = <0.01; C26:0 = 0.01	C12:1=1.44				C17:1 = ≤ 0.1	C20:3 = <0.01-0.19; C20:5 = <0.01-1.91		

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Cynara Cardunculus Seed Oil [Artichoke][181]	Elaeis Guineensis (Palm) Oil[26]	Elaeis Guineensis (Palm) Kernel Oil[26]	Elaeis Oleifera Kernel Oil[182]	Euterpe Oleracea Fruit Oil [Acai][183]	Fragaria Ananassa (Strawberry) Seed Oil[64,107,108]	Fragaria Chiloensis (Strawberry) Seed Oil[110]	Garcinia Indica Seed Butter [Kokum][d,121,184]	Gevuina Avellana Oil [Chilean Hazel][185]
Caproic (C6)			0.3	0.1					
Caprylic (C8)			4.4	0.9					
Capric (C10)			3.7	0.8					
Lauric (C12)		0.2	48.3	29.3					
Myristic (C14)		1.1	15.6	25.7		0.05			
Myristoleic (C14:1)									
Palmitic (C16)	12	44	7.8	10.1	22	4.32	3-5	2-8	1.9
Palmitoleic (C16:1)		0.1			2		0-0.2		22.7
Heptadecanoic (C17:0)									
Stearic (C18)	3	4.5	2	1.8	2	1.68	1-2	50-67.4	0.5
Oleic (C18:1)	25	39.2	15.1	26.4	60	10-20	15-18	27-42	39.4
Linoleic (C18:2)	60	10.1	2.7	4.5	12	28.5 – 50	40-46	0.5-2	5.6
Linolenic (C18:3)		0.4			Trace	25-40	30-36		0.1
Arachidic (C20)		0.4			2.5	0.71	0-0.2	0.7	1.4
Eicosenoic (C20:1)							0-0.2		3.1
Eicosadienoic (C20:2)									
Arachidonic (C20:4)									
Behenic (C22)									2.2
Erucic (C22:1)									
Docosadienoic (C22:2)									
Docosahexaenoic (C22:6)									
Lignoceric (C24)									0.5
Others			0.2	0.4		5.5 - 8.5	C18:3 w6=0-0.1		C18:1Δ12 = 6.2; C20:1Δ15 = 6.6; ; C22:1Δ17 = 7.9; ; C22:1Δ19 = 1.6

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Glycine Soja (Soybean) Oil[6]	Gossypium Herbaceum (Cotton) Seed Oil[27]	Guizotia Abyssinica Seed Oil [Ramtil/Niger][6]	Helianthus Annuus (Sunflower) Seed Oil[6]	Sunflower Seed Acid[83]	Hippophae Rhamnoides Fruit Oil[e,117,186]	Hippophae Rhamnoides Seed Oil[119,120,186]	Irvingia Gabonenesis Kernel Butter[121,121]	Juglans Regia (Walnut) Seed Oil[187]
Caproic (C6)									
Caprylic (C8)									
Capric (C10)									
Lauric (C12)								35-51.1	
Myristic (C14)		2			≤2	0.4-0.6		36.8-58	
Myristoleic (C14:1)						0.2			
Palmitic (C16)		21	5.0-13	5.0 - 7.2	6-11	24-42	5-11.3	3.9-5	3-7
Palmitoleic (C16:1)						24-42	4.4		
Heptadecanoic (C17:0)									
Stearic (C18)		Trace	2.0-11	2.0 - 6.5	3-7	0.9-2.1	2-5	0.4-0.7	0.5-3
Oleic (C18:1)	11.5 - 60.0	30	6.0-40	14.7 - 37.2	19-31	3-30	11-30	0.6-2.7	9-30
Linoleic (C18:2)	0000	45	45-77	51.5 - 73.5	57-66		28-45	0.60	57-76
Linolenic (C18:3)	2.9 - 12.1			Trace - 0.3	≤1	1.7-6.8	24.9-38	1.3	2-16
Arachidic (C20)		Trace		0.3 - 1	≤3				
Eicosenoic (C20:1)									
Eicosadienoic (C20:2)									
Arachidonic (C20:4)									
Behenic (C22)									
Erucic (C22:1)									
Docosadienoic (C22:2)									
Docosahexaenoic (C22:6)									
Lignoceric (C24)			2 max						
Others					>C20 = ≤3	Vakccenic C18:1(n-7) = 7.3-7.5; α-Linoleic C18:2 = 4.1-5.5	Vakccenic C18:1(n-7) = 3.2; α-Linoleic C18:2 = 34.1; Others = 3 max		

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued)[a]

Fatty Acids	Limnanthes Alba (Meadowfoam) Seed Oil[6]	Linum Usitatissimum (Linseed) Seed Oil[6]	Luffa Cylindrica Seed Oil[188]	Lupinus Albus Seed Oil[189]	Lycium Barbarum Seed Oil[190]	Macadamia Integrifolia Seed Oil[f,2,122-124]	Mangifera Indica (Mango) Seed Oil[g,6]	Morinda Citrifolia Seed Oil[191]	Moringa Oleifera Seed Oil [Ben/Moringa][125,126,192]	Oenothera Biennis (Evening Primrose) Oil[128,129]
Caproic (C6)										
Caprylic (C8)								1.44		
Capric (C10)										
Lauric (C12)						0.1-1.4				
Myristic (C14)			0.1			0.7-1.5			Trace	
Myristoleic (C14:1)										
Palmitic (C16)		5.5	12.2	14.44-21.57		6-12	5-8	9.0	5-9.3	4-10
Palmitoleic (C16:1)			0.1	0.36-1.03		12-25		0.12	1.5-3	
Heptadecanoic (C17:0)								0.13		
Stearic (C18)		3.5	0.1	1.37-3.91	3	0.5-8	33-48	4.07	3-8	2-4
Oleic (C18:1)		19.1	19.6	42.78-52.87	19.1	50-67	35-50	17.45	65-80	5-12
Linoleic (C18:2)		15.3	59.7	9.20-17.23	68.3	1.5-5	4.0-8	59.45	1.5-5	60-85
Linolenic (C18:3)		57		4.81-9.02	2.8	0.5-1.9		0.27	1-1.5	
Arachidic (C20)				1.61-2.30		1.5-5	1-7	0.51	2-5	
Eicosenoic (C20:1)	52 - 77			3.86-5.30		1.5-3.1		0.2	2.5-4	
Eicosadienoic (C20:2)										
Arachidonic (C20:4)					0.68					
Behenic (C22)				4.75-5.99		0.3-1			8-8.6	
Erucic (C22:1)	8.0 - 29			0.51-1.47		1			3	
Docosadienoic (C22:2)	7.0 - 20									
Docosahexaenoic (C22:6)										
Lignoceric (C24)									Trace	
Others										α-Linolenic (C18:3) = 1% γ-Linolenic = 7-12%

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Olea Europaea (Olive) Oil[6]	Olea Europaea (Olive) Husk Oil[130]	Olive Acid[83]	Orbignya Cohune Seed Oil [Cohune][6]	Orbignya Oleifera Seed Oil [Babassu][6]	Orbignya Speciosa Kernel Oil[193]	Oryza Sativa (Rice) Bran Oil[132]	Oryza Sativa (Rice) Germ Oil[28]	Passiflora Edulis Seed Oil [Passion Fruit][133]
Caproic (C6)									
Caprylic (C8)				7.5	4 to 8	2-10			
Capric (C10)				6.5	4 to 8	2-12			
Lauric (C12)				46.5	44 - 47	35-50			
Myristic (C14)	Trace		≤1.0	16	15 - 20	12-25		6.92[28]	0.03
Myristoleic (C14:1)									
Palmitic (C16)	7.5 - 20	14.96	9-15	9.5	6 to 9	4-15	14	9.28	8.57
Palmitoleic (C16:1)	0.3 - 3.5	2.18	≤2					4.41[28]	0.23
Heptadecanoic (C17:0)			≤0.5						
Stearic (C18)	0.5 - 3.5	1	2-5	3	3 to 5	1-7	2	7.91[28]	1.66
Oleic (C18:1)	53 - 86	64.08	69-78	10	10 to 12	5-20	45	17.81[28]	16.25
Linoleic (C18:2)	3.5 - 20	16.09	8-14	1	1 to 3	<3	34	16.22[28]	72.69
Linolenic (C18:3)	0 - 1.5	0.71	≤3.5				1	15.56[28]	0.26
Arachidic (C20)	Trace							3.08[28]	
Eicosenoic (C20:1)									
Eicosadienoic (C20:2)									
Arachidonic (C20:4)								5.48[28]	
Behenic (C22)	Trace								
Erucic (C22:1)									
Docosadienoic (C22:2)									
Docosahexaenoic (C22:6)									
Lignoceric (C24)	Trace								
Others								Arachidontrienoic = 5.21[28]	Unspecified other fatty acids = 0.31

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Perilla Ocymoides Seed Oil [Perilla][6]	Persea Gratissima (Avocado) Oil[6]	Pistacia Vera Seed Oil [Pistachio][71]	Plukenetia Volubilis Seed Oil [Sacha Inchi][194]	Prunus Amygdalus (Sweet Almond) Oil[6,67,135-137,195]	Prunus Armeniaca (Apricot) Kernel Oil[140]	Prunus Avium (Sweet) Cherry Seed Oil[h,138,139]	Prunus Domestica Seed Oil [Prune/Plum][141,142]
Caproic (C6)								
Caprylic (C8)								
Capric (C10)								
Lauric (C12)								
Myristic (C14)			0.09	0.02	1			
Myristoleic (C14:1)								
Palmitic (C16)		13-17	7.4	4.72	4-9	4.6-6	4-10	4-9
Palmitoleic (C16:1)		3 - 5.1	0.7	0.04	0.8	1-2		1
Heptadecanoic (C17:0)				0.12	0.2			
Stearic (C18)			0.9	3.33	2-3	0.5-1.2	1-4	3
Oleic (C18:1)	14-23	67-72	58.2	10.46	62-86	58-65.7 (total 18:1) 29-33	23-55	60-80
Linoleic (C18:2)	16	10 to 12	30.3	37.64	20-30	28.5 (undef. 18:2)	30-55	15-25
Linolenic (C18:3)	63-70		0.4	48.96	0.4	05-1.0 (undef 18:3)	13	1
Arachidic (C20)			0.6	0.09	0.2	0.2	2	
Eicosenoic (C20:1)			0.6	0.3	0.3			
Eicosadienoic (C20:2)								
Arachidonic (C20:4)								
Behenic (C22)			0.3		0.2			
Erucic (C22:1)			0.6		0.1			
Docosadienoic (C22:2)								
Docosahexaenoic (C22:6)								
Lignoceric (C24)								
Others				C17:1 = 0.06; gamma C18:3 = 0.24;Others = 0.02	<C16:0 = 0.1	Oleic/Linoleic = 90-93%	Eleostearic (C18:3 conj) = 10%	

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Prunus Persica (Peach) Kernel Oil[143]	Punica Granatum Seed Oil [Pomegranate][144,145]	Pyrus Malus (Apple) Seed Oil[146]	Ribes Nigrum (Black Currant) Seed Oil[147-149]	Ribes Rubrum (Currant) Seed Oil[150,196]	Rosa Canina Seed Oil [Dog Rose][176,197]	Rubus Chamaemorus Seed Oil[151]	Rubus Idaeus (Raspberry) Seed Oil[64,152-154]
Caproic (C6)								
Caprylic (C8)								
Capric (C10)								
Lauric (C12)								
Myristic (C14)						0.11-0.21		0.07
Myristoleic (C14:1)								
Palmitic (C16)	2.0 - 7	1-10	6.51-6.60	6-10	4.6-4.8	1.71-4.6		2-2.43
Palmitoleic (C16:1)			0-0.05			0.24-1.01		
Heptadecanoic (C17:0)						0.04		
Stearic (C18)	0.5 - 3.5	1-5	1.75-1.96	1-4	2-3	1.69-2.47		0.9-1
Oleic (C18:1)	55 - 70	3-12	37.49-38.55	9-16	17.1-17.8	14.71-21.7	13-19	8-13
Linoleic (C18:2)	22 - 33	2-12	50.70-51.40	40-54	36-48	47.9-54.41	40-52	47-63
Linolenic (C18:3)	≤ 1		0.19-0.30	11-18	15-30	16.42-21.8	27-38	25-40
Arachidic (C20)			1.49-1.54	1		1.0-2.61		0.37
Eicosenoic (C20:1)			0.51-0.56	3		0.3		
Eicosadienoic (C20:2)						0.07		
Arachidonic (C20:4)								
Behenic (C22)			0-0.40	1		0.1-0.64		
Erucic (C22:1)				1				
Docosadienoic (C22:2)								
Docosahexaenoic (C22:6)								
Lignoceric (C24)						0.04		
Others		Punicic (C18:3conj) = 60-80; Other C18:3conj = 18%		C18:3 (n-6) = 11-18 C18:4 (n-3) = 2-5	C18:1n-7 = 0.5-0.6; C18:3n-6 = 5.6-12; C18:4n-3 = 2-5; Others = 0-0.3	C17:1 = 0.01; C21:0= 0.01, C23:0 = 0.03		

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Schinziophyton Rautanenii Kernel Oil[155]	Sclerocarya Birrea Seed Oil [Marula][156,198]	Sesamum Indicum (Sesame) Seed Oil[25,55]	Silybum Marianum Seed Oil [Thistle][199]	Solanum Lycopersicum (Tomato) Seed Oil[157]	Solanum Lycopersicum (Tomato) Fruit Oil[i,200]	Theobroma Cacao (Cocoa) Seed Butter[6]	Theobroma Grandiflorum Seed Butter [Cupuacu][201]
Caproic (C6)		1.41						
Caprylic (C8)								
Capric (C10)								
Lauric (C12)					Trace-0.3			
Myristic (C14)		2.12	<0.5		1.5-2.3			Trace
Myristoleic (C14:1)					Trace			
Palmitic (C16)	8	9-12; 22.56	7.0 - 12.0	9.4	16.9-23.4	47	24-29	7.2
Palmitoleic (C16:1)		0.05 - 0.15	<0.5		3.3-6.8			0.1
Heptadecanoic (C17:0)								0.2
Stearic (C18)	9	5-8; 50.76	3.5 - 6.0	6.6	4.0-9.5	3	34-36	30.8
Oleic (C18:1)	15	4.13; 70 - 78	35 - 50	21.3	18.3-29.7	30	30-40	43.9
Linoleic (C18:2)	37	4.0 - 7.0	35 - 50	53.3	37.6-42.8	12	2.4	4.6
Linolenic (C18:3)	25	0.1 - 0.6	<1.0	trace	Trace-0.7			Trace
Arachidic (C20)		0.3 - 0.7	<1.0	3.8	0.8-1.3			11
Eicosenoic (C20:1)		0.1 - 0.5	<0.5	0.5				
Eicosadienoic (C20:2)								
Arachidonic (C20:4)		8.46						
Behenic (C22)		5.14	<0.5	2.4	Trace-0.7			
Erucic (C22:1)		0.1 - 0.5						
Docosadienoic (C22:2)								
Docosahexaenoic (C22:6)								
Lignoceric (C24)		4.13		0.7				
Others		Butyric = 0.35%	Trace of components below C14			Other (C14 + C20) = 8		

Table 4. Total fatty acid composition of plant-derived fatty acid oils (%) (continued).

Fatty Acids	Torreya Nucifera Seed Oil [Kaya][202]	Triticum Vulgare (Wheat) Germ Oil[30,52]	Vaccinium Corymbosum (Blueberry) Seed Oil[64,158,159]	Vaccinium Macrocarpon (Cranberry) Seed Oil[64,160-163]	Vaccinium Myrtillus Seed Oil [Bilberry][164,203]	Vaccinium Vitis-Idaea Seed Oil [Lingonberry][165,203]	Vitis Vinifera (Grape) Seed Oil[6]	Zea Mays (Corn) Oil[53,166,167]	Zea Mays (Corn) Oil[53,166,167]
Caproic (C6)									
Caprylic (C8)									
Capric (C10)									
Lauric (C12)			0.02	0.14					
Myristic (C14)	Trace		0.09	0.08	2.2-2.5	1.6-2.6		0.1 - 1.7	0.1 - 1.7
Myristoleic (C14:1)									
Palmitic (C16)	6.03	11.0 - 16	3-8	4-6	4.8-7.4	4.4-6.7	7-9.5	8-16.5	8-16.5
Palmitoleic (C16:1)	Trace							0.2 - 1.6	0.2 - 1.6
Heptadecanoic (C17:0)	Trace								
Stearic (C18)	2.51	1.0 - 6	0.5-3.5	1-1.25	2.2-2.5	1.2-1.9	3.5-5.5	0-4.5	0-4.5
Oleic (C18:1)	30.35	8.0 - 30	15-25	15-25.3	17.4-23	10-25	14-44	19 – 49	19 – 49
Linoleic (C18:2)	51.26	44 - 65	35-45	32-42	35-47.5	30-46.8	46-74	34-66	34-66
Linolenic (C18:3)	0.23	4.0 - 10	22-38	30-40	23.1-40	25.2-55		0-2	0-2
Arachidic (C20)			0.25	0.07				1	1
Eicosenoic (C20:1)	0.28							1	1
Eicosadienoic (C20:2)	0.98								
Arachidonic (C20:4)									
Behenic (C22)									
Erucic (C22:1)									
Docosadienoic (C22:2)									
Docosahexaenoic (C22:6)									
Lignoceric (C24)									
Others	C18:1 Δ11 = 0.57; C18:3 Δ5,9,12 = 0.08; C20:2 Δ 5,11 = 0.79; C20:3 Δ5,11,14 = 6.68; Others = 0.24	0 - 1.2 C20-22 Saturated acids		α-Linolenic (C18:3) = 34-35%					

[a]As Bassia Butyracea seed fat. [b]As Bassia Latifolia seed fat or Madhuca Indica seed fat. [c]As Caryocar Brasiliense pulp oil. [d]As Garcinia Indica seed fat. [e]As Hippophae pulp oil.
[f]Macadamia Integrifolia and Macadamia Ternifolia are synonyms; information is being reported under the more common name. [g]As mango kernel fat. [h]As cherry kernel oil. [i]With palm oil.

Table 5a. **Frequency and concentration of use according to duration and exposure - ingredients not previously reviewed by the CIR**

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses[48]	Conc of Use (%)	No. of Uses[48]	Conc of Use (%)	No. of Uses[48]	Conc of Use (%)
	Actinidia Chinensis (Kiwi) Seed Oil		**Adansonia Digitata Oil**		**Aleurities Moluccana Seed Oil**		**Anacardium Occidentale (Cashew) Seed Oil**		**Argania Spinosa Kernel Oil**		**Astrocaryum Murumuru Seed Butter**	
Totals*	**7**	**0.1**	**6**	**0.01**	**141**	**0.00001-5**	**10**	**0.002-1**	**100**	**0.001-10**	**192**	**0.001-7**
Duration of Use												
Leave-On	*5*	*NR*	*4*	*0.01*	*87*	*0.00002-5*	*9*	*0.04-1*	*87*	*0.001-10*	*171*	*0.001-7*
Rinse-Off	*2*	*0.1*	*2*	*NR*	*54*	*0.00001-3*	*1*	*0.002*	*13*	*0.001-2*	*21*	*0.001-0.2*
Exposure Type												
Eye Area	NR	NR	NR	NR	6	0.0001-0.005	NR	NR	11	0.1-1	21	0.06-0.5
Possible Ingestion	1	NR	NR	0.01	1	0.01	NR	NR	9	0.1-1	22	1-7
Inhalation	1	NR	NR	NR	15	0.1	NR	NR	NR	0.01	NR	NR
Dermal Contact	5	NR	5	0.01	76	0.00001-5	9	0.002-1	88	0.001-10	178	0.001-7
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.001	NR	NR
Hair - Non-Coloring	2	0.1	1	NR	58	0.00002-0.1	1	NR	8	0.01-1	11	0.001-0.2
Hair - Coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.07-0.1	3	NR
Nail	NR	NR	NR	NR	4	NR	NR	NR	2	0.001-0..1	NR	NR
Mucous Membrane	NR	NR	NR	NR	5	0.00001-0.4	NR	NR	2	0.001-2	3	NR
Bath Products	NR	NR	NR	NR	6	0.01-0.3	NR	NR	1	0.05	NR	NR
Baby Products	NR	NR	1	NR	NR	NR	NR	NR	NR	NR	NR	NR

	Sodium Astrocaryum Murumuruate		**Avena Sativa (Oat) Kernel Oil**		**Bassia Latifolia Seed Butter**		**Bertholletia Excelsa Seed Oil**		**Borago Officinalis Seed Oil**		**Brassica Campestris (Rapeseed) Seed Oil**	
Totals	**NR**	**0.002-0.005**	**43**	**0.01-3**	**22**	**0.001-2**	**55**	**0.0003-0.5**	**180**	**0.001-1**	**27**	**0.007-17**
Duration of Use												
Leave-On	*NR*	*0.002*	*37*	*0.1-3*	*17*	*0.001-0.05*	*18*	*0.0003-0.5*	*160*	*0.001-1*	*23*	*0.007-17*
Rinse-Off	*NR*	*0.002-0.005*	*6*	*0.001-0.1*	*5*	*0.001-2*	*37*	*0.01-0.2*	*20*	*0.001-0.01*	*4*	*0.1-1*
Exposure Type												
Eye Area	NR	NR	NR	0.2	4	0.01	1	NR	7	0.001-0.5	2	NR
Possible Ingestion	NR	NR	NR	2	NR	NR	NR	NR	NR	0.01	1	9
Inhalation	NR	NR	NR	NR	NR	NR	1	NR	3	0.1	NR	NR
Dermal Contact	NR	0.002-0.005	41	0.001-3	22	00.01-2	29	0.0003-0.5	168	0.001-1	27	0.007-17
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	2	0.1	NR	0.001-0.5	12	0.03-0.2	10	NR	NR	0.1
Hair - Coloring	NR	NR	NR	NR	NR	NR	14	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.002	2	0.01-0.1	5	NR	7	0.01	4	0.001-0.01	1	NR
Bath Products	NR	NR	1	NR	NR	NR	3	NR	1	NR	NR	NR
Baby Products	NR	NR	6	0.1	NR	NR	NR	NR	3	NR	NR	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Hydrogenated Rapeseed Oil		**Brassica Oleracea Italica (Broccoli) Seed Oil**		**Butyrospermum Parkii (Shea) Oil**		**Butyrospermum Parkii (Shea) Butter**		**Butyrospermum Parkii (Shea) Butter Unsaponifiables**		**Hydrogenated Shea Butter**	
Totals	**1**	**0.3-4**	**NR**	**0.001-3**	**22**	**0.01-15**	**1950**	**0.0005-60**	**38**	**0.06-3**	**4**	**1**
Duration of Use												*1*
Leave-On	*NR*	*0.3-4*	*NR*	*3*	*16*	*0.01-15*	*1680*	*0.001-60*	*35*	*0.06-3*	*2*	*1*
Rinse-Off	*1*	*NR*	*NR*	*0.001-0.5*	*22*	*0.6-1*	*270*	*0.0005-30*	*3*	*NR*	*2*	*1*
Exposure Type												
Eye Area	NR	2	NR	NR	1	NR	108	0.1-8	7	0.2-0.7	NR	NR
Possible Ingestion	NR	NR	NR	NR	NR	15	128	0.5-26	2	3-Jan	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR	17	0.001-3	NR	NR	NR	NR
Dermal Contact	1	0.3-4	NR	NR	22	0.6-15	1724	0.001-45	33	0.06-3	4	1
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	2	1	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	210	0.0005-3	5	2	NR	NR
Hair - Coloring	NR	NR	NR	0.001-3	NR	NR	4	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	0.01-1	7	0.01-60	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	3	0.6	101	0.003-5	NR	NR	NR	NR
Bath Products	NR	NR	NR	NR	3	1	13	1	NR	NR	2	NR
Baby Products	NR	NR	NR	NR	NR	NR	24	0.01-5	NR	NR	NR	NR

	Camelina Sativa Seed Oil		**Camellia Japonica Seed Oil**		**Camellia Kissi Seed Oil**		**Camellia Oleifera Seed Oil**		**Hydrogenated Camellia Oleifera Seed Oil**		**Camellia Sinensis Seed Oil**	
Totals	**76**	**0.002-1**	**NR**	**0.01-0.2**	**47**	**0.1-10**	**25**	**0.003-3**	**1**	**NR**	**12**	**0.1**
Duration of Use												
Leave-On	*61*	*0.002-1*	*NR*	*0.01-0.2*	*34*	*0.1-10*	*23*	*0.003-3*	*1*	*NR*	*8*	*0.1*
Rinse-Off	*15*	*1*	*NR*	*0.1*	*13*	*0.1-3*	*2*	*0.01-0.1*	*NR*	*NR*	*4*	*0.1*
Exposure Type												
Eye Area	NR	0.05	NR	0.01	4	0.1	NR	2	NR	NR	NR	NR
Possible Ingestion	34	0.05-0.5	NR	0.1	1	0.1	3	3	NR	NR	1	0.1
Inhalation	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	47	0.002-1	NR	0.01-0.2	36	0.1-10	23	0.003-3	1	NR	10	0.1
Deodorant (Underarm)	NR	NR	NR	0.01	NR	NR	NR	NR	NR	NR	NR	0.1
Hair - Non-Coloring	29	1	NR	0.1	11	0.1-1	2	2	NR	NR	2	0.1
Hair - Coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	0.1	1	0.1	NR	0.01-0.1	NR	NR	2	0.1
Bath Products	NR	NR	NR	NR	1	0.3	NR	0.05	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Canola Oil		Canola Oil Unsaponifiables		Hydrogenated Canola Oil		Carica Papaya Seed Oil		Caryocar Brasiliense Fruit Oil		Chenopodium Quinoa Seed Oil	
Totals	**132**	**0.0002-73**	**NR**	**0.001**	**3**	**NR**	**NR**	**0.1**	**31**	**0.0005-0.2**	**1**	**0.3**
Duration of Use												
Leave-On	*112*	*0.002-73*	*NR*	*NR*	*2*	*NR*	*NR*	*0.1*	*29*	*0.0005-2*	*1*	*NR*
Rinse-Off	*20*	*0.02-33*	*NR*	*0.0001*	*1*	*NR*	*NR*	*NR*	*2*	*NR*	*NR*	*0.3*
Exposure Type												
Eye Area	3	0.002-0.03	NR	NR	NR	NR	NR	NR	12	NR	NR	NR
Possible Ingestion	62	0.3-70	NR	NR	NR	NR	NR	NR	12	0.2	NR	NR
Inhalation	1	0.0002-17	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	113	0.0002-73	NR	NR	3	NR	NR	0.1	30	0.0005-0.2	NR	NR
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	19	0.006-24	NR	0.001	NR	NR	NR	NR	1	NR	1	NR
Hair - Coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.3
Nail	NR	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.02-1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bath Products	1	1-33	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

	Citrullus Lanatus (Watermelon) Seed Oil		Citrullus Vulgaris (Watermelon) Seed Oil**		Citrus Limon (Lemon) Seed Oil		Citrus Paradisi (Grapefruit) Seed Oil		Crambe Abyssinica Seed Oil		Cucumis Sativus (Cucumber) Seed Oil	
Totals	**1**	**2**	**5**	**NR**	**6**	**6**	**NR**	**0.01-20**	**6**	**NR**	**6**	**NR**
Duration of Use												
Leave-On	*1*	*2*	*3*	*NR*	*5*	*5*	*NR*	*0.08-20*	*5*	*NR*	*5*	*NR*
Rinse-Off	*NR*	*NR*	*2*	*NR*	*1*	*1*	*NR*	*0.01-1*	*1*	*NR*	*1*	*NR*
Exposure Type												
Eye Area	NR	NR	NR	NR	NR	1	NR	NR	NR	NR	1	NR
Possible Ingestion	NR	NR	NR	NR	NR	NR	NR	5	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR	NR	2	NR	NR	NR	NR
Dermal Contact	1	2	5	NR	6	5	NR	2-5	6	NR	5	NR
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	1	NR	0.01-20	NR	NR	1	NR
Hair - Coloring	NR	NR	NR	NR	NR	NR	NR	9	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	NR	1	NR	NR	NR	1	NR	NR	NR
Bath Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Cucurbita Pepo (Pumpkin) Seed Oil		**Palm Kernel Acid**		**Potassium Palm Kernelate**		**Potassium Palmate**		**Sodium Palm Kernelate**		**Sodium Palmate**	
Totals	**18**	**0.003-0.1**	**72**	**0.2-12**	**7**	**0.3-30**	**5**	**0.3-3**	**194**	**12-44**	**212**	**3-68**
Duration of Use												
Leave-On	*17*	*0.003-0.1*	*3*	*NR*	*NR*	*NR*	*NR*	*NR*	*10*	*NR*	*7*	*NR*
Rinse-Off	*1*	*NR*	*69*	*0.2-12*	*7*	*0.3-30*	*5*	*0.3-3*	*184*	*12-44*	*205*	*3-68*
Exposure Type												
Eye Area	1	0.003	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Inhalation	1	NR	NR	NR	NR	NR	NR	NR	1	NR	1	NR
Dermal Contact	18	0.003-0.1	71	0.2-12	7	0.3-30	5	0.3-3	194	12-44	212	3-68
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	1	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	64	0.2-3	1	0.3-30	2	0.3-3	173	16-44	189	3-68
Bath Products	NR	NR	NR	NR	NR	NR	NR	NR	3	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	4	NR	3	NR

	Palm Acid		**Elaeis Oleifera Kernel Oil**		**Euterpe Oleracea Fruit Oil**		**Garcinia Indica Seed Butter**		**Gevuina Avellana Oil**		**Glycine Soja (Soybean) Oil**	
Totals	**33**	**1-17**	**5**	**NR**	**29**	**0.00001-0.5**	**30**	**0.1-2**	**5**	**0.002-0.2**	**912**	**0.0002-95**
Duration of Use												
Leave-On	*1*	*NR*	*NR*	*NR*	*19*	*0.00001-0.5*	*27*	*0.1-2*	*5*	*0.04-0.2*	*718*	*0.0005-95*
Rinse-Off	*32*	*1-17*	*5*	*NR*	*10*	*0.05*	*3*	*NR*	*NR*	*0.002-0.01*	*194*	*0.0002-95*
Exposure Type												
Eye Area	NR	NR	NR	NR	2	0.5	1	NR	NR	NR	53	0.04-2
Possible Ingestion	NR	NR	NR	NR	1	0.002	3	0.1-2	NR	NR	103	0.6-4
Inhalation	1	NR	NR	NR	1	NR	NR	NR	NR	NR	6	0.03-0.5
Dermal Contact	33	1-17	NR	NR	14	0.00001-0.5	30	0.1-2	4	0.002-0.2	800	0.0005-93
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.01-0.5
Hair - Non-Coloring	NR	NR	2	NR	15	NR	NR	NR	NR	NR	97	0.0002-95
Hair - Coloring	NR	NR	3	NR	NR	NR	NR	NR	NR	NR	5	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	6	0.02-95
Mucous Membrane	31	1-4	NR	NR	3	NR	1	NR	NR	NR	70	0.01-52
Bath Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	19	0.1-78
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	21	2

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Glycine Soja (Soybean) Oil Unsaponifiables		**Hydrogenated Soybean Oil**		**Helianthus Annuus (Sunflower) Seed Oil**		**Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables**		**Hydrogenated Sunflower Oil**		**Hippophae Rhamnoides Oil**	
Totals	**12**	**0.0001-0.2**	**36**	**0.001-42**	**1414**	**0.000007-96**	**10**	**0.005-2**	**NR**	**6-35**	**15**	**0.2-0.7**
Duration of Use												
Leave-On	*12*	*0.0001-0.2*	*33*	*0.001-39*	*1054*	*0.0002-96*	*10*	*0.005-2*	*NR*	*6-35*	*10*	*0.2-0.7*
Rinse-Off	*NR*	*NR*	*3*	*0.05-42*	*360*	*0.000007-92*	*NR*	*0.002*	*NR*	*15-35*	*5*	*0.2*
Exposure Type												
Eye Area	NR	NR	4	0.03-7	64	0.0005-19	2	0.02	NR	7	NR	NR
Possible Ingestion	NR	NR	3	0.1-39	260	0.08-41	NR	NR	NR	6	NR	NR
Inhalation	NR	NR	NR	NR	3	0.0002-85	NR	NR	NR	NR	NR	NR
Dermal Contact	12	0.0001-0.2	34	0.01-39	707	0.0002-96	10	0.005-2	NR	6-35	1	0.2-0.7
Deodorant (Underarm)	NR	NR	NR	NR	1	0.0003-4	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	0.1	179	0.000007-92	NR	NR	NR	NR	6	NR
Hair - Coloring	NR	NR	NR	NR	85	0.03-35	NR	NR	NR	15-35	NR	NR
Nail	NR	NR	NR	0.001-25	8	0.05-30	NR	NR	NR	NR	8	NR
Mucous Membrane	NR	NR	NR	0.05-6	52	0.0003-4	NR	0.002	NR	NR	1	0.2
Bath Products	NR	NR	NR	5-42	11	0.005-75	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	18	0.2	NR	NR	NR	NR	NR	NR

	Hippophae Rhamnoides Fruit Oil		**Irvingia Gabonensis Kernel Butter**		**Juglans Regia (Walnut) Seed Oil**		**Limnanthes Alba (Meadowfoam) Seed Oil**		**Linum Usitatissimum (Linseed) Seed Oil**		**Linseed Acid**	
Totals	**7**	**0.004-2**	**109**	**0.003-0.4**	**15**	**0.00003-0.2**	**316**	**0.002-74**	**102**	**0.001-10**	**3**	**NR**
Duration of Use												
Leave-On	*7*	*0.004-2*	*109*	*0.003-0.4*	*12*	*0.01-0.2*	*225*	*0.002-74*	*52*	*0.002-10*	*3*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*3*	*0.00003-0.1*	*91*	*0.01-2*	*50*	*0.001-0.4*	*NR*	*NR*
Exposure Type												
Eye Area	1	NR	2	NR	1	NR	30	0.1-20	3	0.01	NR	NR
Possible Ingestion	NR	NR	64	0.003-0.3	NR	NR	67	0.6-26	NR	0.01	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR	1	0.1-3	3	NR	NR	NR
Dermal Contact	6	2	108	0.003-0.4	15	0.003-0.2	211	0.002-74	58	0.003-4	3	NR
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.05-0.1	NR	NR
Hair - Non-Coloring	NR	NR	1	NR	NR	0.00003-0.1	47	0.1-1	42	0.001-0.1	NR	NR
Hair - Coloring	NR	NR	NR	NR	NR	NR	46	0.2-2	NR	NR	NR	NR
Nail	1	0.004	NR	NR	NR	NR	NR	0.5	2	0.002-0.05	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	4	0.001-0.6	5	0.003-0.4	NR	NR
Bath Products	NR	NR	NR	NR	2	NR	2	0.5-0.9	1	0.02-0.2	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	1	NR	2	NR	1	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Luffa Cylindrica Seed Oil		**Lupinus Albus Seed Oil**		**Lycium Barbarum Seed Oil**		**Macadamia Integrifolia Seed Oil**		**Macadamia Ternifolia Seed Oil**		**Macadamia Nut Oil****	
Totals	**21**	**0.01**	**1**	**NR**	**2**	**NR**	**41**	**0.00006-5**	**533**	**0.0003-30**	**208**	**NS**
Duration of Use												
Leave-On	*21*	*NR*	*1*	*NR*	*2*	*NR*	*25*	*0.00006-5*	*482*	*0.001-30*	*191*	*NS*
Rinse-Off	*NR*	*0.01*	*NR*	*NR*	*NR*	*NR*	*16*	*0.006-3*	*51*	*0.0003-10*	*17*	*NS*
Exposure Type												
Eye Area	1	NR	NR	NR	1	NR	3	0.1	16	0.1-15	22	NS
Possible Ingestion	9	NR	NR	NR	1	NR	4	1	33	0.1-30	11	NS
Inhalation	NR	NR	NR	NR	NR	NR	NR	0.5	12	0.007-16	2	NS
Dermal Contact	21	0.01	1	NR	2	NR	36	0.00006-5	493	0.001-30	170	NS
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NS
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	12	0.01-0.03	33	0.0003-16	9	NS
Hair - Coloring	NR	NR	NR	NR	NR	NR	NR	NR	3	0.02	NR	NS
Nail	NR	NR	NR	NR	NR	NR	NR	3	1	0.001-0.5	NR	NS
Mucous Membrane	NR	0.01	NR	NR	NR	NR	10	2	12	0.02-10	NR	NS
Bath Products	NR	NR	NR	NR	NR	NR	1	0.5	2	1-10	1	NS
Baby Products	NR	NR	NR	RN	NR	NR	NR	NR	4	NR	NR	NS

	Mangifera Indica (Mango) Seed Oil		**Mangifera Indica (Mango) Seed Butter**		**Sodium Mangoseedate**		**Moringa Oleifera Seed Oil**		**Moringa Pterygosperma Seed Oil**		**Oenothera Biennis (Evening Primrose) Oil**	
Totals	**72**	**0.003-6**	**175**	**0.0005-3**	**1**	**NR**	**NR**	**0.001**	**15**	**0.003-3**	**150**	**0.00002-58**
Duration of Use												
Leave-On	*64*	*0.003-6*	*134*	*0.01-5*	*NR*	*NR*	*NR*	*0.001*	*13*	*0.004-3*	*113*	*0.00002-58*
Rinse-Off	*8*	*0.05-0.2*	*41*	*0.0005-0.5*	*1*	*NR*	*NR*	*NR*	*2*	*0.003*	*37*	*0.002-0.2*
Exposure Type												
Eye Area	13	5	6	0.02	NR	NR	NR	NR	4	3	4	0.00002-0.5
Possible Ingestion	7	0.03-6	25	1-5	NR	NR	NR	NR	1	NR	14	0.1-15
Inhalation	1	NR	2	0.02	NR	NR	NR	NR	NR	NR	2	NR
Dermal Contact	60	0.003-6	147	0.0005-5	1	NR	NR	0.001	11	0.003-3	109	0.00002-58
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.2
Hair - Non-Coloring	12	0.05-0.2	12	0.02-0.5	NR	NR	NR	NR	1	0.02	37	0.05-0.1
Hair - Coloring	NR	0.05	16	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	0.5	NR	NR	NR	NR	NR	NR	4	0.001-3
Mucous Membrane	2	0.1	10	0.0005-0.5	1	NR	NR	NR	NR	0.003	4	0.1-0.2
Bath Products	NR	NR	1	NR	NR	NR	NR	NR	NR	NR	2	0.2
Baby Products	NR	NR	3	NR	NR	NR	NR	NR	NR	NR	3	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Hydrogenated Evening Primrose Oil		**Olea Europaea (Olive) Fruit Oil**		**Olea Europaea (Olive) Oil Unsaponifiables**		**Hydrogenated Olive Oil**		**Hydrogenated Olive Oil Unsaponifiables**		**Potassium Olivate**	
Totals	**14**	**NR**	**915**	**0.0005-100**	**77**	**0.0001-3**	**50**	**0.0005-12**	**2**	**0.05-5**	**3**	**NR**
Duration of Use												
Leave-On	*14*	*NR*	*617*	*0.001-100*	*68*	*0.0001-3*	*36*	*0.1-12*	*2*	*0.05-5*	*NR*	*NR*
Rinse-Off	*NR*	*NR*	*298*	*0.0005-94*	*9*	*0.04-0.3*	*14*	*0.0005-0.1*	*NR*	*NR*	*3*	*NR*
Exposure Type												
Eye Area	1	NR	26	0.004-17	12	0.02-0.4	13	0.1-3	NR	0.3-2	NR	NR
Possible Ingestion	NR	NR	26	0.7-26	1	0.08	7	0.1-12	NR	NR	NR	NR
Inhalation	NR	NR	6	0.2-5	NR	3	NR	NR	NR	NR	NR	NR
Dermal Contact	14	NR	711	0.0005-100	67	0.0001-3	34	0.0005-12	2	0.05-5	3	NR
Deodorant (Underarm)	NR	NR	3	0.02-0.1	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	190	0.006-94	6	0.02-0.3	11	0.01-0.1	NR	NR	NR	NR
Hair - Coloring	NR	NR	NR	0.2-0.5	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	5	1-40	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	121	0.0005-3	4	NR	1	0.0005	NR	NR	1	NR
Bath Products	NR	NR	14	0.9-17	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	9	0.2	NR	0.04	NR	0.4	NR	NR	NR	NR

	Sodium Olivate		**Orbignya Cohune Seed Oil**		**Orbignya Oleifera Seed Oil**		**Sodium Babassuate**		**Orbignya Speciosa Kernel Oil**		**Passiflora Edulis Seed Oil**	
Totals	**16**	**4-18**	**1**	**NR**	**161**	**0.0009-27**	**NR**	**8**	**8**	**0.5-0.9**	**62**	**0.0007-3**
Duration of Use												
Leave-On	*5*	*NR*	*NR*	*NR*	*118*	*0.0009-4*	*NR*	*NR*	*1*	*0.9*	*53*	*0.003-5*
Rinse-Off	*11*	*4-18*	*1*	*NR*	*43*	*0.01-27*	*NR*	*8*	*7*	*0.5*	*9*	*0.0007-0.005*
Exposure Type												
Eye Area	NR	NR	NR	NR	7	0.5-0.6	NR	NR	NR	NR	3	0.8
Possible Ingestion	NR	NR	NR	NR	57	0.001-2	NR	NR	NR	NR	14	0.6-3
Inhalation	NR	NR	NR	NR	5	0.02-2	NR	NR	NR	NR	3	NR
Dermal Contact	16	4-18	NR	NR	110	0.0009-27	NR	8	NR	NR	49	0.003-3
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.003
Hair - Non-Coloring	NR	NR	1	NR	43	0.02-2	NR	NR	5	0.5-0.9	10	0.007-0.5
Hair - Coloring	NR	NR	NR	NR	8	NR	NR	NR	3	NR	3	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	9	4-18	NR	NR	5	27	NR	8	NR	NR	1	NR
Bath Products	NR	NR	NR	NR	2	0.01-0.1	NR	NR	NR	NR	NR	0.01-0.05
Baby Products	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Perilla Ocymoides Seed Oil		**Persea Gratissima (Avocado) Oil Unsaponifiables**		**Hydrogenated Avocado Oil**		**Persea Gratissima (Avocado) Butter**		**Sodium Avocadoate**		**Pistacia Vera Seed Oil**	
Totals	**7**	**NR**	**63**	**0.2-6**	**11**	**0.5**	**15**	**NR**	**1**	**NR**	**158**	**0.003-1**
Duration of Use												
Leave-On	*5*	*NR*	*57*	*0.5-6*	*9*	*NR*	*15*	*NR*	*NR*	*NR*	*107*	*0.08-0.2*
Rinse-Off	*2*	*NR*	*6*	*0.2*	*2*	*0.5*	*NR*	*NR*	*1*	*NR*	*51*	*0.003-1*
Exposure Type												
Eye Area	2	NR	9	0.5	NR	NR	NR	NR	NR	NR	7	NR
Possible Ingestion	NR	NR	2	3	2	NR	11	NR	NR	NR	6	NR
Inhalation	NR	NR	4	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	5	NR	56	0.2-3	8	NR	15	NR	1	NR	133	0.003-0.2
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	2	6	3	0.5	NR	NR	NR	NR	16	0.05-1
Hair - Coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	3	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR	1	NR	19	NR
Bath Products	NR	NR	4	NR	NR	NR	NR	NR	NR	NR	8	NR
Baby Products	NR	NR	1	NR	NR	NR	NR	NR	NR	NR	3	NR

	Plukenetia Volubilis Seed Oil		**Hydrogenated Sweet Almond Oil**		**Sodium Sweet Almondate**		**Prunus Armeniaca (Apricot) Kernel Oil**		**Hydrogenated Apricot Kernel Oil**		**Prunus Avium (Sweet Cherry) Seed Oil**	
Totals	**13**	**0.05-0.6**	**21**	**0.5**	**4**	**15**	**588**	**0.00001-89**	**2**	**NR**	**2**	**0.01-0.02**
Duration of Use												
Leave-On	*12*	*0.05-0.6*	*13*	*0.5*	*4*	*NR*	*449*	*0.0001-40*	*2*	*NR*	*NR*	*NR*
Rinse-Off	*1*	*NR*	*8*	*0.5*	*NR*	*15*	*139*	*0.00001-89*	*NR*	*NR*	*2*	*0.01-0.02*
Exposure Type												
Eye Area	1	NR	NR	NR	NR	NR	25	0.002-18	NR	NR	NR	NR
Possible Ingestion	3	0.6	1	NR	NR	NR	38	0.001-5	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR	5	0.0009-1	NR	NR	NR	NR
Dermal Contact	13	0.6	15	0.5	4	15	486	0.00001-18	2	NR	2	0.01-0.02
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	1	0.003-0.1	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	6	0.5	NR	NR	78	0.0001-89	NR	NR	NR	NR
Hair - Coloring	NR	NR	NR	NR	NR	NR	10	0.1	NR	NR	NR	NR
Nail	NR	0.05	NR	NR	NR	NR	10	0.002-40	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	NR	NR	15	24	0.01-9	NR	NR	2	0.01-0.02
Bath Products	NR	NR	1	NR	NR	NR	8	4	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	7	NR	NR	NR	NR	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Prunus Domestica Seed Oil		**Prunus Persica (Peach) Kernel Oil**		**Punica Granatum Seed Oil**		**Pyrus Malus (Apple) Seed Oil**		**Ribes Nigrum (Black Currant) Seed Oil**		**Rosa Canina Fruit Oil**	
Totals	**NR**	**0.04**	**22**	**0.003-22**	**46**	**0.001-1**	**8**	**NR**	**53**	**0.000001-0.3**	**121**	**0.001-19**
Duration of Use												
Leave-On	*NR*	*NR*	*16*	*0.05-22*	*44*	*0.001-1*	*8*	*NR*	*45*	*0.000001-0.3*	*106*	*0.001-19*
Rinse-Off	*NR*	*0.04*	*6*	*0.003-6*	*2*	*0.001-0.1*	*NR*	*NR*	*8*	*0.05*	*15*	*0.001-0.5*
Exposure Type												
Eye Area	NR	NR	NR	NR	2	NR	NR	NR	2	0.08	17	0.1-0.5
Possible Ingestion	NR	NR	NR	0.04-22	30	1	1	NR	7	0.03-0.1	7	0.001-2
Inhalation	NR	NR	NR	2	NR	NR	NR	NR	NR	NR	1	NR
Dermal Contact	NR	0.04	18	0.003-22	46	0.001-1	8	NR	43	0.000001-0.3	109	0.008-19
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	4	NR	NR	NR	NR	NR	5	NR	9	0.001-0.5
Hair - Coloring	NR	NR	NR	0.1	NR	0.1	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	0.001	NR	NR	5	0.2	1	0.1-2
Mucous Membrane	NR	NR	1	NR	2	0.001	NR	NR	2	NR	3	0.001
Bath Products	NR	NR	1	0.1-1	NR	NR	NR	NR	NR	NR	1	0.5
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

	Rubus Chamaemorus Seed Oil		Rubus Idaeus (Raspberry) Seed Oil		Schinziophyton Rautanenii Kernel Oil		Sclerocarya Birrea Seed Oil		Silybum Marianum Seed Oil		Solanum Lycopersicum (Tomato) Fruit Oil	
Totals	**3**	**0.1**	**10**	**0.1-5**	**6**	**NR**	**29**	**1**	**NR**	**0.5**	**NR**	**0.01-1**
Duration of Use												
Leave-On	*3*	*0.1*	*8*	*0.1-5*	*4*	*NR*	*23*	*1*	*NR*	*0.5*	*NR*	*0.001-1*
Rinse-Off	*NR*	*NR*	*2*	*NR*	*2*	*NR*	*6*	*1*	*NR*	*NR*	*NR*	*NR*
Exposure Type												
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.01
Possible Ingestion	NR	NR	1	NR	NR	NR	6	NR	NR	NR	NR	0.001
Inhalation	NR	NR	NR	NR	NR	NR	2	NR	NR	NR	NR	NR
Dermal Contact	3	0.1	8	0.1-5	3	NR	23	1	NR	0.5	NR	0.001-1
Deodorant (Underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	3	NR	6	1	NR	NR	NR	NR
Hair - Coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	NR	NR	NR	2	NR	NR	NR	NR	NR
Bath Products	NR	NR	1	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Solanum Lycopersicum (Tomato) Seed Oil		**Theobroma Cacao (Cocoa) Seed Butter**		**Theobroma Grandiflorum Seed Butter**		**Triticum Vulgare (Wheat) Germ Oil Unsaponifiables**		**Wheat Germ Acid**		**Vaccinium Macrocarpon (Cranberry) Seed Oil**	
Totals	**1**	**NR**	**442**	**0.000002-37**	**153**	**0.00005-7**	**17**	**0.2**	**16**	**NR**	**21**	**0.002-2**
Duration of Use												
Leave-On	*1*	*NR*	*367*	*0.000002-37*	*119*	*0.00005-7*	*17*	*0.2*	*3*	*NR*	*18*	*0.002-2*
Rinse-Off	*NR*	*NR*	*75*	*0.0001-2*	*34*	*0.001-1*	*NR*	*NR*	*13*	*NR*	*3*	*0.003-0.1*
Exposure Type												
Eye Area	NR	NR	11	0.0002-9	21	0.1-2	1	NR	NR	NR	2	NR
Possible Ingestion	NR	NR	33	37	49	7	NR	NR	NR	NR	NR	0.3
Inhalation	NR	NR	2	0.4	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	417	0.000002-37	141	0.00005-7	17	0.2	NR	NR	17	0.002-2
Deodorant (Underarm)	NR	NR	NR	0.001-1	NR	0.1	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	24	0.01-2	9	0.001-1	NR	NR	16	NR	4	0.01-0.1
Hair - Coloring	NR	NR	NR	0.1	3	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	0.1-1	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	35	0.02-2	19	0.05-0.1	NR	NR	NR	NR	1	0.003-0.1
Bath Products	NR	NR	4	0.1-1	4	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	8	0.01	NR	NR	NR	NR	NR	NR	NR	NR

	Vaccinium Myrtillus Seed Oil		**Vaccinium Oxycoccos (Cranberry) Seed Oil****		**Vaccinium Vitis-Idaea Seed Oil**		**Vegetable (Olus) Oil**		**Hydrogenated Vegetable Oil**		**Vitis Vinifera (Grape) Seed Oil**	
Totals	**33**	**0.01-0.1**	**4**	**NS**	**9**	**NR**	**165**	**0.0005-31**	**457**	**0.0004-60**	**465**	**0.001-43**
Duration of Use												
Leave-On	*32*	*0.01-0.12*	*3*	*NS*	*9*	*NR*	*135*	*0.0005-11*	*439*	*0.0005-60*	*368*	*0.001-41*
Rinse-Off	*1*	*NR*	*1*	*NS*	*NR*	*NR*	*30*	*0.002-31*	*18*	*0.0004-8*	*97*	*0.001-43*
Exposure Type												
Eye Area	NR	NR	NR	NS	NR	NR	11	0.01-11	102	0.008-49	14	0.01-5
Possible Ingestion	29	0.01	NR	NS	NR	NR	74	0.03-11	216	0.8-60	34	0.03-7
Inhalation	NR	NR	NR	NS	NR	NR	1	0.0005-0.02	1	3	6	0.001-7
Dermal Contact	33	0.01-0.1	4	NS	1	NR	143	0.0005-31	450	0.005-60	401	0.001-41
Deodorant (Underarm)	NR	NR	NR	NS	NR	NR	NR	---	NR	NR	NR	0.001-0.2
Hair - Non-Coloring	NR	NR	NR	NS	NR	NR	2	0.02-2	2	0.0005-0.09	46	0.01-0.3
Hair - Coloring	NR	NR	NR	NS	NR	NR	18	---	NR	0.0004-1	10	43
Nail	NR	NR	NR	NS	8	NR	1	2	1	0.2	8	0.001-35
Mucous Membrane	NR	NR	NR	NS	NR	NR	1	0.03-2	2	2-4	21	0.001-7
Bath Products	NR	NR	NR	NS	NR	NR	2	0.002-0.02	NR	0.5	8	0.01-2
Baby Products	NR	NR	NR	NS	NR	NR	1	---	NR	NR	5	NR

Table 5a. Frequency and concentration of use according to duration and exposure. - ingredients not previously reviewed by the CIR (continued)

	No. of Uses	Conc of Use (%)	No. of Uses	Conc of Use (%)
	Hydrogenated Grapeseed Oil		**Sodium Grapeseedate**	
Totals	**7**	**0.3-0.5**	**4**	**NR**
Duration of Use				
Leave-On	*4*	*0.3-0.5*	*4*	*NR*
Rinse-Off	*3*	*0.5*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	NR	NR
Possible Ingestion	1	0.5	NR	NR
Inhalation	NR	NR	NR	NR
Dermal Contact	5	0.5	NR	NR
Deodorant (Underarm)	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	4	NR
Hair - Coloring	NR	NR	NR	NR
Nail	1	0.3	NR	NR
Mucous Membrane	1	NR	NR	NR
Bath Products	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

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

NR - not reported to the VCRP or Council

NS - not surveyed

**not listed as an INCI name; included because of similarity

Table 5b. **Current and historical frequency and concentration of use according to duration and type of exposure - previously reviewed ingredients**

	# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)	
	Arachis Hypogaea (Peanut) Oil				**Hydrogenated Peanut Oil**				**Carthamus Tinctorius (Safflower) Seed Oil**				**Cocos Nucifera (Coconut) Oil**			
data year	*1998*	*2010*	*1984*	*2010*	*1998*	*2010*	*1998*	*2010*	*2002*	*2010*	*2003*	*2010*	*2007*	*2010*	*2008*	*2010*
Totals*	**22**	**74**	**mostly ≤25; >50 (1 use)**	**0.0001-30**	**19**	**12**	******	**2-5**	**142**	**508**	**0.00005-84**	**NS**	**626**	**798**	**0.0001-80**	**NS**
Duration of Use																
Leave-On	*14*	*59*	**	*0.0001-1*	*19*	*12*	**	*2-5*	*114*	*402*	*0.00005-84*	*NS*	*243*	*409*	*0.005-80*	*NS*
Rinse Off	*8*	*15*	**	*0.0002-30*	*NR*	*NR*	**	*NR*	*28*	*106*	*0.001-72*	*NS*	*383*	*389*	*0.0001-16*	*NS*
Exposure Type																***NS***
Eye Area	NR	4	**	NR	NR	NR	**	NR	5	15	1-6	NS	7	25	0.01-80	NS
Possible Ingestion	3	NR	**	NR	NR	NR	**	2	18	83	0.1-60	NS	19	44	0.2-51	NS
Inhalation	NR	2	**	NR	NR	NR	**	NR	3	5	5	NS	7	10	0.01-26	NS
Dermal Contact	19	53	**	0.0001-1	19	12	**	2-5	113	395	0.001-72	NS	380	548	0.005-80	NS
Deodorant (underarm)	NR	NR	**	NR	NR	NR	**	NR	NR	NR	NR	NS	NR	NR	0.1-16	NS
Hair - Non-Coloring	3	21	**	25-30	NR	NR	**	NR	28	79	0.00005-27	NS	97	176	0.0001-13	NS
Hair-Coloring	NR	NR	**	NR	NR	NR	**	NR	NR	20	1	NS	145	69	NR	NS
Nail	NR	NR	**	NR	NR	NR	**	NR	1	32	84	NS	2	5	0.005-2	NS
Mucous Membrane	4	2	**	NR	NR	NR	**	NR	NR	31	NR	NS	12	161	0.0005-16	NS
Bath Products	NR	NR	**	NR	NR	NR	**	NR	NR	3	7	NS	141	15	0.004-23	NS
Baby Products	NR	NR	**	NR	NR	NR	**	NR	NR	6	10	NS	12	15	0.010-0.3	NS

	Hydrogenated Coconut Oil				**Magnesium Cocoate**				**Potassium Cocoate**				**Sodium Cocoate**			
data year	*2007*	*2010*	*2008*	*2010*	*2007*	*2010*	*2008*	*2010*	*2007*	*2010*	*2008*	*2010*	*2007*	*2010*	*2008*	*2010*
Totals	**62**	**105**	**0.001-50**	**NS**	**11**	**9**	**NR**	**NS**	**24**	**40**	**0.003-40**	**NS**	**230**	**340**	**1-52**	**NS**
Duration of Use																
Leave-On	*55*	*79*	*0.001-50*	*NS*	*NR*	*NR*	*NR*	*NS*	*4*	*NR*	*28*	*NS*	*12*	*16*	*NR*	*NS*
Rinse-Off	*7*	*26*	*0.001-38*	*NS*	*11*	*9*	*NR*	*NS*	*20*	*40*	*0.03-40*	*NS*	*218*	*324*	*1-52*	*NS*
Exposure Type																
Eye Area	9	7	0.2-22	NS	NR	NR	NR	NS	NR	NR	NR	NS	NR	NR	NR	NS
Possible Ingestion	6	10	0.7-29	NS	NR	NR	NR	NS	NR	NR	NR	NS	NR	NR	NR	NS
Inhalation	NR	NR	0.3	NS	NR	NR	NR	NS	NR	NR	NR	NS	1	NR	NR	NS
Dermal Contact	3	102	0.001-25	NS	11	9	NR	NS	22	38	0.3-40	NS	175	269	1-52	NS
Deodorant (underarm)	NR	NR	NR	NS	NR	NR	NR	NS	NR	NR	NR	NS	NR	NR	NR	NS
Hair - Non-Coloring	3	3	0.001-2	NS	NR	NR	NR	NS	2	2	15	NS	55	71	2	NS
Hair-Coloring	NR	NR	0.5-0.6	NS	NR	NR	NR	NS	NR	NR	0.003	NS	NR	NR	NR	NS
Nail	NR	NR	0.8-25	NS	NR	NR	NR	NS	NR	NR	NR	NS	NR	NR	NR	NS
Mucous Membrane	NR	18	1-17	NS	NR	NR	NR	NS	NR	8	0.3	NS	1	238	1-2	NS
Bath Products	1	NR	0.5-39	NS	NR	NR	NR	NS	11	NR	0.3-40	NS	149	3	1-52	NS
Baby Products	1	1	2-50	NS	NR	NR	NR	NS	NR	NR	NR	NS	2	5	NR	NS

Table 5b. Current and historical frequency and concentration of use according to duration and type of exposure - previously reviewed ingredients (continued)

	# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)	
	Coconut Acid				**Hydrogenated Coconut Acid**				**Corylus Americana (Hazel) Seed Oil**				**Corylus Avellana (Hazel) Seed Oil**			
data year	*2007*	*2010*	*2008*	*2010*	*2007*	*2010*	*2008*	*2010*	*1998[#]*	*2010*	*1998*	*2010*	*1998[#]*	*2010*	*1997*	*2010*
Totals	**142**	**141**	**0.03-14**	**NS**	**NR**	**NR**	**6-10**	**NS**	**#**	**10**	******	**NR**	**85**	**150**	**≤100**	**0.005-98**
Duration of Use																
Leave-On	*18*	*17*	*NR*	*NS*	*NR*	*NR*	*6*	*NS*	*#*	*9*	**	*NR*	*74*	*131*	**	*0.005-98*
Rinse Off	*124*	*124*	*0.03-14*	*NS*	*NR*	*NR*	*10*	*NS*	*#*	*1*	**	*NR*	*11*	*19*	**	*0.005-5*
Exposure Type				***NS***				***NS***								
Eye Area	1	1	NR	NS	NR	NR	NR	NS	#	NR	**	NR	2	9	**	0.1
Possible Ingestion	NR	NR	NR	NS	NR	NR	NR	NS	#	NR	**	NR	NR	NR	**	14
Inhalation	NR	NR	NR	NS	NR	NR	NR	NS	#	NR	**	NR	NR	2	**	NR
Dermal Contact	140	140	0.04-14	NS	NR	NR	6-10	NS	#	10	**	NR	83	147	**	0.005-98
Deodorant (underarm)	NR	NR	NR	NS	NR	NR	NR	NS	#	NR	**	NR	NR	NR	**	NR
Hair - Non-Coloring	2	1	0.03-0.3	NS	NR	NR	NR	NS	#	NR	**	NR	1	2	**	NR
Hair-Coloring	NR	NR	NR	NS	NR	NR	NR	NS	#	NR	**	NR	NR	NR	**	NR
Nail	NR	NR	NR	NS	NR	NR	NR	NS	#	NR	**	NR	1	1	**	NR
Mucous Membrane	1	101	0.04-2	NS	NR	NR	NR	NS	#	1	**	NR	4	1	**	NR
Bath Products	93	NR	0.04-14	NS	NR	NR	NR	NS	#	NR	**	NR	2	2	**	NR
Baby Products	1	1	NR	NS	NR	NR	NR	NS	#	NR	**	NR	NR	1	**	NR

	Elaeis Guineensis (Palm) Oil				**Elaeis Guineensis (Palm) Kernel Oil**				**Hydrogenated Palm Kernel Oil**				**Hydrogenated Palm Oil**			
data year	*1997*	*2010*	*1997*	*2010*	*1997*	*2010*	*1997*	*2010*	*1997*	*2010*	*1997*	*2010*	*1997*	*2010*	*1997*	*2010*
Totals	**36**	**272**	******	**0.002-48**	**11**	**77**	******	**0.05-23**	**29**	**47**	******	**0.4-13**	**13**	**152**	******	**0.2-30**
Duration of Use																
Leave-On	*28*	*171*	**	*0.008-13*	*9*	*60*	**	*0.8-3*	*27*	*45*	**	*0.4-13*	*13*	*134*	**	*0.2-30*
Rinse-Off	*8*	*101*	**	*0.002-48*	*2*	*17*	**	*0.05-23*	*2*	*2*	**	*0.6-2*	*NR*	*18*	**	*2*
Exposure Type																
Eye Area	NR	12	**	0.04-2	NR	10	**	0.8	5	2	**	2-10	1	61	**	0.2-30
Possible Ingestion	NR	11	**	2	NR	6	**	NR	2	5	**	3-13	3	12	**	2-30
Inhalation	1	3	**	NR	NR	NR	**	NR	NR	1	**	NR	NR	NR	**	1
Dermal Contact	36	229	**	0.002-48	11	71	**	0.05-2	24	47	**	0.4-13	12	123	**	0.4-30
Deodorant (underarm)	NR	NR	**	NR	NR	NR	**	NR	NR	NR	**	NR	NR	NR	**	NR
Hair - Non-Coloring	NR	43	**	2-34	NR	6	**	0.9-23	NR	NR	**	NR	NR	NR	**	NR
Hair-Coloring	NR	NR	**	NR	NR	NR	**	NR	NR	NR	**	NR	NR	NR	**	NR
Nail	NR	NR	**	NR	NR	NR	**	3	NR	NR	**	NR	NR	NR	**	NR
Mucous Membrane	7	68	**	0.002-48	NR	10	**	0.05	2	2	**	0.9-2	NR	17	**	2
Bath Products	NR	NR	**	NR	NR	1	**	NR	NR	NR	**	NR	NR	NR	**	NR
Baby Products	1	2	**	NR	NR	NR	**	NR	NR	NR	**	NR	NR	NR	**	NR

Table 5b. Current and historical frequency and concentration of use according to duration and type of exposure - previously reviewed ingredients (continued)

	# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)		# of Uses		Conc. of Use (%)	
	Gossypium Herbaceum (Cotton) Seed Oil				**Hydrogenated Cottonseed Oil**				**Oryza Sativa (Rice) Bran Oil**				**Oryza Sativa (Rice) Germ Oil**			
data year	*1998*	*2010*	*1998*	*2010*	*1998*	*2010*	*1998*	*2010*	*2002*	*2010*	*2000-2003*	*2010*	*2002*	*2010*	*2000-2003*	*2010*
Totals	**4**	**83**		**0.004-32**	**272**	**362**	**	**0.001-24**	**39**	**371**	**0.1-39**	**0.0003-78**	**6**	**34**	**0.1**	**0.003-3**
Duration of Use																
Leave-On	*1*	*68*		*0.08-32*	*272*	*358*	**	*0.001-24*	*32*	*267*	*0.1-8*	*0.0003-78*	*5*	*29*	*0.1*	*0.003-3*
Rinse Off	*3*	*15*	**	*0.004-29*	*NR*	*4*	**	*0.01-0.1*	*7*	*104*	*0.2-39*	*0.005-6*	*1*	*5*	*NR*	*0.003-3*
Exposure Type																
Eye Area	NR	4		0.1-11	116	155	**	0.5-24	NR	5	0.1-1	0.5-0.8	NR	2	NR	0.01-1
Possible Ingestion	NR	9	**	0.2-1	151	NR	**	8-12	NR	17	0.1-1	0.1-8	NR	4	NR	0.1-3
Inhalation	NR	12	**	0.2	NR	NR	**	NR	NR	11	NR	0.1	NR	NR	NR	NR
Dermal Contact	4	78	**	0.004-29	156	356	**	0.001-24	36	321	0.1-39	0.0003-27	6	32	0.1	0.003-3
Deodorant (underarm)	NR	1	**	0.2	NR	NR	**	NR	NR	NR	NR	0.5	NR	NR	NR	0.003
Hair - Non-Coloring	NR	2	**	NR	NR	4	**	0.01-0.1	3	42	0.3	0.005-0.5	NR	NR	NR	NR
Hair-Coloring	NR	NR	**	NR	NR	NR	**	NR	NR	NR	NR	0.3	NR	NR	NR	NR
Nail	NR	1	**	0.5-32	NR	NR	**	NR	2	5	NR	0.02-78	NR	NR	NR	NR
Mucous Membrane	NR	7	**	0.004-0.01	NR	NR	**	NR	NR	48	1	0.0006-6	NR	1	NR	0.003-0.005
Bath Products	NR	NR	**	NR	NR	NR	**	NR	1	17	1-39	0.2	NR	1	NR	0.5
Baby Products	NR	NR	**	NR	NR	8	**	NR	NR	1	NR	NR	NR	NR	NR	NR

	Persea Gratissima (Avocado) Oil				**Prunus Amygdalus Dulcis (Sweet Almond) Oil**				**Sesamum Indicum (Sesame) Seed Oil**				**Sesamum Indicum (Sesame) Oil Unsaponifiables**			
data year	*2001*	*2010*	*2001*	*2010*	*2002*	*2010*	*2002*	*2010*	*2009*	*2010*	*2008*	*2010*	*2009*	*2010*	*2008*	*2010*
Totals	**188**	**883**	**0.001-23**	**0.0001-98**	**375**	**1127**	**0.004-76**	**0.0001-77**	**402**	**480**	**0.0001-73**	**NS**	**6**	**17**	**0.01-0.03**	**NS**
Duration of Use																
Leave-On	*40*	*657*	*0.001-23*	*0.0005-98*	*302*	*791*	*0.004-76*	*0.001-77*	*313*	*374*	*0.0001-73*	*NS*	*NR*	*17*	*0.01-0.03*	*NS*
Rinse-Off	*148*	*226*	*0.1-5*	*0.0001-15*	*73*	*336*	*0.01-2*	*0.0001-43*	*89*	*106*	*0.001-68*	*NS*	*NR*	*NR*	*NR*	*NS*
Exposure Type																
Eye Area	8	24	0.1-3	0.05-2	6	28	0.4	0.1-22	11	14	0.0008-10	NS	NR	NR	0.01	NS
Possible Ingestion	29	60	0.7-21	0.05-26	3	55	0.5	0.1-19	57	52	0.1-16	NS	NR	11	0.03	NS
Inhalation	2	11	0.02-3	0.01-8	3	18	1-3	0.5-39	5	5	2	NS	NR	NR	NR	NS
Dermal Contact	165	685	0.001-23	0.0005--98	323	986	0.04-11	0.001-46	346	414	0.0008-73	NS	6	17	0.01-0.03	NS
Deodorant (underarm)	NR	NR	NR	0.1	NR	2	0.004	0.02-1	NR	NR	NR	NS	NR	NR	NR	NS
Hair - Non-Coloring	11	189	0.002-3	0.0001-41	46	116	0.3-3	0.001-19	50	59	0.0001-30[a]	NS	NR	NR	NR	NS
Hair-Coloring	8	NR	NR	0.3	2	2	0.1	0.02	NR	NR	0.03-0.8[b]	NS	NR	NR	NR	NS
Nail	4	7	0.4-19	0.001-34	4	13	1-76	0.001-77	6	7	≤1-10	NS	NR	NR	NR	NS
Mucous Membrane	NR	43	0.1-5	0.002-3	19	93	0.5	<0.1-23	4	28	NR	NS	NR	NR	NR	NS
Bath Products	5	25	0.1-5	0.6-6	10	41	0.01-0.1	0.1-43	27	5	0.09-68	NS	NR	NR	NR	NS
Baby Products	NR	9	NR	NR	7	14	NR	2-3	1	3	6	NS	NR	NR	NR	NS

Table 5b. Current and historical frequency and concentration of use according to duration and type of exposure - previously reviewed ingredients (continued)

	# of Uses		*Conc. of Use (%)*		*# of Uses*		*Conc. of Use (%)*		*# of Uses*		*Conc. of Use (%)*		*# of Uses*		*Conc. of Use (%)*	
	Triticum Vulgare (Wheat) Germ Oil				**Zea Mays (Corn) Oil**				**Zea Mays (Corn) Oil Unsaponifiables**				**Zea Mays (Corn) Germ Oil**			
data year	*2001*	*2010*	*2001*	*2010*	*2007*	*2010*	*2006*	*2010*	*2007*	*2010*	*2006*	*2010*	*2007*	*2010*	*2006*	*2010*
Totals	**303**	**527**	**0.00002-18**	**0.0001-28**	**498**	**598**	**0.00003-14**	**NS**	**7**	**1**	**NR**	**NS**	**37**	**53**	**0.2-25**	**NS**
Duration of Use																
Leave-On	*80*	*373*	*0.00002-18*	*0.0001-28*	*241*	*361*	*0.00003-14*	*NS*	*6*	*1*	*NR*	*NS*	*25*	*34*	*3-25*	*NS*
Rinse Off	*223*	*154*	*0.00002-5*	*0.001-2*	*257*	*237*	*0.001-0.07*	*NS*	*1*	*NR*	*NR*	*NS*	*12*	*19*	*0.2-3*	*NS*
Exposure Type																
Eye Area	9	12	0.00004-3	0.0001-0.5	39	35	0.0008-0.2	NS	NR	NR	NR	NS	NR	NR	NR	NS
Possible Ingestion	33	29	0.1-3	0.3-5	29	30	0.003-10	NS	NR	NR	NR	NS	NR	NR	NR	NS
Inhalation	2	7	0.0002-0.01	0.0001-0.0005	1	1	0.001-0.1	NS	NR	NR	NR	NS	NR	NR	NR	NS
Dermal Contact	220	360	0.00002-18	0.0005-23	276	371	0.00003-14	NS	7	1	NR	NS	31	50	3-25	NS
Deodorant (underarm)	NR	NR	0.02	NR	1	4	NR	NS	NR	NR	NR	NS	NR	NR	NR	NS
Hair - Non-Coloring	63	142	0.0001-2	0.0001-<1	38	40	0.0001-0.02	NS	NR	NR	NR	NS	4	3	0.2	NS
Hair-Coloring	12	20	0.1	0.01-0.2	182	183	0.004-0.007	NS	NR	NR	NR	NS	NR	NR	NR	NS
Nail	4	2	0.1-4	0.1-28	1	3	0.001-5	NS	NR	NR	NR	NS	NR	NR	NR	NS
Mucous Membrane	3	22	0.02-1	0.01-0.5	2	2	0.004-0.01	NS	NR	NR	NR	NS	4	3	3	NS
Bath Products	1	2	0.001-2	0.5	NR	NR	0.001-0.01	NS	NR	NR	NR	NS	3	4	NR	NS
Baby Products	1	9	0.5	NR	8	8	0.004	NS	NR	NR	NR	NS	2	4	NR	NS

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

NR - not reported to the VCRP or the Council

NS - not surveyed; ingredients that were recently reviewed were not resurveyed for concentration of use

** concentration of use data were not given in the original report

- was not distinguished whether C. Americana or C. Avellana was reported; arbitrarily reported under C. Avellana (Hazel) Seed Oil for this table

[a] 15% after dilution.

[b] 0.4 after dilution.

Table 5c**. Ingredients with no reported use concentrations or uses.**

Adansonia Digitata Seed Oil
Aleurites Moluccanus Bakoly Seed Oil
Amaranthus Hypochondriacus Seed Oil
Arctium Lappa Seed Oil
Babassu Acid
Bassia Butyracea Seed Butter
Brassica Campestris (Rapeseed) Oil Unsaponifiables
Brassica Napus Seed Oil
Brassica Oleracea Acephala Seed Oil
Canarium Indicum Seed Oil
Carya Illinoensis (Pecan) Seed Oil
Citrus Aurantifolia (Lime) Seed Oil
Citrus Aurantifolia (Lime) Seed Oil Unsaponifiables
Citrus Aurantium Dulcis (Orange) Seed Oil
Citrus Aurantium Dulcis (Orange) Seed Oil Unsaponifiables
Citrus Grandis (Grapefruit) Seed Oil
Citrus Grandis (Grapefruit) Seed Oil Unsaponifiables
Cocos Nucifera (Coconut) Seed Butter
Coix Lacryma-Jobi (Job's Tears) Seed Oil
Corn Acid
Cottonseed Acid
Cynara Cardunculus Seed Oil
Elaeis (Palm) Fruit Oil
Elaeis Guineensis (Palm) Butter
Fragaria Ananassa (Strawberry) Seed Oil
Fragaria Chiloensis (Strawberry) Seed Oil
Fragaria Vesca (Strawberry) Seed Oil
Fragaria Virginiana (Strawberry) Seed Oil
Guizotia Abyssinica Seed Oil
Hippophae Rhamnoides Seed Oil
Hydrogenated Adansonia Digitata Seed Oil
Hydrogenated Apricot Kernel Oil Unsaponifiables
Hydrogenated Argania Spinosa Kernel Oil
Hydrogenated Black Currant Seed Oil
Hydrogenated Camelina Sativa Seed Oil
Hydrogenated Cranberry Seed Oil
Hydrogenated Grapefruit Seed Oil
Hydrogenated Grapefruit Seed Oil Unsaponifiables
Hydrogenated Hazelnut Oil
Hydrogenated Kukui Nut Oil
Hydrogenated Lime Seed Oil
Hydrogenated Lime Seed Oil Unsaponifiables
Hydrogenated Macadamia Seed Oil
Hydrogenated Meadowfoam Seed Oil
Hydrogenated Orange Seed Oil
Hydrogenated Orange Seed Oil Unsaponifiables
Hydrogenated Palm Acid
Hydrogenated Passiflora Edulis Seed Oil
Hydrogenated Peach Kernel Oil
Hydrogenated Pistachio Seed Oil
Hydrogenated Pumpkin Seed Oil
Hydrogenated Punica Granatum Seed Oil
Hydrogenated Raspberry Seed Oil
Hydrogenated Rice Bran Oil
Hydrogenated Rosa Canina Fruit Oil
Hydrogenated Safflower Seed Oil
Hydrogenated Sesame Seed Oil
Hydrogenated Sweet Almond Oil Unsaponifiables
Hydrogenated Wheat Germ Oil
Hydrogenated Wheat Germ Oil Unsaponifiables
Lupinus Albus Oil Unsaponifiables
Morinda Citrifolia Seed Oil
Olea Europaea (Olive) Husk Oil
Olive Acid
Oryza Sativa (Rice) Seed Oil
Peanut Acid
Potassium Babassuate
Potassium Cornate
Potassium Hydrogenated Cocoate
Potassium Hydrogenated Palmate
Potassium Peanutate
Potassium Rapeseedate
Potassium Safflowerate
Potassium Soyate
Prunus Amygdalus Dulcis (Sweet Almond) Oil Unsaponifiables
Prunus Armeniaca (Apricot) Kernel Oil Unsaponifiables
Rapeseed Acid
Ribes Rubrum (Currant) Seed Oil
Rice Bran Acid
Safflower Acid
Sesamum Indicum (Sesame) Seed Butter
Sodium Cocoa Butterate
Sodium Hydrogenated Cocoate
Sodium Hydrogenated Palmate
Sodium Macadamiaseedate
Sodium Peanutate
Sodium Rapeseedate
Sodium Safflowerate
Sodium Sesameseedate
Sodium Soyate
Sodium Theobroma Grandiflorum Seedate
Soy Acid
Sunflower Seed Acid
Torreya Nucifera Seed Oil
Triticum Aestivum (Wheat) Germ Oil
Triticum Vulgare (Wheat) Germ Oil Unsaponifiables
Vaccinium Corymbosum (Blueberry) Seed Oil

Table 6. **Examples of non-cosmetic uses of oils.**

Oil	Use[6,112,204-209]
Aleurities Moluccana Seed Oil [Kukui]	wood preservative, varnishes, paint oil, illumination, soap making, waterproofing paper, rubber substitute, insulating material
Arachis Hypogaea (Peanut) Oil	pharmaceutical, soap making, lubricants, emulsions for insect control, diesel engine fuel
Brassica Napus Seed Oil [Rapeseed]/Canola Oil	rubber additive · lubricants · fat liquoring of leather · varnishes and lacquers · textile chemicals · detergent additives · plasticizers · weed control
Butyrospermum Parkii (Shea) Oil	illumination
Camelina Sativa Seed Oil [False Flax]	drying oil · manufacturing of varnishes and paints
Citrullus Lanatus (Watermelon) Seed Oil	illumination
Cocos Nucifera (Coconut) Oil	lubricants, hydraulic fluid, paints, synthetic rubber, plastics, illumination
Elaeis Guineensis (Palm) Oil	crayon and candle manufacturing · tin plate industry
Elaeis Guineensis (Palm) Kernel Oil	detergent production · pharmaceutical · crayon and candle manufacturing · tin plate industry
Garcinia Indica Seed Butter [Kokum]	candle and soap making, sizing of cotton yarn, pharmaceutical
Guizotia Abyssinica Seed Oil [Niger/Ramtil]	paint · lubricant · pharmaceutical
Helianthus Annuus (Sunflower) Seed Oil	manufacturing of lacquers, copolymers, polyester films, modified resins, plasticizers, alkyl resins, other similar products
Juglans Regia (Walnut) Seed Oil	paints, soap making
Linum Usitatissimum (Linseed) Seed Oil	manufacturing of linoleum, cloth oil, printing and lithographic inks, core oils, linings, packings, oil-modified alkyd resins, caulking compounds, putties, leather-finishing compounds, lubricants, greases, polishes, pyrotechnic compositions · pigment binder in petrochemicals · concrete protector · stabilizer/plasticizer for vinyl plastics · industrial stains · jute textiles · drying oil in paints and varnishes
Mangifera Indica (Mango) Seed Butter	substitute for cocoa butter
Olea Europaea (Olive) Fruit Oil	textile industry · pharmaceutical
Orbignya Cohune Seed Oil	manufacturing of soaps, candles, and nightlights · cotton dyeing · ointment base · substitute for cocoa butter in food
Perilla Ocymoides Seed Oil [Perilla]	substitute for linseed oil in the manufacture of paints, varnishes, linoleum, oilclothes, and printing inks
Prunus Amygdalus Dulcis (Sweet Almond) Oil	pharmaceutical, energy source
Prunus Armeniaca (Apricot) Kernel Oil	pharmaceutical
Theobroma Cacao (Cocoa) Seed Butter	pharmaceutical
Vitis Vinifera (Grape) Seed Oil	substitute for linseed oil in the manufacture of paints, and varnishes

Table 7a. **Dermal effects – Non-Human studies**

Ingredient	Concentration	Animals	Procedure	Results	Reference
			Adansonia Digitata Seed Oil		
Adansonia Digitata (Baobab) Oil	100%		MatTek EpiDerm MTT viability assay; 100 µl of test material for 1-24 h	classified as non-irritating	210
			Arachis Hypogaea (Peanut) Oil		
Arachis Hypogaea (Peanut) Oil		Hartley and/or Himalayan guinea pigs	Single drops of a store-bought peanut oil were applied to clipped skin on the backs of 4 guinea pigs. Applications were made at 2-6 wk intervals, for a total of 7 applications over a 5-mo period. It appears that the test sites were not covered. The test sites were scored 24 h after application. Well-defined erythema was considered a positive reaction.	None of the animals had a positive reaction following the initial application. Two animals had positive reactions following application at wks 6 and 12, while one animal had a positive reaction following dosing at wk 12 only	17
			Butyrospermum Parkii (Shea) Butter		
Butyrospermum Parkii (Shea) Butter	not specified	3 male New Zealand White (NZW) rabbits	0.5 ml applied to the shaved dorso-lumbar region under an occlusive patch for 4 h	very slight erythema with or without edema was observed in 2 rabbits; resolved by day 3 or 4	211
Butyrospermum Parkii (Shea) Butter	induction: 75% challenge: 20 and 50%	10 female albino Hartley/Dunkin guinea pigs	maximization study with Freund's complete adjuvant (FCA) during induction	no evidence of delayed hypersensitivity	212
			Crambe Abyssinica Seed Oil		
Crambe Abyssinica Seed Oil	undiluted		dermal irritation study; details not provided	not a dermal irritant	213
			Hippophae Rhamnoides Seed Oil		
Hippophae Rhamnoides Seed Oil		albino rabbits, number not specified	0.5 ml applied under an occlusive patch for 4 h	no irritation	214
			Olea Europaea (Olive) Fruit Oil		
Olea Europaea (Olive) Fruit Oil		12 Harley and/or Himalayan guinea pigs	Single drops of a USP-grade olive oil that had been stored in its original metal container for 10 yrs were applied to a clipped area on the backs of 12 guinea pigs. (The composition of the oil was not determined.) Applications were made at 2-6 wk intervals over a period of 5 mos. Four guinea pigs were treated similarly using store-bought virgin olive oil.	None of the animals had a positive reaction following the initial application of either oil. With 10-yr-old olive oil, 11/12 of the animals had a positive reaction at some point. Some, but not all, of these guinea pigs reacted consistently following the first positive reaction; 2 animals had only 1 positive reaction; 2 guinea pigs in this group died by wk 16. In the group dosed with virgin olive oil, 1 animal had a positive reaction at wk 2 and 1 animal had a positive reaction at wks 4 and 6	215
		22 guinea pigs sensitive to the 10-yr-old USP olive oil	cross-reactivity to store-bought olive oil, another store-bought olive oil (not specified as virgin olive oil), corn oil, and peanut oil was determined. The 5 oils were applied simultaneously to the backs of the guinea pigs	18 of the animals reacted to the virgin olive oil, and 18 reacted to the other store-bought olive oil. (Overlap of these animals was not complete.) Cross-reactivity to corn or peanut oil was not observed.	
		8 sensitized and 4 non-sensitized guinea pigs	single drops of the unsaponifiable fraction of the 10-yr-old oil were applied	All of the sensitized animals reacted to the unsaponifiable fraction, while the non-sensitized animals did not.	
			Zea Mays (Corn) Oil		
corn oil, store-bought		6 Hartley and/or Himalayan guinea pigs	sensitization study, details not specified	0 of the animals had a positive reaction following the initial application; 2 animals had positive reactions following application at wks 4 and 6, while 1 animal had a positive reaction following application at wk 12	215

Table 7a. **Dermal effects – Non-Human studies**

Ingredient	Concentration	Animals	Procedure	Results	Reference
			PHOTOTOXICITY		
			Butyrospermum Parkii (Shea) Butter		
Butyrospermum Parkii (Shea) Butter	10 and 20% in acetone	10 Pirbright white guinea pigs	animals were treated with test compound, then irradiated with UV-B light for 80 seconds followed by UV-A light for 80 min	not phototoxic	216

Table 7b. Dermal effects – Non-Human studies- – summarized from previous CIR reports

Ingredient	Concentration	Animals	Procedure	Results	Reference
Arachis Hypogaea (Peanut) Oil					
Undiluted technical grade Arachis Hypogaea (Peanut) Oil was moderately irritating to rabbits and guinea pig skin and mildly irritating to rat skin following exposure; there was no indication that the test site was occluded. However, in a 48 h occlusive patch test using miniature swine, technical grade Arachis Hypogaea (Peanut) Oil was not irritating					17
Carthamus Tinctorius (Safflower) Oil					
Undiluted Carthamus Tinctorius (Safflower) Seed Oil was minimally irritating in a repeat open patch test using rabbits and was not a primary irritant or sensitizer in a maximization study using guinea pigs.					32
Cocos Nucifera (Coconut) Oil					
Undiluted Cocos Nucifera (Coconut) Oil was non- irritating to rabbit skin. In guinea pigs, undiluted Cocos Nucifera (Coconut) Oil was not a sensitizer in a Magnusson-Kligman maximization study.					33
Hydrogenated Coconut Oil					
Undiluted hydrogenated coconut oil was non-irritating to rabbit skin. In guinea pigs, undiluted hydrogenated coconut oil was not a sensitizer in a Buehler test.					33
Coconut Acid					
Undiluted coconut acid was minimally irritating to rabbit skin.					33
Sodium Cocoate					
In single-insult occlusive patch tests of a 5% aq. solution of a bar soap containing 13% sodium cocoate, scores of 1.6-4.0/8.0 were reported.					33
Elaeis Guineensis (Palm) Oil					
Undiluted Elaeis Guineensis (Palm) Oil was practically non- to minimally irritating to rabbit skin. Elaeis Guineensis (Palm) Oil, 5%, was non-allergenic in a maximization study.					26
Gossypium Herbaceum (Cotton) Seed Oil					
Cosmetic formulations containing 3.4-8.97% hydrogenated cottonseed oil were not irritating to rabbit skin.					27
Oryza Sativa (Rice) Bran Oil					
Undiluted Oryza Sativa (Rice) Bran Oil was not irritating to rabbits, and in a guinea pig maximization study, no reactions were observed when 5% was used at induction and 25% and 50% Oryza Sativa (Rice) Bran Oil were used at challenge. An Oryza Sativa (Rice) Bran Oil /Oryza Sativa (Rice) Germ Oil mixture, concentrations not stated, did not cause a contact allergy response. Undiluted hydrolyzed rice protein was also not irritating or sensitizing.					28
Oryza Sativa (Rice) Germ Oil					
Oryza Sativa (Rice) Germ Oil was not a primary dermal irritant.					28
Prunus Amygdalus Dulcis (Sweet Almond) Oil					
Undiluted Prunus Amygdalus Dulcis (Sweet Almond) Oil and two moisturizer formulations, each containing 25% Prunus Amygdalus Dulcis (Sweet Almond) Oil, were tested for skin irritancy in rabbits using occlusive patches. Undiluted Prunus Amygdalus Dulcis (Sweet Almond) Oil was nonirritating (PII = 0/4). The formulations containing 25% Prunus Amygdalus Dulcis (Sweet Almond) Oil were minimally irritating (PIIs = 0.28 and 0.72, respectively). In a 60-day cumulative irritation test, 10 and 100% Prunus Amygdalus Dulcis (Sweet Almond) Oil was applied to rabbits. When tested in 7 separate trials, 100% Prunus Amygdalus Dulcis (Sweet Almond) Oil produced mean maximum irritation indices (MMIIs) ranging from 0.34 to 1.34 (maximum score = 8). At a concentration of 10%, MMIIs for this ingredient ranged from 0-0.66. Results indicated that, when applied to the skin over a long period of time, Prunus Amygdalus Dulcis (Sweet Almond) Oil is slightly irritating; whereas, at 10% it is practically nonirritating. A maximization assay was used to determine the sensitizing potential of Prunus Amygdalus Dulcis (Sweet Almond) Oil. using guinea pigs. Intradermal induction used concentrations of 5% Amygdalus Dulcis (Sweet Almond) Oil, the dose-range phase of the experiment used a single dermal application of 5%, 10%, or 100% Prunus Amygdalus Dulcis (Sweet Almond) Oil, a booster induction injection of 100% Prunus Amygdalus Dulcis (Sweet Almond) Oil was applied occlusively for 48 h 1 wk later, challenge was with 5% Prunus Amygdalus Dulcis (Sweet Almond) Oil in petrolatum applied topically under occlusion for 24 h. Prunus Amygdalus Dulcis (Sweet Almond) Oil was non-sensitizing.					217

Table 7b. Dermal effects – Non-Human studies- – summarized from previous CIR reports

Ingredient	Concentration	Animals	Procedure	Results	Reference
Undiluted Prunus Amygdalus Dulcis (Sweet Almond) Oil was tested for irritancy in groups of 6 male albino rabbits. The test material was applied under occlusion to the clipped intact and abraded dorsal skin of each animal. Twenty-three hours later, patches were removed; sites were scored at 24 and 48 hours. The Primary Irritation Indices (PIIs) for seven test samples of Prunus Amygdalus Dulcis (Sweet Almond) Oil ranged from 0 to 0.18 (maximum score = 8), indicating that this ingredient is practically nonirritating to skin.					
Sesamum Indicum (Sesame) Seed Oil					
Undiluted Sesamum Indicum (Sesame) Seed Oil was non- or minimally irritating to rabbit skin.					55
Triticum Vulgare (Wheat) Germ Oil					
Triticum Vulgare (Wheat) Germ Oil, undiluted and at 2% in formulation, was non- to mildly irritating, and undiluted Triticum Vulgare (Wheat) Germ Oil was not sensitizing to guinea pigs.					30
PHOTOTOXICITY					
Elaeis Guineensis (Palm) Oil					
A facial lotion containing 1.5% Elaeis Guineensis (Palm) Oil was not phototoxic in the phototoxicity yeast assay.					26
Oryza Sativa (Rice) Bran Oil					
Oryza Sativa (Rice) Bran Oil, tested undiluted during induction at 10% at challenge, was not a photosensitizer in guinea pigs.					28
Oryza Sativa (Rice) Germ Oil					
Oryza Sativa (Rice) Germ Oil, ≤75%, was not phototoxic or photosensitizing.					28
COMEDOGENICITY					
Corylus Avellana (Hazel) Seed Oil					
A comedogenicity study was conducted in which 0.1 ml of Corylus Avellana (Hazel) Seed Oil (pH 6) was applied to the pinna of the ear of albino rabbits. No local irritation was noted at the application site. A “slight difference in the number and size of the pilosebaceous follicles” was noted via magnifying glass. A “slight excess of sebum and a dilation of the follicles” was noted upon microscopic examination of the treated areas					41

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
		Adansonia Digitata Seed Oil		
0.01% Adansonia Digitata Seed Oil in a lip product	106	HRIPT with 0.2 g test material, semi-occluded	not a dermal irritant or sensitizer	218
100% Adansonia Digitata Seed Oil	107	HRIPT with 0.02-0.05 ml test material, semi-occluded	not a dermal irritant or sensitizer	219
		Aleurites Moluccana Seed Oil		
0.005% Aleurites Moluccana Seed Oil in scalp conditioner/hair wax	104	HRIPT; occlusive; applied neat	not a dermal irritant or sensitizer	220
~3% in a skin cleanser	110	modified HRIPT; semi-occlusive; 10% dilution in distilled water	not a dermal irritant or sensitizer	221
		Arachis Hypogaea (Peanut) Oil		
dermatologic product containing 0.01% fluocinolone and refined Arachis Hypogaea (Peanut) Oil	peanut-sensitive subjects; 8 children, 6 adults	skin prick test with peanut extracts, a soln, of 50% glycerin (negative control), a solution of 1.8 mg/ml histamine phosphate in 50% glycerin (positive control), the complete test product, vehicle only (without fluocinolone), and refined Arachis Hypogaea (Peanut) Oil	1 child had a trace positive reaction	222
		patch test with product, vehicle only, and refined Arachis Hypogaea (Peanut) Oil	no reactions	
		Argania Spinosa Kernel Oil		
5% Argania Spinosa Kernel Oil in a face serum	108	primary cutaneous irritation	no primary irritation	223
5% Argania Spinosa Kernel Oil in a face serum	108	HRIPT; occlusive; applied neat	not an irritant or a sensitizer	223
10% Argania Spinosa Kernel Oil in a skin salve	209	HRIPT; occlusive; applied neat	not a sensitizer	224
10% Argania Spinosa Kernel Oil in a skin salve	51	4-wk use test; applied to lips, hands/nails, elbows, knees, feet/heels	did not elicit significant dermal irritation or dryness; 2 subjects had level 1(mild, very slight erythema) on the lips, and 5 had level 1 erythema on the elbows, lips, or knees; 15 subjects reported subjective irritation	225
		Astrocaryum Murumuru		
1% Astrocaryum Murumuru Seed Butter in a lipstick	97	HRIPT with 150 mg test material, semi-occluded	not a dermal irritant or sensitizer	226
4% Astrocaryum Murumuru Seed Butter in a lipstick	108	HRIPT, occluded	not a dermal irritant or sensitizer	227
4% Astrocaryum Murumuru Seed Butter in a lipstick	108	HRIPT, occluded	not a dermal irritant or sensitizer	228
4% Astrocaryum Murumuru Seed Butter in a lipstick	108	HRIPT, occluded	not a dermal irritant or sensitizer	229
4% Astrocaryum Murumuru Seed Butter in a lipstick	106	HRIPT, occluded	not a dermal irritant or sensitizer	230
4% Astrocaryum Murumuru Seed Butter in a lipstick	106	HRIPT, occluded	not a dermal irritant or sensitizer	231
4% Astrocaryum Murumuru Seed Butter in a lipstick	108	HRIPT, occluded	not a dermal irritant or sensitizer	232

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
Avena Sativa (Oat) Kernel Oil				
3% Avena Sativa (Oat) Kernel Oil in a body and hand formulation	100	HRIPT with 0.2 ml, occluded	not a dermal irritant or sensitizer	233
Bassia Latifolia Seed Butter				
2% Bassia Latifolia Seed Butter in a body scrub	110	HRIPT with 1% aq. solution of the formulation, semi-occluded	not a dermal irritant or sensitizer	234
Borago Officinalis Seed Oil				
1% Borago Officinalis Seed Oil in a body and hand formulation	213	HRIPT with 0.2 g, occluded	not a dermal irritant or sensitizer	235
2% Borago Officinalis Seed Oil in a face serum	108	primary cutaneous irritation	no primary irritation	223
2% Borago Officinalis Seed Oil in a face serum	108	HRIPT; occlusive; applied neat	not an irritant or a sensitizer	223
Brassica Campestris (Rapeseed) Oil				
5% Hydrogenated Rapeseed Oil in a baby oil	105	HRIPT with 0.2 ml, semi-occluded	not a dermal irritant or sensitizer	236
Brassica Oleracea Italica (Broccoli) Seed Oil				
0.5% Brassica Oleracea Italica (Broccoli) Seed Oil in a hair conditioner	102	HRIPT with 150 µl of test material, 10% dilution, semi-occluded	not a dermal irritant or sensitizer	237
Butyrospermum Parkii (Shea) Butter				
Butyrospermum Parkii (Shea) Butter and fractions of unsaponifiable lipids from Butyrospermum Parkii (Shea) Butter; the "liquid" sample was obtained from a supplier; the unsaponifiable fraction was obtained through low temperature crystallization of the supplied sample	21	single applications to normal skin and sodium lauryl sulfate (SLS)-irritated skin; right volar forearm was treated with 50 µl of each test material in 12 mm Finn chambers for 48 h; the left volar forearm was treated with 50 µl of 14% aq. SLS for 7 h, rinsed, dried, and then treated with 50 µl of each test material for 17 h; cutaneous blood flow (CBF) and transepidermal water loss (TEWL) were measured	normal skin: barely perceptible erythema observed in a "small" number of subjects at 24 h after treatment with shea butter; no irritation to the shea unsaponifiable fraction; no sig. difference in CBF or TEWL SLS-treated skin: 2 subjects had a slight- and moderate reaction to the unsaponifiable fraction; no sig. difference in CBF or TEWL	238
0.1% Butyrospermum Parkii (Shea) Butter in a scalp conditioner	114	primary cutaneous irritation; formulation diluted to 1%	no primary irritation	239
2% Butyrospermum Parkii (Shea) Butter in a cream	119	primary cutaneous irritation	no primary irritation	240
0.1% Butyrospermum Parkii (Shea) Butter in a scalp conditioner	110	HRIPT; occlusive; formulation diluted to 1%	not a dermal irritant or sensitizer	239
2% Butyrospermum Parkii (Shea) Butter in a cream	118 (irritation)/ 116 (sensitization)	HRIPT; occlusive	not a dermal irritant or sensitizer	240
4% Butyrospermum Parkii (Shea) Butter in a face cream	51	HRIPT with 20 µl test material, occluded	not a dermal irritant or sensitizer	241
4% Butyrospermum Parkii (Shea) Butter in an eye cream	108	HRIPT with 20 µl test material, occluded	not a dermal irritant or sensitizer	242
23.5% Butyrospermum Parkii (Shea) Butter in a lip gloss	104	HRIPT	not a dermal irritant or sensitizer	243
23.7% Butyrospermum Parkii (Shea) Butter in a lip gloss	104	HRIPT	irritation on induction days 5-9 in one subject; no sensitization	244

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
24.1% Butyrospermum Parkii (Shea) Butter in a lip wax	113	HRIPT	not a dermal irritant or sensitizer	245
24.1% Butyrospermum Parkii (Shea) Butter in a lip wax	2 runs	Episkin	average viability 67.3% - no irritation potential	246
24.7% Butyrospermum Parkii (Shea) Butter in a lip gloss	40	28-day use study, 2-6 times /day	1 subject with desquamation	247
45% Butyrospermum Parkii (Shea) Butter in a body/hand massage	109[a]	HRIPT	not a dermal irritant or sensitizer	248
45% Butyrospermum Parkii (Shea) Butter in a body/hand massage	109[a]	HRIPT	not a dermal irritant or sensitizer	249
45% Butyrospermum Parkii (Shea) Butter in a body/hand massage	109[a]	HRIPT	not a dermal irritant or sensitizer	250
45% Butyrospermum Parkii (Shea) Butter in a body/hand massage	109[a]	HRIPT	not a dermal irritant or sensitizer	251
45% Butyrospermum Parkii (Shea) Butter in a body/hand massage	31	2-week use study, 2 time per day	no erythema, edema, or dryness	252
60% Butyrospermum Parkii (Shea) Butter in a cuticle cream	111	HRIPT	not a dermal irritant or sensitizer	253
Camelina Sativa Seed Oil				
0.25% Camelina Sativa Seed Oil in a body powder	204	HRIPT with 0.1 g, semi-occluded	not a dermal sensitizer	254
7% Camelina Sativa Seed Oil in an oil treatment	103	HRIPT with 200 µl test material, semi-occluded	Grade 1 (mild erythema) reactions in 4 subjects for 1 or 2 patches in the induction phase, grade 1 (mild erythema in different subjects at the 48 h challenge reading. Study concluded test material was not a dermal irritant or sensitizer.	255
Camellia Sinensis Seed Oil				
0.0985% Camellia Sinensis Seed Oil in a lipstick	108	HRIPT with 0.2 g, occluded	not a dermal irritant or sensitizer	256
0.0985% Camellia Sinensis Seed Oil in a lipstick	108	HRIPT with 0.2 g, occluded	not a dermal irritant or sensitizer	257
Canola Oil				
74.7% Canola Oil in a body oil	101	HRIPT with 150 µl test material, semi-occluded	not a dermal irritant or sensitizer	258
Carthamus Tinctorius (Safflower) Oil				
5% Carthamus Tinctorius (Safflower) Seed Oil in a cleansing oil rinse-off	214	HRIPT with 0.2 ml of a 10% v/v aqueous solution, semi-occluded	3 subjects had a "?" reaction following a patch during the induction and 1 subject had definite erythema with no edema or damage to the epidermis (+D) following the 7th patch. No reactions were observed at a new test site. No other reactions were observed. Study concluded test material was not a dermal sensitizer.	259

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
30% Carthamus Tinctorius (Safflower) Seed Oil in a massage oil	107	HRIPT with 0.2 ml test material, semi-occluded	1 subject had slight erythema following the 7th patch that did not reoccur, no other reactions observed. Not a dermal irritant or sensitizer.	260
Caryocar Brasiliense Fruit Oil				
0.1% Caryocar Brasiliense Fruit Oil in a lipstick	100	HRIPT with 200 mg test material, semi-occluded	not a dermal irritant or sensitizer	261
Chenopodium Quinoa Seed Oil				
1% Chenopodium Quinoa Seed Oil in a UV SPF cream	105	HRIPT with 0.02 ml test material, occluded	"An acceptable level of irritation" was observed in the induction phase consisting of grade 1 (mild erythema) in 39 subjects, with one additional subject exhibiting a grade 2 (moderate erythema) reaction. No evidence of skin sensitization was observed.	262
1% Chenopodium Quinoa Seed Oil in a UV SPF cream	102	HRIPT with 0.02 ml test material, occluded	"An acceptable level of irritation" was observed in the induction phase, with 54% of the subjects exhibiting a grade 1 (mild erythema) reaction and 3% of the subjects exhibiting a grade 2 (moderate erythema) reaction. One subject had a strong reaction to the 3rd induction patch and discontinued the induction phase after the 6th application. At challenge, the subject had only papules at 96 h. Due to reactions to other materials tested at the same time, it could not be determined if the test material was the causative agent. No evidence of skin sensitization was observed in the remaining subjects.	263
Citrullus Lanatus (Watermelon) Seed Oil				
2% Citrullus Lanatus (Watermelon) Seed Oil in a facial oil	105	HRIPT, semi-occluded	not a dermal irritant or sensitizer	264
Cocos Nucifera (Coconut) Fruit Oil				
0.15% Cocos Nucifera (Coconut) Oil in a scalp conditioner/hair wax	104	HRIPT; occlusive; applied neat	not a dermal irritant or sensitizer	220
31% Cocos Nucifera (Coconut) Oil in a lip balm	222	HRIPT with 0.2 g test material, occluded	2 subjects had low-level, transient (±) reactions during the induction, no other reactions were observed. Study concluded that test material was not a dermal sensitizer.	265
Corylus Avellana (Hazel Seed) Oil				
1% Corylus Avellana (Hazel) Seed Oil in a moisturizing cream	25	Amended Draize patch test, 10% standard concentration	Non-irritating	266

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
1% Corylus Avellana (Hazel) Seed Oil in a moisturizing cream	32	60 day clinical study	"Fairly good acceptability"	267
5% Corylus Avellana (Hazel) Seed Oil in a massage oil	107	HRIPT with 0.2 ml test material, semi-occluded	1 subject had slight erythema following the 7th patch that did not reoccur, no other reactions observed. Not a dermal irritant or sensitizer.	260
		Crambe Abyssinica Seed Oil		
5% Crambe Abyssinica Seed Oil in a face and neck product	54	HRIPT; semi-occluded, undiluted	not a dermal irritant or sensitizer	268
100% Crambe Abyssinica Seed Oil in an unspecified product	107	HRIPT; undiluted	not a dermal irritant or sensitizer	213
		Elaeis Guineensis (Palm) Oil		
15.7% Sodium Palm Kernelate in a soap	42	28-day use test	good acceptability for use	269
61.6% Sodium Palmate in a soap	42	28-day use test	good acceptability for use	269
		Euterpe Oleracea Fruit Oil		
0.5% Euterpe Oleracea Fruit Oil in an eye treatment	104	HRIPT with 150 µl test material, semi-occluded	not a dermal irritant or sensitizer	270
		Glycine Soja (Soybean) Oil		
0.19% Glycine Soja (Soybean) Unsaponifiables in a face and neck product	50	HRIPT, occluded	not a dermal irritant or sensitizer	271
39% Hydrogenated Soybean Oil in a lipstick	108	HRIPT, occluded	not a dermal irritant or sensitizer	272
		Garcinia Indica Seed Butter		
0.3869% Garcinia Indica Seed Butter in a body and hand product	101	HRIPT, 0.2 g applied, occlusive	not a sensitizer; irritation was observed in one subject	273
		Gossypium Herbaceum (Cotton) Seed Oil		
3.6% Hydrogenated Cottonseed Oil in a lip balm	222	HRIPT with 0.2 g test material, occluded	2 subjects had low-level, transient (±) reactions during the induction, no other reactions were observed. Study concluded that test material was not a dermal sensitizer.	265
		Helianthus Annuus (Sunflower) Seed Oil		
6% Helianthus Annuus (Sunflower) Seed Oil in a skin cream	108	primary cutaneous irritation	no primary irritation	274
20% Helianthus Annuus (Sunflower) Seed Oil in a face serum	108	primary cutaneous irritation	no primary irritation	223
0.264% Helianthus Annuus (Sunflower) Seed Oil in a cream	57	HRIPT; Finn chambers, applied neat	not a dermal irritant or sensitizer	275
6% Helianthus Annuus (Sunflower) Seed Oil in a skin cream	106	HRIPT, occlusive	not a dermal irritant or sensitizer	274

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
20% Helianthus Annuus (Sunflower) Seed Oil in a face serum	108	HRIPT; occlusive; applied neat	not an irritant or a sensitizer	223
1% Helianthus Annuus (Sunflower) Seed Oil in a soap	42	28-day use test	good acceptability for use	269
39.8% Helianthus Annuus (Sunflower) Seed Oil in a massage oil	107	HRIPT with 0.2 ml test material, semi-occluded	1 subject had slight erythema following the 7th patch that did not reoccur, no other reactions observed. Not a dermal irritant or sensitizer.	260
Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables				
2% Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables in a night product	100	HRIPT, semi-occluded	not a dermal irritant or sensitizer	271
2% Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables in a face and neck product	100	HRIPT, semi-occluded	not a dermal irritant or sensitizer	271
Hippophae Rhamnoides Seed Oil				
5% Hippophae Rhamnoides Seed Oil	10	cutaneous local tolerance test, 0.02 ml single 48 h occlusive application	not an irritant; average irritation score of 0	276
Irvingia Gabonensis Kernel Butter				
0.31% Irvingia Gabonensis Kernel Butter in a face and neck product	52	HRIPT, occluded	not a dermal irritant or sensitizer	271
Limnanthes Alba (Meadowfoam) Seed Oil				
71.3% Limnanthes Alba (Meadowfoam) Seed Oil in a facial repair product	109	HRIPT, semi-occluded	7 subjects had ± on the first day of the induction only, no other reactions. Not a dermal irritant or sensitizer.	277
Linum Usitatissimum (Linseed) Seed Oil				
9.4% Linum Usitatissimum (Linseed) Seed Oil in mascara	105	HRIPT with 0.2 g test material, semi-occluded	not a dermal irritant or sensitizer	278
Luffa Cylindrica Seed Oil				
0.01% Luffa Cylindrica Seed Oil in a body wash	102	HRIPT; 0.2 ml of a 1% dilution using distilled water was applied to a 1" x 1" pad applied with a semi-occlusive patch	not a dermal irritant or sensitizer	279
Macadamia Ternifolia Seed Oil				
0.5% Macadamia Ternifolia Seed Oil in a cleansing oil rinse-off	214	HRIPT with 0.2 ml of a 10% v/v aqueous solution, semi-occluded	3 subjects had a "?" reaction following a patch during the induction and 1 subject had definite erythema with no edema or damage to the epidermis (+D) following the 7th patch. No reactions were observed at a new test site. No other reactions were observed. Study concluded test material was not a dermal sensitizer.	259
30% Macadamia Ternifolia Seed Oil in a body and hand product	55	HRIPT; semi-occluded, undiluted	not a dermal irritant or sensitizer	268

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
Mangifera Indica (Mango) Seed Oil				
2% Mangifera Indica (Mango) Seed Oil in a lipstick	100	HRIPT with 150 µl test material, semi-occluded	not a dermal irritant or sensitizer	280
3.87% Mangifera Indica (Mango) Seed Oil in an eyeliner	102	HRIPT with 0.2 g of test material, semi-occluded	not a dermal irritant or sensitizer	281
Mangifera Indica (Mango) Seed Butter				
1% Mangifera Indica (Mango) Seed Butter in a facial lotion	100	HRIPT with 200 µl test material, semi-occluded	not a dermal irritant or sensitizer	282
9% Mangifera Indica (Mango) Seed Butter in a body product	102	HRIPT with 0.2 g, semi-occluded	not a sensitizer	283
Moringa Oleifera Seed Oil				
0.01% Moringa Oleifera Seed Oil in a cleansing oil rinse-off	214	HRIPT with 0.2 ml of a 10% v/v aqueous solution, semi-occluded	3 subjects had a "?" reaction following a patch during the induction and 1 subject had definite erythema with no edema or damage to the epidermis (+D) following the 7th patch. No reactions were observed at a new test site. No other reactions were observed. Study concluded test material was not a dermal sensitizer.	259
Moringa Pterygosperma Seed Oil				
3% Moringa Pterygosperma Seed Oil in an eye treatment	104	HRIPT with 150 µl test material, semi-occluded	not a dermal irritant or sensitizer	284
Oenothera Biennis (Evening Primrose) Oil				
1.99% Oenothera Biennis (Evening Primrose) Oil in a foundation	600	HRIPT, occluded	not a dermal irritant or sensitizer	285
Olea Europaea (Olive) Fruit Oil				
0.7% Olea Europaea (Olive) Fruit Oil in a scalp conditioner	114	primary cutaneous irritation; formulation diluted to 1%	no primary irritation	239
0.1595% Olea Europaea (Olive) Fruit Oil in a scalp conditioner/hair wax	104	HRIPT; occlusive; applied neat	not a dermal irritant or sensitizer	220
0.7% Olea Europaea (Olive) Fruit Oil in a scalp conditioner	110	HRIPT; occlusive; formulation diluted to 1%	not a dermal irritant or sensitizer	239
1.6% Olea Europaea (Olive) Fruit Oil in a body lotion	110	HRIPT with 0.02 ml test material , occluded	1 subject had slight erythema following the 7th patch that did not reoccur, no other reactions observed. Not a dermal irritant or sensitizer.	286
10% Olea Europaea (Olive) Fruit Oil in a skin salve	209	HRIPT; occlusive applied neat	not a sensitizer	224
22% Olea Europaea (Olive) Fruit Oil in a body moisturizer	105	HRIPT, semi-occluded	not a dermal irritant or sensitizer	287
58.7% Olea Europaea (Olive) Fruit Oil in a conditioning hair oil	102	HRIPT with 0.2 ml, semi-occluded	not a dermal irritant or sensitizer	288

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
69.6% Olea Europaea (Olive) Fruit Oil in a foundation	209	HRIPT with 200 µl test material, occluded	not a dermal irritant or sensitizer	289
10% Olea Europaea (Olive) Oil in a skin salve	51	4-wk use test; applied to lips, hands/nails, elbows, knees, feet/heels	did not elicit significant dermal irritation or dryness; 2 subjects had level 1(mild, very slight erythema on the lips, and 5 had level 1 erythema on the elbows, lips, or knees; 15 subjects reported subjective irritation	225
Olea Europaea (Olive) Oil Unsaponfiables				
2.5% Olea Europaea (Olive) Oil Unsaponfiables in a bath body mist	107	HRIPT with 150 µl test material, semi-occluded	not a dermal irritant or sensitizer	290
Hydrogenated Olive Oil				
12% Hydrogenated Olive Oil in a lipstick	108	HRIPT, occluded	not a dermal irritant or sensitizer	272
Hydrogenated Olive Oil Unsaponifiables				
2% Hydrogenated Olive Oil Unsaponifiables in a face and neck product	50	HRIPT, occluded	not a dermal irritant or sensitizer	271
5% Hydrogenated Olive Oil Unsaponifiables in a skin cleansing product	57	HRIPT, semi-occluded, 10% dilution of product	not a dermal irritant or sensitizer	271
Sodium Olivate				
17.64% Sodium Olivate in a body bar soap	107	HRIPT, semi-occluded	not a dermal irritant or sensitizer	291
Orbignya Oleifera Seed Oil				
3.79% Orbignya Oleifera Seed Oil in a cream cleanser	104	HRIPT with 0.2 ml of a 10% dilution of formulation, semi-occluded	not a dermal irritant or sensitizer	292
Orbignya Speciosa Kernel Oil				
0.4125% Orbignya Speciosa Kernel Oil in a hair conditioner	104	modified HRIPT; semi-occlusive; 10% dilution in distilled water	not a dermal irritant or sensitizer	293
Persea Gratissima (Avocado) Oil				
0.2% Persea Gratissima (Avocado) Oil in a scalp conditioner	114	primary cutaneous irritation; formulation diluted to 1%	no primary irritation	239
0.2% Persea Gratissima (Avocado) Oil in a scalp conditioner	110	HRIPT; occlusive; formulation diluted to 1%	not a dermal irritant or sensitizer	239
10% Persea Gratissima (Avocado) Oil in a skin salve	51	4-wk use test; applied to lips, hands/nails, elbows, knees, feet/heels	did not elicit significant dermal irritation or dryness; 2 subjects had level 1(mild, very slight erythema on the lips, and 5 had level 1 erythema on the elbows, lips, or knees; 15 subjects reported subjective irritation	225

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
Plukenetia Volubilis Seed Oil				
0.51% Plukenetia Volubilis Seed Oil in a lipstick	108	HRIPT; occlusive; applied neat	not an irritant or a sensitizer	294
Prunus Amygdalus Dulcis (Sweet Almond) Oil				
7% Prunus Amygdalus Dulcis (Sweet Almond) Oil in an oil treatment	103	HRIPT with 200 µl test material, semi-occluded	Grade 1 (mild erythema) reactions in 4 subjects for 1 or 2 patches in the induction phase, grade 1 (mild erythema in different subjects at the 48 h challenge reading. Study concluded test material was not a dermal irritant or sensitizer.	255
10% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a face serum	108	primary cutaneous irritation	no primary irritation	223
10% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a face serum	108	HRIPT; occlusive; applied neat	not an irritant or a sensitizer	223
10% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a skin salve	209	HRIPT; occlusive applied neat	not a sensitizer	224
10% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a skin salve	51	4-wk use test; applied to lips, hands/nails, elbows, knees, feet/heels	did not elicit significant dermal irritation or dryness; 2 subjects had level 1(mild, very slight erythema on the lips, and 5 had level 1 erythema on the elbows, lips, or knees; 15 subjects reported subjective irritation	225
15% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a massage oil	107	HRIPT with 0.2 ml test material, semi-occluded	1 subject had slight erythema following the 7th patch that did not reoccur, no other reactions observed. Not a dermal irritant or sensitizer.	260
25% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a lip balm	222	HRIPT with 0.2 g test material, occluded	2 subjects had low-level, transient (±) reactions during the induction, no other reactions were observed. Study concluded that test material was not a dermal sensitizer.	265
~31% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a facial oil	108	modified HRIPT; semi-occlusive; applied neat	not a dermal irritant or sensitizer	295
45.25% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a facial oil	109	HRIPT; semi-occlusive; applied neat	not a dermal irritant or sensitizer	296
46% Prunus Amygdalus Dulcis (Sweet Almond) Oil in a cuticle softener	106	modified Draize assay with an induction phase (3x/wk for 10 applications) and a challenge phase, applied neat, occlusive	not a dermal irritant or sensitizer	297
Prunus Armeniaca (Apricot) Kernel Oil				
2% Prunus Armeniaca (Apricot) Kernel Oil in a face cream	51	HRIPT with 20 µl test material, occluded	not a dermal irritant or sensitizer	241
2% Prunus Armeniaca (Apricot) Kernel Oil in an eye cream	108	HRIPT with 20 µl test material, occluded	not a dermal irritant or sensitizer	242
2.5% Prunus Armeniaca (Apricot) Kernel Oil in a cream	119	primary cutaneous irritation	no primary irritation	240

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
19.749% Prunus Armeniaca (Apricot) Kernel Oil in a face serum	108	primary cutaneous irritation	no primary irritation	223
0.005% Prunus Armeniaca (Apricot) Kernel Oil in a scalp conditioner/hair wax	104	HRIPT; occlusive; applied neat	not a dermal irritant or sensitizer	220
1% Prunus Armeniaca (Apricot) Kernel Oil in a cream	57	HRIPT; Finn chambers, applied neat	not a dermal irritant or sensitizer	275
2.5% Prunus Armeniaca (Apricot) Kernel Oil in a cream	118 (irritation)/ 116 (sensitization)	HRIPT; occlusive	not a dermal irritant or a sensitizer	240
19.749% Prunus Armeniaca (Apricot) Kernel Oil in a face serum	108	HRIPT; occlusive; applied neat	not an irritant or a sensitizer	223
Prunus Domestica Seed Oil				
0.04% Prunus Domestica Seed Oil in a preshave lotion	105	HRIPT with 0.2 ml, occluded	not a sensitizer	298
Prunus Persica (Peach) Kernel Oil				
24% Prunus Persica (Peach) Kernel Oil in a lip balm	222	HRIPT with 0.2 g test material, occluded	2 subjects had low-level, transient (+) reactions during the induction, no other reactions were observed. Study concluded that test material was not a dermal sensitizer.	265
Ribes Nigrum (Black Currant) Seed Oil				
0.1% Ribes Nigrum (Black Currant) Oil in a scalp conditioner	114	primary cutaneous irritation; diluted to 1%	no primary irritation	239
0.25% Ribes Nigrum (Black Currant) Oil in a cream	119	primary cutaneous irritation	no primary irritation	240
0.1% Ribes Nigrum (Black Currant) Oil in a scalp conditioner	110	HRIPT; occlusive; diluted to 1%	not a dermal irritant or sensitizer	239
0.2% Ribes Nigrum (Black Currant) Seed Oil is an eye mask	228	HRIPT, occluded	4 subjects had "?" or "+" reaction during induction that were not considered clinically relevant, no other reactions observed. Not sensitizing	299
0.2% Ribes Nigrum (Black Currant) Oil in a skin cream	106	HRIPT, occlusive	not a dermal irritant or sensitizer	274
0.25% Ribes Nigrum (Black Currant) Oil in a cream	118 (irritation)/ 116 (sensitization)	HRIPT; occlusive	not a dermal irritant or a sensitizer	240
0.2% Ribes Nigrum (Black Currant) Seed Oil is an eye mask	195	4-week safety in-use study	No adverse reactions reported. Product considered suitable for sensitive skin.	300
Rosa Canina Fruit Oil				
0.39% Rosa Canina Fruit Oil in a skin cream	108	primary cutaneous irritation	no primary irritation	274
0.39% Rosa Canina Fruit Oil in a skin cream	106	HRIPT, occlusive	not a dermal irritant or sensitizer	274
Rubus Chamaemorus Seed Oil				
2.5% Rubus Chamaemorus Seed Oil in product	10	Single occlusive patch test for 48 h with 25 µl	not an irritant	301

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
Rubus Idaeus (Raspberry) Seed Oil				
5% Rubus Idaeus (Raspberry) Seed Oil in a face and neck product	102	HRIPT, occluded	not a dermal irritant or sensitizer	271
Sesamum Indicum (Sesame) Seed Oil				
25% Sesamum Indicum (Sesame) Seed Oil in a face serum	108	primary cutaneous irritation	no primary irritation	223
8% Sesamum Indicum (Sesame) Seed Oil in a skin salve	209	HRIPT; occlusive applied neat	not a sensitizer	224
25% Sesamum Indicum (Sesame) Seed Oil in a face serum	108	HRIPT; occlusive; applied neat	not an irritant or a sensitizer	223
8% Sesamum Indicum (Sesame) Seed Oil in a skin salve	51	4-wk use test; applied to lips, hands/nails, elbows, knees, feet/heels	did not elicit significant dermal irritation or dryness; 2 subjects had level 1(mild, very slight erythema on the lips, and 5 had level 1 erythema on the elbows, lips, or knees; 15 subjects reported subjective irritation	225
Solanum Lycopersicum (Tomato) Seed Oil				
0.0023% Solanum Lycopersicum (Tomato) Seed Oil in a cream cleanser	104	HRIPT with 0.2 ml of a 10% dilution of the formulation, semi-occluded	not a dermal irritant or sensitizer	302
Theobroma Cacao (Cocoa) Seed Butter				
50.1% Theobroma Cacao (Cocoa) Seed Butter in a lip balm	106	HRIPT with 150 µl test material, semi-occluded	not a dermal irritant or sensitizer	303
Theobroma Grandiflorum Seed Butter[304]				
5% Theobroma Grandiflorum Seed Butter in a lip balm	106	HRIPT with 150 µl test material, semi-occluded	not a dermal irritant or sensitizer	305
Triticum Vulgare (Wheat) Germ Oil				
0.005% Triticum Vulgare (Wheat) Germ Oil in a scalp conditioner/hair wax	104	HRIPT; occlusive; applied neat	not a dermal irritant or sensitizer	220
Vaccinium Macrocarpon (Cranberry) Seed Oil				
0.04% Vaccinium Macrocarpon (Cranberry) Seed Oil in a face and neck product	53	HRIPT, occluded	not a dermal irritant or sensitizer	271
Vaccinium Myrtillus Seed Oil				
~1% Vaccinium Myrtillus Seed Oil in a facial oil	116	modified HRIPT; semi-occlusive; volatilized	not a dermal irritant or sensitizer	304
Vaccinium Vitis-Idaea Seed Oil				
5% Vaccinium Vitis-Idaea Seed Oil in product	10	Single occlusive patch test of 48 h with 0.02 ml	not an irritant	306
Vegetable Oil				
4% Vegetable Oil in a foundation	115	HRIPT, semi-occluded	1 subject had ± on the first day of the induction only, no other reactions. Not a dermal irritant or sensitizer.	307
4% Vegetable Oil in a lipstick	106	HRIPT with 0.2 g, occluded	not a dermal irritant or sensitizer	308
11% Vegetable Oil in an eye shadow	106	HRIPT, semi-occluded	not a dermal irritant or sensitizer	309

Table 8a. Dermal effects – Human studies

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
		Vitis Vinifera (Grape) Seed Oil		
39% Vitis Vinifera (Grape)Seed Oil in a preshave lotion	105	HRIPT with 0.2 ml, occluded	not a sensitizer	298
90% Vitis Vinifera (Grape) Seed Oil in a fragranced oil	105	HRIPT; semi-occluded; applied neat	not a dermal irritant or sensitizer	310
0.5% Hydrogenated Grapeseed Oil in a lip product	53	HRIPT; semi-occluded	not a dermal irritant or sensitizer	311
		Zea Mays (Corn) Germ Oil		
20% Zea Mays (Corn) Germ Oil in a cleansing oil rinse-off	214	HRIPT with 0.2 ml of a 10% v/v aqueous solution, semi-occluded	3 subjects had a "?" reaction following a patch during the induction and 1 subject had definite erythema with no edema or damage to the epidermis (+D) following the 7th patch. No reactions were observed at a new test site. No other reactions were observed. Study concluded test material was not a dermal sensitizer.	259
		COMEDOGENICITY		
		Ribes Nigrum (Black Currant) Seed Oil		
0.2% Ribes Nigrum (Black Currant) Seed Oil in an eye mask formulation	6	applied undiluted; occlusive	avg. score of 0.00 comedones/cm^2; non-comedogenic	312

[a] Same 109 panelists tested these 4 formulations hat differed only in color and fragrance.

Table 8b. Dermal effects – Human studies – summarized from previous CIR reports

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
Carthamus Tinctorius (Safflower) Oil				
Cosmetic formulations containing 3-5% Carthamus Tinctorius (Safflower) Seed Oil were not irritating to humans in occlusive patch tests and were not primary irritants or sensitizers in repeated insult patch tests.				32
Cocos Nucifera (Coconut) Fruit Oil				
An RIPT was performed using 103 subjects with a tanning butter containing 2.5% Cocos Nucifera (Coconut) Oil no erythematous reactions were seen at challenge; A bar soap containing 13% Cocos Nucifera (Coconut) Oil produced very mild irritation when tested as a 1% aq. solution on 106 subjects, and it was minimally to mildly irritating in a soap chamber test with a 8% aq. solution; the soap produced no unusual irritation response in a 2-wk normal use test; undiluted Cocos Nucifera (Coconut) Oil was not an allergen in 12 subjects.				43
Hydrogenated Coconut Oil				
Four lipstick formulations containing 10% hydrogenated coconut oil were tested with a single 48-h application on 204 females; there was no evidence of primary irritation and no indication of sensitization on retests performed 14 d later.				43
Potassium Cocoate				
In a test using 40 healthy subjects and 480 patients with active skin disease, 5% aq. potassium cocoate produced 5 positive responses.				43
Corylus Avellana (Hazel Seed) Oil				
A patch testing reference book by de Groot noted that the published literature does not contain recommended test concentrations concerning Hazel Seed Oil. To serve as a guide to the reader, de Groot reported that an unpublished (and at the time, ongoing) study found no irritant reaction in 1 to 20 patients suffering from or suspected to suffer from cosmetic product contact allergy who had been patch tested with 30% Hazel Seed Oil in petrolatum.				41
Elaeis Guineensis (Palm) Oil				
Elaeis Guineensis (Palm) Oil, 15% in petrolatum or cosmetic formulations containing 1.0-2.0%, was not an irritant or sensitizer in clinical studies. Bar soap flakes, tested at dilutions that contained ≤ 2.13% palm kernel oil, were not irritating or sensitizing.				26
Gossypium Herbaceum (Cotton) Seed Oil				
Patients that were hypersensitive to cottonseed proteins were not sensitive to cottonseed oil in a skin prick test				27
Hydrogenated Cottonseed Oil				
In a clinical patch test, the irritation potential of a cosmetic formulation containing 3.4% hydrogenated cottonseed oil was mildly low, and the severity of reaction to 10.4% hydrogenated cottonseed oil was acceptably low in a use study. Cosmetic formulations containing 10.6-20.86% hydrogenated cottonseed oil were not irritating or sensitizing.				27
Oryza Sativa (Rice) Bran Oil				
Rice is generally regarded as hypoallergenic, although some case studies of allergic reactions to raw rice have been reported. In clinical testing, formulations containing 1.04-8.0% Oryza Sativa (Rice) Bran Oil were not irritating or sensitizing. . Hydrolyzed rice protein was not irritating to human subjects.				28
Persea Gratissima (Avocado) Oil				
Persea Gratissima (Avocado) Oil was not an irritant or sensitizer when human subjects were patch tested with cosmetic formulations containing up to 10.7% Persea Gratissima (Avocado) Oil or in patch tests using 100% Persea Gratissima (Avocado) Oil.				31
Prunus Amygdalus Dulcis (Sweet Almond) Oil				
Undiluted Prunus Amygdalus Dulcis (Sweet Almond) Oil was non-irritating in a single insult patch test with 101 subjects, and it was non-irritating and non-sensitizing in an HRIPT using 52 subjects. Cosmetic formulations containing 0.1-25% were practically non-irritating and non-sensitizing in HRIPTs performed with 6906 subjects. In the Lanman-Maibach 21-day Cumulative Irritancy Assay, a moisturizer containing 25% Prunus Amygdalus Dulcis (Sweet Almond) Oil had a total irritancy score of 14/630.				217

Table 8b. Dermal effects – Human studies – summarized from previous CIR reports

Ingredient and Concentration	Subjects Completed	Method	Results	Reference
Sesamum Indicum (Sesame) Seed Oil				
In clinical testing, undiluted Sesamum Indicum (Sesame) Seed Oil was not irritating. Cosmetic formulations containing 8-14.3% Sesamum Indicum (Sesame) Seed Oil were non- to essentially non-irritating. Prophetic patch testing with formulations containing 10-11% Sesamum Indicum (Sesame) Seed Oil were not irritating with or without UV light. Patients with contact allergy to Sesamum Indicum (Sesame) Seed Oil were patch tested, and most had positive reactions to sesamol, sesamin, and sesamolin.				55
Triticum Vulgare (Wheat) Germ Oil				
In clinical testing, Triticum Vulgare (Wheat) Germ Oil was not an irritant or a sensitizer.				30
PHOTOTOXICITY/PHOTOSENSITIZATION				
Cocos Nucifera (Coconut) Oil				
Bar soaps made with 13% Cocos Nucifera (Coconut) Oil, tested as a 3% aqueous solution, tested using 10 subjects, and a similar soap, prepared as 1 or 3% aqueous solutions, tested on 52 panelists, did not produce any evidence of photosensitization.				33
Sodium Cocoate				
Bar soaps 13% sodium cocoate, prepared as a 3% aqueous solution, tested using 10 subjects did not produce any evidence of photosensitization.				33
Prunus Amygdalus Dulcis (Sweet Almond) Oil				
Formulations containing 0.1% - 2.0% Prunus Amygdalus Dulcis (Sweet Almond) Oil, tested for photosensitization in a total of 764 subjects, did not manifest photosensitivity in any of the test subjects.				217
Oryza Sativa (Rice) Bran Oil				
Formulations containing 1.04% Oryza Sativa (Rice) Bran Oil were not photosensitizing.				*28*

Table 9a. Ocular irritation – Non-Human and Human

Ingredient	Concentration	Test Group	Procedure	Results	Reference
NON-HUMAN					
Adansonia Digitata Seed Oil					
baobab oil	100%		MatTek EpiOcular MTT viability assay; 100 µl of test material for 16-256 min	non-irritating	210
Aleurites Moluccana Seed Oil					
Aleurites Moluccana oil			Draize test	not an ocular irritant	313
Aleurites Moluccana oil			in vitro conjunctival cell assay	not cytotoxic	313
Aleurites Moluccana oil			ocular burn treatment efficacy test	no adverse effects	314
Butyrospermum Parkii (Shea) Butter					
Butyrospermum Parkii (Shea) Butter	undiluted	3 male Kleinrussen Chbb:HM rabbits	0.1 ml instilled into the conjunctival sac of one eye for 24 h	not irritating; mild conjunctival reactions	315
Crambe Abyssinica Seed Oil					
Crambe Abyssinica Seed Oil	undiluted		details not provided	an ocular irritant, but not corrosive	213
Fragaria Ananassa (Strawberry) Seed Oil					
Fragaria Ananassa (Strawberry) Seed Oil	5-50% in a lipophilic solvent		neutral red release test	IC_{50} >50%; negligible cytotoxicity	316
Hippophae Rhamnoides Seed Oil					
Hippophae Rhamnoides Seed Oil	5-50% in a lipophilic solvent		neutral red release test	IC_{50} >50%; negligible cytotoxicity	317
Linum Usitatissimum (Linseed) Seed Oil					
mascara containing 9.4% Linum Usitatissimum (Linseed) Oil	diluted at 0-50% in mineral oil		neutral red release test	NR_{50}>50%; slightly cytotoxic	318
mascara containing 9.4% Linum Usitatissimum (Linseed) Oil	67.1% solution in mineral oil		hen's egg test-chorioallantoic membrane assay (HET-CAM)	moderately irritating	318
mascara containing 9.4% Linum Usitatissimum (Linseed) Oil	66.9% solution in mineral oil		reconstituted epithelial culture assay	slightly cytotoxic	318
Olea Europaea (Olive) Fruit Oil					
Olea Europaea (Olive) Fruit Oil, "high purity"	undiluted	rabbits; number not specified	Draize test	not irritating	313
Olea Europaea (Olive) Fruit Oil, "high purity"			in vitro study using human conjunc-tival epithelial cells	did not induce cellular necrosis or apoptosis	313
Ribes Nigrum (Black Currant) Seed Oil					
eye mask containing 0.2% Black Ribes (Black Currant) Seed Oil	50% dilution		HET-CAM assay	practically no irritation	319
Rubus Chamaemorus Seed Oil					
product containing 2.5% Rubus Chamaemorus Seed Oil			neutral red release assay	negligible cytotoxicity; product was considered well tolerated	320
Vaccinium Vitis-Idaea Seed Oil					
Vaccinium Vitis-Idaea Seed Oil	5-50% in a lipophilic solvent		neutral red release test	IC_{50}> 50%; negligible cytotoxicity	321

Table 9a. Ocular irritation – Non-Human and Human

Ingredient	Concentration	Test Group	Procedure	Results	Reference
			Zea Mays (Corn) Oil		
Zea Mays (Corn) Oil, "high purity"	undiluted	rabbits, number not specified	Draize test	not irritating	313
Zea Mays (Corn) Oil, "high purity"			in vitro study using human conjunctival epithelial cells	did not induce necrosis or apoptosis	313
			HUMAN STUDIES		
			Linum Usitatissimum (Linseed) Seed Oil		
9.4% Linum Usitatissimum (Linseed) Seed Oil in a mascara		33 female subjects	4 wk study; 16 wore contact lenses, 17 had "sensitive" eyes	no subjective irritation and no adverse reports; clinically safe for use by contact lens-wearers	322
			Ribes Nigrum (Black Currant) Seed Oil		
0.2% Ribes Nigrum (Black Currant) Seed Oil in an eye mask	undiluted	52 subjects	4-wk in-use study	no adverse reactions; safe for contact-lens wearers	323

Table 9b. Ocular irritation – Non-Human - summarized from previous CIR reports

Ingredient	Concentration	Test Group	Procedure	Results	Reference
Cocos Nucifera (Coconut) Oil					
Undiluted Cocos Nucifera (Coconut) Oil, instilled into rabbit eyes without rinsing, produced minimal eye irritation.					33
Hydrogenated Coconut Oil					
Undiluted hydrogenated coconut oil produced mild irritation in one study, minimal irritation in another, negligible or minimal irritation in eight additional tests. Two lipstick formulations containing 10% hydrogenated coconut oil both produced slight conjunctivitis.					33
Coconut Acid					
Undiluted coconut acid produced mild irritation in rabbit eyes in two studies and minimal irritation in a third.					33
Elaeis Guineensis (Palm) Oil					
Undiluted Elaeis Guineensis (Palm) Oil and cosmetic lotions and creams containing 1.5-2.0% Elaeis Guineensis (Palm) Oil were minimally irritating to the eyes of rabbits, while one lotion containing 1.5% Elaeis Guineensis (Palm) Oil was moderately irritating.					26
Hydrogenated Palm Oil					
Hydrogenated palm oil suppositories were mildly irritating to rabbit eyes.					26
Hydrogenated Cottonseed Oil					
Cosmetic formulations containing 3.4-12.3% hydrogenated cottonseed oil were mildly irritating to the eyes of rabbits.					27
Oryza Sativa (Rice) Bran Oil					
A mixture of Oryza Sativa (Rice) Bran Oil and Oryza Sativa (Rice) Germ Oil, concentrations not stated, were not irritating to rabbit eyes. Undiluted Oryza Sativa (Rice) Bran Oil was considered minimally irritating.					28
Oryza Sativa (Rice) Germ Oil					
Oryza Sativa (Rice) Germ Oil, concentration not stated, was not a primary irritant.					28
Prunus Amygdalus Dulcis (Sweet Almond) Oil					
The ocular irritation potential of undiluted Prunus Amygdalus Dulcis (Sweet Almond) Oil and cosmetic formulations containing up to 25% Prunus Amygdalus Dulcis (Sweet Almond) Oil were evaluated using rabbits. Undiluted Prunus Amygdalus Dulcis (Sweet Almond) Oil was practically nonirritating or minimally irritating, and formulations containing up to 25% Prunus Amygdalus Dulcis (Sweet Almond) Oil were nonirritating to minimally irritating. In most instances, reactions that occurred were limited to conjunctival irritation, which cleared by the third day of observation.					217
Sesame Indicum (Sesame) Seed Oil					
Undiluted Sesamum Indicum (Sesame) Seed Oil was non- to minimally irritating to rabbit eyes, and a lipstick containing 10-11% Sesamum Indicum (Sesame) Seed Oil was not an ocular irritant.					55
Triticum Vulgare (Wheat) Germ Oil					
Undiluted Triticum Vulgare (Wheat) Germ Oil was, at most, a minimal ocular irritant, and 2% in a water emulsion was not irritating.					30

Table 10. **Clinical Trials/Case Studies**

Ingredient	Patients/Condition	Effect/Observation	Reference
Aleurites Moluccana Seed Oil			
Aleurites Moluccana oil	15; mild, stable plaque psoriasis	efficacy study "just enough (oil) to moisten the plaque" was applied 3 x daily for 12 wks; no side effects or adverse events were reported.	324
Anacardium Occidentale (Cashew) Seed Oil			
Anacardium Occidentale (Cashew) Seed Oil	37-year-old male resin researcher	presentation of bullae on his right leg after dropping pure oil from a bottle on his right thigh; skin was thoroughly washed immediately; erythema developed 10 days after exposure Patch testing was performed with cashew nut oil 3% alcohol, cashew nut oil 0.3% alcohol, cashew nut oil 0.03% alcohol, and urushiol 0.01% petrolatum.; a "+" reaction was reported on day 2 and "++" reactions on days 3 and 4 to the 3% dilution,; a "+" reactions to the 0.3% dilution and urushiol was reported on days 2-4; a "?+" reaction was observed on days 2 and 3 and a "+" reaction was observed on day 4 to the 0.03% dilution	325
Cocos Nucifera (Coconut) Oil			
Cocos Nucifera (Coconut) Oil		*did not produce adverse effects in several therapeutic studies*	33
Glycine Soja (Soybean) Oil			
Glycine Soja (Soybean) Oil	7; history of immediate hypersensitivity reaction after the ingestion of soybeans	a double-blind crossover study; the patients were first skin tested by the puncture method with a crude whole soybean extract, a partially hydrogenated oil, a non-hydrogenated oil, and a cold-pressed soybean oil; olive oil from a retailer was used as a negative control. Since all 7 patients had negative skin tests to the oils and positive reactions to the crude soybean extract, they were challenged orally with capsules of each of the oils in random order on 4 separate days. None of the patients reacted to the oral challenges; the researchers remarked that while a reaction to the cold-pressed soybean oil did not occur in this study, cold-pressed oils may contain soybean protein and should be avoided	63
soy oil proteins	4; known allergy to soybean	Sera was used to examine the allergenicity; neither the IgE nor the IgG_4 in the sera reacted to protein in the soy oil	23
Helianthus Annuus (Sunflower) Oil			
refined and cold-pressed sunflower oils	patients had anaphylactic reactions following ingestion of sunflower seeds	no reactions were seen upon oral or open challenge with refined or cold-pressed sunflower oils, both of which were shown to contain detectable amounts of protein.	18
	1 woman; desensitized to mugwort (of the Compositae family) pollen for a yr, then had an anaphylactic reaction to sunflower (also of the Compositae family) seeds	a delayed positive reaction to sunflower oil in a skin prick test was discovered; prick test results with 10 control subjects were negative. In an oral challenge test, a delayed reaction was again observed, with symptoms occurring 2.25-8 h after administration.	326
Macadamia Seed Oil			
Macadamia Seed Oil in a lipstick (species description or concentration were not reported)	28-year-old woman; chelitis	Chelitis case reported after lipstick use; patient was patch tested with ingredients contained in the lipstick, Positive reactions to diisostearyl malate and Macadamia Seed Oil were reported; the condition . improved after discontinuing use of lipsticks containing these 2 ingredients	327
Olea Europaea (Olive) Fruit Oil			
Olea Europaea (Olive) Fruit Oil		Throughout the literature, it is stated that sensitization to Olea Europaea (Olive) Fruit Oil is considered rare. Case reports have been described, however, and generally involved patients with venous eczema, some type of dermatitis or lesion, or an occupational exposure. Patch testing with Olea Europaea (Olive) Fruit Oil produced positive reactions in most of these cases, and these results were usually regarded as allergenic. The concentrations of Olea Europaea (Olive) Fruit Oil tested were not always given, but when stated, test concentrations giving positive results, ranged from 30-100%. When the constituents of olive oil were tested as well, the results of that testing were negative.	328-335
Olea Europaea (Olive) Fruit Oil		Whether the reactions to olive oil were contact sensitization or irritation were investigated using open and occlusive testing. It was concluded that olive oil presented as a weak irritant rather than a contact sensitizer in the few case studies observed.	336

Table 10. **Clinical Trials/Case Studies**

Ingredient	Patients/Condition	Effect/Observation	Reference
Persea Gratissima (Avocado) Oil			
Persea Gratissima (Avocado) Oil	1 female; dermatitis around the eyes and earlobes	Patch testing with her sunscreen resulted in positive results. In subsequent patch testing of the individual ingredients, a positive reaction to undiluted oil, but not to the active ingredient, was observed; 20 controls subjects were used, and reactions to Persea Gratissima (Avocado) Oil were not seen	337
Sesamum Indicum (Sesame) Seed Oil			
Sesamum Indicum (Sesame) Seed Oil in an ointment	female	Pruritic erythema, papules, and vesicles appeared after application of the ointment; patch testing was performed with the ointment and with the individual ingredients, including undiluted Sesamum Indicum (Sesame) Seed Oil Both the ointment and Sesamum Indicum (Sesame) Seed Oil produced positive reactions on days 2, 3, 4, and 1; the other components did not cause a reaction Results were negative in patch testing of Sesamum Indicum (Sesame) Seed Oil using 20 healthy subjects.	338

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Final Report of the Cosmetic Ingredient Review Expert Panel

Amended Safety Assessment of Triethylene Glycol and Polyethylene Glycols (PEGs)-4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEGs ≥ 4 as used in Cosmetics

June 29, 2010

The 2010 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D.

Cosmetic Ingredient Review

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ABSTRACT

The safety of Polyethylene Glycols (PEGs) as used in cosmetics was reviewed. In general, PEGs are not oral toxicants, exhibit little ocular irritation, and have minimal dermal irritation and sensitization. PEGs are not genotoxic or carcinogenic. PEGs are not reproductive or developmental toxicants. Use of antimicrobial creams with a PEG vehicle was associated with renal toxicity when applied to burned skin, but studies of extensively tape stripped skin demonstrated that the levels of PEGs that could penetrate in a worst case analysis are >100 times less than the renal toxicity no observable effect level, providing a margin of safety. Triethylene Glycol and PEGs ≥ 4 are considered safe for use in cosmetics in the present practices of use and concentration.

INTRODUCTION

Polyethylene Glycols (PEGs) are condensation polymers of ethylene oxide used for a wide range of purposes in cosmetics depending on molecular weight (see Table 1). The Cosmetic Ingredient Review (CIR) Expert Panel previously evaluated (Andersen 1993) the safety of Polyethylene Glycol (PEGs) -6, -8, -32, -75, -150, -14M and -20M, concluding that these ingredients are safe for use in cosmetics at the use concentrations and in the product categories included in the report, except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin. The CIR Expert Panel also reviewed the safety of Triethylene Glycol and PEG-4, concluded that these two ingredients are safe as cosmetic ingredients in the practices of use and concentration described in the safety assessment. Additional data have been evaluated that address the "damaged skin" caveat.

In addition, other PEGs now listed as cosmetic ingredients have been added to the group. Ingredients in this safety assessment include: Triethylene Glycol and Polyethylene Glycols (PEGs) -4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEG ≥ 4 that may be used as a cosmetic ingredient in the future.

There is a mixture of terminology for PEGs because Triethylene Glycol is a specific chain length polymer (three ethylene oxide units only, no PEG-2, PEG-4, etc.), whereas, for example, PEG-4 is a mixture where the average chain length of polymers is four, but which can contain polymers ranging from two to eight repeated units.

PEG derivatives previously have been reviewed by the CIR Expert panel, with following conclusions:

- *PEG-30, -33, -35, -and -40 Castor Oils are safe for use in cosmetics at concentrations up to 50% and PEG-30 and -40 Hydrogenated Castor Oil are safe for use at concentrations up to 100% as cosmetic ingredients in the present practices of concentration and use (Andersen 1999a).*
- *The available data are insufficient to support the safety of PEG-2, -3, -5, -10, -15, and -20 Cocamine for use in cosmetic products (Andersen 1999b), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*
- *PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate and PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate are safe for use in cosmetics at concentrations up to 25% (Andersen 2000a), except that the Expert Panel expressed concern regarding sensitization and toxicity when applied to damaged skin.*
- *PEG-2, -3, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150 and -175 Distearate are safe for use in cosmetic formulations under the present practices of use (Andersen 1999c), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*
- *PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate are safe as used in rinse-off products and safe up to 10% in leave-on products (Andersen 1999d), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*
- *PEG-20, -27, -30, -40, -50, -60, -75, and -85 Lanolin are safe as presently used in cosmetic products (Elder 1982).*
- *PEG-5, -10, -24, -25, -35, -55, -100, and -150 Lanolin; PEG-5, -10, -20, -24, -30, and -70 Hydrogenated Lanolin; PEG-75 Lanolin Oil; and PEG-75 Lanolin Wax (Andersen 1999e) are safe for use in cosmetic products under the present practices of use , except that the Expert Panel expressed concern regarding sensitization and toxicity when applied to damaged skin.*
- *PEG-10 Propylene Glcol; PEG-8 Propylene Glycol Cocoate; PEG-55 PropyleneGlycol Oleate; and PEG-25, -75, and -120 Propylene Glycol Stearate are safe as used in cosmetic products (Andersen 2001a), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*
- *PEG-20 Sorbitan Cocoate, PEG-40 Sorbitan Diisostearate, PEG-2, -5, -20 Sorbitan Isostearate, PEG-40 and -75 Sorbitan Lanolate, PEG-10, -40, -44, -75, and -80 Sorbitan Laurate, PEG-3 and -6 Sorbitan Oleate, PEG-80 Sorbitan Palmitate, PEG-40 Sorbitan Perisostearate, PEG-40 Sorbitan Peroleate, PEG-3, -6, -40, and -60 Sorbitan Stearate, PEG-20, -30, -40, and -60 Sorbitan Tetraoleate, PEG-60 Sorbitan Tetrastearate, PEG-20 and -160 Sorbitan Triisostearate, PEG-18 Sorbitan Trioleate, PEG-40 and -50 Sorbitan Hexaoleate, PEG-30 Sorbitol Tetraoleate Laurate, and PEG-60 Sorbitol Tetrastearate are safe for use under the present practices of use (Andersen 2000b), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*

- *PEG-5, -10, -16, -25, -30, and -40 Soy Sterol are safe as used in cosmetic products (Andersen 2004), except that the cosmetic industry is advised to avoid using PEGs Soy Sterol in cosmetic formulations that may be used on damaged skin.*
- *PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates are safe as cosmetic ingredients in the present practices of concentration and use (Elder 1983).*
- *Sorbeth-6, -8, and -20 Beeswax (formerly PEG-6, -8, and -20 Sorbitan Beeswax) are safe for use as cosmetic ingredients under the present practices of use (Andersen 2001b), but the Expert Panel recommends that cosmetic formulations containing the PEG-6, PEG-20, and PEG-75 not be used on damaged skin.*

The "damaged skin" caveat from the original safety assessment of PEGs was carried over to the safety assessments of PEG esters in which it appeared in either the discussion or the conclusion, including:

- PEG-2, -3, -5, -10, -15, and -20 Cocamine;
- PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate and PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate;
- PEG-2, -3, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150 and -175 Distearate;
- PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate;
- PEG-5, -10, -24, -25, -35, -55, -100, and -150 Lanolin; PEG-5, -10, -20, -24, -30, and -70 Hydrogenated Lanolin; PEG-75 Lanolin Oil; and PEG-75 Lanolin Wax;
- PEG-10 Propylene Glycol; PEG-8 Propylene Glycol Cocoate; PEG-55 PropyleneGlycol Oleate; and PEG-25, -75, and -120 Propylene Glycol Stearate;
- PEG-20 Sorbitan Cocoate, PEG-40 Sorbitan Diisostearate, PEG-2, -5, -20 Sorbitan Isostearate, PEG-40 and -75 Sorbitan Lanolate, PEG-10, -40, -44, -75, and -80 Sorbitan Laurate, PEG-3 and -6 Sorbitan Oleate, PEG-80 Sorbitan Palmitate, PEG-40 Sorbitan Perisostearate, PEG-40 Sorbitan Peroleate, PEG-3, -6, -40, and -60 Sorbitan Stearate, PEG-20, -30, -40, and -60 Sorbitan Tetraoleate, PEG-60 Sorbitan Tetrastearate, PEG-20 and -160 Sorbitan Triisostearate, PEG-18 Sorbitan Trioleate, PEG-40 and -50 Sorbitan Hexaoleate, PEG-30 Sorbitol Tetraoleate Laurate, and PEG-60 Sorbitol Tetrastearate;
- PEG-5, -10, -16, -25, -30, and -40 Soy Sterol; and
- PEG-6, -8, and -20 Sorbitan Beeswax

Based on the amended conclusion for this safety assessment, conforming changes in each of these safety assessments will be made to remove the "damaged skin" caveat.

CHEMISTRY

DEFINITION AND STRUCTURE

Table 1 summarizes the CAS numbers, definitions, functions and synonyms for PEGs included in this safety assessment.

As two different naming conventions are commonly used for these ingredients, the potential exists for some confusion. The official name for each ingredient is that given in the International Cosmetic Ingredient Dictionary and Handbook, the INCI name (e.g. PEG-4), but it is also common to use the molecular weight name (e.g. PEG 200) for the same ingredient. Table 2 gives the official INCI name, the molecular weight name, and the corresponding molecular weight. All INCI names include dashes and the numbers represent the average number of moles of ethylene oxide. When the PEG name does not include a dash, the number is the average molecular weight.

PHYSICAL AND CHEMICAL PROPERTIES

PEGs with a molecular weight below 700 are clear to slightly hazy, colorless liquids that are slightly hygroscopic. PEGs between 700 and 900 are semisolids, and PEGs over 1000 are white waxy solids, flakes, or free-flowing powders (FAO 1983). The properties of several individual PEGs are listed in Tables 3 and 4. "Carbowax" 1500 is a solid blend of equal weights of PEG-6 and PEG-32 (Smyth et al. 1950).

Tensile data show a maximum in extensibility at a polyethylene glycol (PEG) molecular weight of 1450, while ultimate strength increases with increasing segment length (Silver et al. 1994). When the PEGs are hydrated, there is a significant drop in the modulus, ultimate stress and ultimate elongation. Dynamic contact angle measurements show that surface hydrophobicity decreases as the soft segment molecular weight increases. Using electron spectroscopy for chemical analysis (ESCA) to determine the surface composition, it was found that the hard segment content at the surface increases as the polyol block length decreases.

With increasing molecular weight, PEGs can have some degree of branching (Webster et al. 2007).

METHODS OF MANUFACTURE

PEGs are the condensation products of ethylene oxide and water, with the chain length controlled by number of moles of ethylene oxide that are polymerized (Hunting 1983). Triethylene Glycol is prepared from ethylene oxide and ethylene. It is manufactured by forming a ether-ester of $HOCH_2COOH$ with glycol and then hydrogenating (Budavari 1989).

ANALYTICAL METHODS

Solid PEGs can be quantitatively determined in biological materials using gravimetric and calorimetric methods based upon the reaction of the PEGs with silicotungstic acid and phosphomolybdic acid (Shaffer and Critchfield 1947a).

According to Robinson et al. (2006), the combination of high-field asymmetric waveform ion mobility spectrometry (FAIMS) with Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) can be used in the analysis of PEG samples of low molecular weight. The high ion transmission obtained using FAIMS combined with the high sensitivity of FTICR-MS detection make possible separation of multiple gas-phase conformers of PEG molecular cations that have low abundance (less than 0.2% relative abundance) and that have not been detected previously.

PEG-4

Triethylene Glycol and PEG-4 may be analyzed using gas chromatography-mass spectrometry (Kawai et al. 1978) and gas-liquid chromatography (Sigma-Adldrich 2001a, b). Triethylene Glycol has been measured in rat and rabbit urine using vapor phase chromatography and colorimetry (McKennis et al. 1962). PEG-4 has been identified from a mixture of low molecular weight PEGs using thin-layer and gel permutation chromatography (Sloan et al. 1983).

PEG-8

PEG-8 can be extracted from biological fluids and analyzed by liquid chromatography (Delahunty and Hollander 1986) and gas-liquid chromatography (Chadwick et al. 1977).

PEG-12

A high-performance liquid chromatographic (HPLC) method has been developed for the determination of PEG-12 in human urine, which includes a pre-column dibenzoate derivatisation step. The dibenzoate derivatives of PEG-12 can be quantitatively prepared, and this, coupled with ultraviolet detection at 230 nm, has greatly improved the limit of detection for the determination of PEGs by HPLC. A suitable extraction procedure has also been developed which enabled PEG levels in urine to be monitored with much greater sensitivity than any previously reported method (Kinahan and Smyth 1991).

IMPURITIES

Silverstein et al. (1984) reported that PEG-6 may contain small amounts of ethylene oxide monomer and dimers. The amounts were not quantified.

Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75 (Hamburger et al. 1975). The amount of peroxide in PEGs is dependent upon the molecular weight of the PEG and its age. The older the compound, the greater the concentration of peroxides. In a colorimetric assay used to determine the peroxide concentrations in several production lots of PEGs, PEG-6 and PEG-8 were each added to acidified potassium iodide solution, and the iodine liberated was titrated against a standard thiosulfate solution. PEG-6 had peroxide concentrations ranging from 1.4 to 9.3 μEq thiosuIfate/mI glycol. PEG-8 had concentrations ranging from 3.24 to 5.7 μEq thiosulfate/ml glycol. The specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide (McGinity et al. 1975).

PEGs may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation (Robinson and Ciurczak 1980). 1,4-Dioxane is a known animal carcinogen (Kociba et al. 1974). Commercial grade Triethylene Glycol has been found to contain < 1 ppm dioxane (Union Carbide 1990a). The cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations (Elder 1983).

USE

COSMETIC

Functions in cosmetics of Triethylene Glycol and other PEGs are shown in Table 1.

The CIR Expert Panel recognized that certain ingredients in this group are reportedly used in a given product category, but the concentration of use was not available. For other ingredients in this group, information regarding use concentration for specific product categories was provided, but the number of such products was unknown. In still other cases, an ingredient was not in current use, but may be used in the future. The information available on the types of products and at what concentration indicate a pattern of use, within which some of these ingredients likely would be used.

Table 5 presents the available product use information provided by manufacturers to the Food and Drug Administration (FDA) under the Voluntary Cosmetic Registration Program (VCRP) for the various PEGs (FDA 2008), along with recent information on the concentration of use provided to the Personal Care Products Council (Council 2009). There are gaps in the available data. For example, 2 uses of PEG-45M were reported in the VCRP in the other baby products category, but no use concentration data were available. Also, use concentrations were provided for PEG-180M in non-coloring hair products, but no uses were reported in the VCRP. The following are reported to be in use: Triethylene Glycol and PEGs -4, -6, -8, -9, -10, -12, -14, -20, -32, -40, -75, -90, -150,

-180, -220, -240, -350, -400, -450, -2M, -5M, -7M, -14M, -23M, -45M, -90M, and -180M, with the highest reported use concentration of 85% in a non-coloring hair product for PEG-8.

The ingredients in this safety assessment are not restricted in Japan (Ministry of Health, Labor and Welfare (MHLW) 2001a, b). These ingredients are not restricted in any way under the rules governing cosmetic products in the European Union (European Commission 2002).

NON-COSMETIC

PEGs are used in pharmaceuticals as vehicles for water soluble drugs (Bartoli Klugmann et al. 1986), as ointment bases, and in suppositories (Silverstein et al.1984). They also are used in metal and rubber processing, as additives to food and animal feed, and as laboratory reagents (Hawley 1971). PEG-150 is used in water paints, paper coatings, polishes, and in the ceramics industry (Windholz 1983).

PEGs have been used as laboratory tools to induce cell fusion of plant protoplasts, bacterial protoplasts, plant protoplasts with animal cells, and animal cells in culture (Blow et al. 1978).

Triethylene Glycol is used in various plastics to increase pliability; in air disinfectants; as a solvent and plasticizer in vinyl, polyester, and polyurethane resins; in dehydration of natural gas; as a humectant in printing inks; as an extraction solvent; and as a fungicide and solvent for nitrocellulose (NTP 2001b). Triethylene Glycol has also been identified as a main ingredient (99.9% Triethylene Glycol) in a brake fluid (Vassiliadis et al. 1999).

The largest industrial use (about 50%) of PEG-4 is in oil refineries as part of a process of aromatic extraction from refined products. The second largest use (about 40 %) of PEG-4 is in the production of plasticizers (Union Carbide 1989). PEG-4 is also used as a water-soluble lubricant for rubber molds, textile fabrics, and metal-forming operations; in food and food packaging; as a chemical intermediate; in the manufacture of plasticizers, softeners and ointments; in water-based paints; in paper coatings; in polishes; in ceramics; and in pharmaceuticals (NTP 2001a).

PEG 3350 is an approved OTC laxative (Miralax, GlycoLax) (Cerner Multum 2008).

GENERAL BIOLOGY

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

In a report on burn patients treated with a PEG-based antimicrobial cream (described later in this report), “appreciable” amounts of monomeric ethylene glycol were found in the serum of the patients. The authors noted that high concentrations of PEG were probably absorbed through the damaged skin, since only 0.01% ethylene glycol was present in the burn cream (Bruns et al. 1982). In reported cases of renal tubular necrosis resulting in the the death of burn patients treated with topical ointments containing PEGs, PEG and its metabolites were present in the serum of these patients (Sturgill et al. 1982). Additional data relevant to dermal penetration of PEGs through damaged skin is provided in the Clinical Assessment Safety section.

Triethylene Glycol

McKennis et al. (1962) gave two female New Zealand White rabbits 200 or 2000 mg/kg Triethylene glycol by stomach tube. Urine from the dosed animals was subsequently collected for 24 hours. Rabbits dosed with 200 or 2000 mg/kg triethylene glycol respectively excreted 34.3 or 28 % of the dose amount as unchanged Triethylene Glycol. The urine of one rabbit contained 35.2 % of the administered dose as a hydroxyacid form of Triethylene Glycol.

These same authors also gave four male albino rats weighing 112 to 145 g a single oral dose of 22.5 mg randomly radiolabeled Triethylene Glycol-C^{14}. The rats were then placed in a metabolic chamber in which urine, feces, and expired air were collected over a period of five days. The radioactivity recovered (in percent of the administered dose) amounted to 0.8 to 1.2 % in expired air, 2.0 to 5.3 % in feces, and 86.1 to 94.0 % in urine. The total recovery of radioactivity was 90.6 to 98.3 % of the administered dose (McKennis et al. 1962).

Triethylene Glycol is believed to be metabolized in mammals by alcohol dehydrogenase to acidic products causing metabolic acidosis. Triethylene Glycol metabolism by alcohol dehydrogenase can be inhibited by 4-methyl pyrazole or ethanol (Borron et al. 1997; Vassiliadis 1999).

PEG-6 and PEG-8

Shaffer et al. (1950) studied the intestinal absorption of PEG-8 in the rat. PEG-8 was administered by stomach tube. For a 25% solution of PEG-8, approximately 62% of the dose was absorbed into the intestines in 5 h.

Metabolic fate of PEG-8 in the dog was also demonstrated by Shaffer et al. (1950). Three dogs were intravenously infused at a constant rate with a 5% solution of PEG-8 in saline, and the rate of excretion was compared with the rate of infusion. For every 100 mg of PEG-8 infused, 75-88 mg was excreted. The authors stated that ethylene glycol was not a metabolite of PEG-8.

Krugliak et al. (1989) stated that PEG-8 was absorbed by rat intestinal epithelium by both passive diffusion and solvent drag (bulk transport).

In a study using PEG-8 to determine the intestinal permeability in humans, Chadwick et al. (1977) evaluated the absorption, metabolic fate, and excretion of PEG-8. Five normal human subjects (males or postmenopausal women) ingested 1, 5, or 15 g of PEG-8 in a liquid randomly on three different occasions. Urine and feces were collected regularly for 48 h after each dose. Gas-liquid chromatography indicated that the amount of PEG-8 recovered in the wastes was directly proportional to the ingested dose. Most of the dose was excreted rapidly in the urine; 55.6% was eliminated in 48 h, and, of this, 94.4% was eliminated within 24 h. In a separate study, four individuals ingested 10 g PEG-8 mixed with 500 ml water in a liquid concoction. The mean recovery of PEG-8 in the urine and feces after 4 days was 92.8% (58.5% in the urine and 34.3% in the feces). The authors suggested that PEG-8 was not metabolized after absorption.

This suggestion was further investigated in vitro by incubating 1g of PEG-8 with 20g aliquots of human feces, or with pure cultures of *Pseudomonas aeruginosa* for 1 wk periods. The mean recovery of PEG-8 in these studies was 96.2% and the percentage composition of PEG-8 was not changed, supporting the suggestion that PEG-8 was not degraded by intestinal bacteria (Chadwick et al. 1977).

The elimination of PEG-8 after oral administration was studied in the rabbit. Two groups of three rabbits were given either 5.7 g or 8.5 g of PEG-8 by stomach tube. Urine and feces were collected and gravimetric methods were used to analyze the amount of PEG-8. The low-dose rabbits eliminated approximately 9% of the dose in their feces, and 20% in their urine after 4 days. The majority of the PEG-8 found in the urine was eliminated within the first 24 h. The same trend was observed in the high-dose rabbits; an average of 36% of the initial PEG dose was eliminated in the urine, and 18% in the feces (Shaffer et al. 1950).

Further investigation was done on renal excretion using intravenous administration of PEG-8. Two groups of three rabbits were given intravenous injections of 0.4g or 0.75g PEG-8, and urine was collected for 24 h. The groups eliminated an average of 47% and 67% of the total dose, respectively. The disposition of the remaining dose was unknown (Shaffer et al. 1950).

Urinary excretion of PEG-8 was studied using human subjects. Three subjects given intravenous injections of 1g PEG-8 in 20 ml of saline solution eliminated an average of 77% of the dose in 12 h. Two subjects injected with 10 g PEG-8 eliminated an average of 47%, and one individual given 5 g eliminated 40% of the dose in 24 h (Shaffer et al.1950).

Carpenter and Shaffer (1952) later demonstrated with rats that subcutaneous and intramuscular injections (2 ml/kg) of PEG-6 and PEG-8 were rapidly removed from the sites of injection and eliminated in the urine. An average of 85% or more of the PEGs was eliminated within 24 h.

PEG-6, PEG-12, and PEG-20

The dependence of permeability on molecular weight (MW) in acetone-disrupted female hairless mouse (strain SKH1-hr) skin in contrast to normal skin was investigated (Tsai et al. 2001). The number of animals used was not provided. Penetration of PEG-6, PEG-12, and PEG-20 over 12 h was measured using diffusion cells. High-performance liquid chromatographic methods with refractive index detection were used to separate and quantitate the individual oligomeric species in the PEG samples. Percutaneous penetration of PEGs exhibited slightly steeper MW dependency at a transepidermal water loss (TEWL) of 30-41 g/m2 per h in comparison with TEWLs of 0-10 (control skin), 10-20, and 20-30 g/m2 per h, with a higher percentage of smaller oligomer PEGs penetrating than larger ones. Increasing the TEWL of the skin increased the penetration of all the PEG oligomers, and the degree of the enhancement relative to penetration through control skin increased with MW and was maximal for oligomers with a MW ranging from 326 to 414 Da. Within the limit of quantitation of the assay, the MW cut-off for PEG penetration across mouse skin with TEWLs of 0-10, 10-20, and 20-30 g/m2 per h was 414, 590, and 942 Da, respectively, while all the measurable oligomers up to MW 1,074 Da were able to penetrate skin with TEWLs in the range 30-41 g/m^2 per h. There was no mention of a change in absorption rate or percent PEG absorbed after damage by the study authors.

The dependence of permeability on MW with different forms of barrier disruption was investigated in female hairless mice (strain SKH1-hr) using a series of PEGs ranging in MW from near 300 to over 1000 Da (Tsai et al. 2003). The number of animals used was not provided. PEGs were used to determine the effects of tape stripping and sodium dodecyl sulfate (SDS) treatment on the MW permeability profiles of mouse skin in vitro. The 12-h percutaneous penetration of all the PEG-6, PEG-12, and PEG-20 generally increased as a function of transepidermal water loss (TEWL) of the skin, either tape-stripped or SDS-treated. In addition, the total penetration of PEG oligomers across control skin, and skin tape-stripped and SDS-treated to different degrees of barrier disruption progressively decreased with increasing MW. There were no significant differences in the percutaneous penetration of the PEG oligomers between skin tape-stripped and SDS-treated to the same degree of barrier disruption. The penetration enhancement relative to control skin was more prominent with larger molecules. The MW cutoff for skin penetration increased with the degree of barrier disruption irrespective of the treatment applied, and was 986 Da (tape stripping) and 766 Da (SDS treatment) at TEWL levels in the range 10-20 g/m(2) per h in comparison with 414 Da for control skin. There was no mention of a change in absorption rate or percent PEG absorbed after damage by the study authors. In accordance with previous findings in acetone-treated mouse skin, the results strongly suggest that, irrespective of the form of barrier disruption applied, not only higher amounts but also more varieties of chemicals (larger molecules) may penetrate skin with a compromised barrier than normal skin.

According to Moolenar et al. (1981), a rectal solution using PEG-12 as a solvent produced a slow, but continuous absorption (of PEG-12) over at least 8 hours in humans.

PEG-32, PEG-75, PEG-150

The extent of gastrointestinal absorption of solid PEGs was studied in the rat. Groups of 30 rats were given 25% solutions of PEGs -32, -75, and -150, and were killed at hourly intervals up to 5 h after dosing. Gravimetric methods were used to determine the amount of PEG absorbed. Less than 2% of PEG-32 was absorbed in 5 h. There was no evidence that PEG-75 or PEG-150 was absorbed, since the initial dose was recovered from the gastrointestinal tract at each time interval (Shaffer and Critchfield 1947b).

The route of PEG-75 excretion after intravenous injection was studied in rats using ^{14}C-PEG-75. Ten rats were given 10 mg (approx. 70 mg/kg) intravenous injections of ^{14}C-PEG-75. After 7 days, the mean cumulative recovery of radioactivity was 81%: 61% was recovered in the urine, and 20% in the feces (the disposition of the remaining dose is unknown. Most of the radioactivity was excreted in the urine within 24 h (Carpenter et al. 1971).

Shaffer and Critchfield (1947b) also reported that PEG-150 was not absorbed from the gastrointestinal tract of humans. Six men ingested 10 g PEG-150 dissolved in 150 ml water, and urine samples were taken at hourly intervals for 4 h after ingestion, and then at longer intervals up to 24 h. The presence of PEG-150 was not detected in the urine at any time.

In a study with dogs, PEG-150 had an identical rate of excretion to creatinine, which indicated that this PEG was excreted by the same mechanism as creatinine:glomerular filtration without tubular participation (Shaffer et al. 1948).

In a study of the excretion of PEG-150, six men were injected intravenously with 20 ml of 5% PEG-150, and urine samples were collected from them at timed intervals for 12 h. Approximately 63% of the injected dose was found in the urine after 1 h, and 96% was recovered after 12 h. The authors found that a PEG of lower molecular weight (PEG-20) was excreted at a slower rate and in smaller quantities. They attributed this observation to the lower molecular weight polymer's ability to diffuse more quickly through tissues (Shaffer and Critchfield 1947b).

HEMATOLOGIC EFFECTS

PEG-8

Since PEGs are used as vehicles for intravenous drug administration, studies were conducted to determine their hemolytic potential. Reed and Yalkowsky (1985) reported that the EC_{50} value for lysis of human erythrocytes by PEG-8 was 30.0% (total volume percent of cosolvent in whole blood). Others have reported that the hemolytic potential of PEG-8 was reduced when combined with various combinations of ethanol, polypropylene glycol, water, and/or saline (Fort et al. 1984; Smith and Cadwaller 1967).

PEG-12

PEG-12 at 1% was thrombogenic in an ex vivo canine blood-contacting model (Silver et al. 1994).

PEG-75 and PEG-150

PEG-75 caused crenation and clumping of erythrocytes of rabbits at concentrations of 10% or greater. This observation was tested in vivo by administering intravenous infusions of 10% PEG-75 to rabbits. Blood from animals that died from pulmonary hemorrhages contained numerous clumps of cellular elements. Animals tested with 5% PEG-150 solutions did not have this reaction (Smyth et al. 1947).

RADIOPROTECTION

PEG-4, PEG-8, PEG-12, PEG-20, PEG-80, and PEG-450

PEG of molecular weights 200 (PEG-4), 400 (PEG-8), and 600 (PEG-12) afforded significant levels of radioprotection against x-rays; PEG of molecular weights 1000 (PEG-20), 1450, 4000 (PEG-80), and 20,000 (PEG-450) when given at maximum tolerated doses (approximately 0.5 LD_{50}) did not (Shaeffer and Schellenberg 1984). The degree of radioprotection by PEG-4 given 20 min before irradiation increased with dose up to the maximum tolerated dose of 6.4 g/Kg.

USE AS DRUG VEHICLE

PEG-6 and PEG-8

The biochemical effects of a series of commonly used drug carrier vehicles, including PEG-6, were investigated in the rat using ^{1}H NMR spectroscopic and pattern recognition based metabonomic analysis (Beckwith-Hall et al. 2002). PEG-6 induced changes in the biochemical composition of urine including increased concentrations of dicarboxylic acids, creatinine, taurine, and sugars. The authors concluded that PEG-6 was bioactive in its own right and that this might confound interpretation of biochemical effects of weakly toxic drugs dosed in this carrier.

ANTICONVULSANT PROPERTIES

PEG-8 and PEG-75

PEG-8 and PEG-75 were tested for anticonvulsant properties using mice in the electroshock, pentetrazole, and strychnine tests. Data from the later two tests indicated that intraperitoneal injection of PEG-8 had slight anticonvulsant activity, and PEG-75 had even more pronounced anticonvulsant activity at dosages considered inert (6.84 and 3.42 g/kg PEG-8; and 6.03 and 3.01 g/kg PEG-75). Neither solvent was active in the electroshock test. Oral administration of the PEGs did not alter the time of seizure onset or death (Bartoli Klugmann et al. 1986).

Lockard and Levy (1978) demonstrated in several studies with monkeys that PEG-8 had anticonvulsant properties. In one study, four chronically epileptic rhesus monkeys were given intravenous infusions of 60% PEG-8 in water solution for 4 wks (1 mI/hr). Prior to and after this treatment, the monkeys were administered saline (1 mI/hr) for 3 wks in order to establish baseline seizure frequency. During PEG-8 administration, a significant decrease in seizure frequency was observed compared to baseline periods.

In another group of eight monkeys given the same treatment, 5 of the animals had statistically significant decreases in seizure frequency. The 3 other monkeys were removed from the study because of signs of toxicity. Follow-up studies confirmed that at concentrations between 35% and 60% PEG-8 had anticonvulsant activity (Lockard and Levy 1978; Lockard et al. 1979).

ANIMAL TOXICOLOGY

ACUTE TOXICITY

Oral

Acute oral toxicity LD_{50} values for Triethylene Glycol and PEGs are summarized in Table 6, with values ranging from 6.4 g/kg in the mouse to >50 g/kg in rats.

PEG-75

Smyth et al. (1942) also determined that 31.6 g/kg was the smallest single oral dose of PEG-75 to cause microscopic renal or hepatic lesions in rats. Since it appeared that only very large single doses affected the liver and kidneys, the authors conducted another large dose study using rabbits. A dose of 50 g/kg PEG-75 greatly increased blood urea concentration and caused slight hepatic cell swelling. Since the intestines were unobstructed, the authors suggested that the increase in urea concentration was due to the direct action of PEG-75 on the kidneys.

Parenteral

Triethylene Glycol

Lauter and Vrla (1940) administered adult albino rats (body weights = 120 - 145 g) a single intramuscular injection of 5.6, 8.4, or 11.3 g/kg Triethylene Glycol (n = 5 animals per group; sex unspecified). Animals in the 5.6 g/kg dose showed only mild signs of toxicity, but all were normal 48 hours after the injection. All animals of the 8.4 g/kg group showed signs of toxicity, three died within 36 hours, and the two surviving animals in this group recovered three days after the injection. All animals of the 11.3 g/kg dose group died with 16 to 36 hours after dosing.

Karel et al. (1947) reported an intraperitoneal LD_{50} of 8.15 g/kg in female mice (strain not provided). Toxic effects observed in Triethylene Glycol-treated mice included damage to the spleen, thymus, renal tubules and glomeruli, as well as high white blood cell counts, pulmonary congestion, and atelectasis (collapse or incomplete expansion of the lung). Animals surviving five to seven days had signs of regeneration of splenic and lymphoid tissues.

Budavari (1989) stated that the intravenous LD_{50} value for Triethylene Glycol in rats is in the range from 7.3 to 9.5 g/kg .

PEG-6

The acute intraperitoneal toxicity of 50% PEG-6 for rats was reported to be 17.0 g/kg (Smyth et al. 1950).

Carpenter and Shaffer (1952) determined that the intravenous LD_{50} for undiluted PEG-6 in rats was 7.1 ml/kg. This dosage was based upon mortality during a 14-day period. Undiluted PEG-6 was injected into Sherman strain albino rats either subcutaneously in the abdominal region or intramuscularly into the multifidus muscle in the right lumbo-sacral region. Groups of 6 rats received subcutaneous injections of 2.5, 5, and 10 ml/kg PEG-6. Tissue reactions were monitored, and necropsy was performed on 2 rats from each group on days 2,4 (or 7), and 14. All dosages caused the skin to blanch and scabs to form on the overlying dermis within 2 days. Increased vascularization and fibroblastic repair tissue were present after 4 days, the extent of which was reduced after 14 days.

Two groups of 6 rats were intramuscularly injected with 0.5 and 2 ml/kg PEG-6, and the same observation schedule was used as in the subcutaneous study. Both dosages caused ischemic necrosis of the muscle fibers when the PEG-6 was deposited within the muscle bundles. When PEG-6 was placed subcutaneously, increased vascularization and fibroblastic proliferation were observed. These responses were transient; no evidence of injury was found after 14 days (Carpenter and Shaffer 1952).

PEG-8, PEG-32, PEG-75, PEG-150

In an acute intraperitoneal toxicity study using rats, 8% or less PEG-8 did not cause any deaths, but the weight of the kidneys of treated rats was less than that of control rats (Smyth et al. 1950).

Bartsch et al. (1976) administered PEG-8 in 0.9% NaCl solution intraperitoneally (10 ml/kg) to SPF-NMRI strain mice and SPF-Sprague-Dawley rats. The median lethal dose was 12.9 ml/kg and 13.1 ml/kg for mice and rats, respectively.

No deaths occurred when 10 rats were administered 16.0 g/kg PEG-32 (melted in a water bath) subcutaneously. Erythema and edema were evident, but no signs of toxicity were observed. At necropsy, two animals had red or mottled lungs, and the stomach and intestines of one rat were filled with a gray-green liquid (Bushy Run Research Center 1987).

The LD_{50} values for 50% aqueous solutions of PEGs -32, -75, and -150 administered by intraperitoneal injection to male Wistar albino rats were 15.39, 11.55, and 6.79 g/kg, respectively. Eighty-percent of the rats that died did so within 30 h of the dose. The remaining rats were observed for 14 days. At necropsy, a few of the rats had swollen livers (Smyth et al. 1947).

In a follow-up study, the toxicity of a different production lot of PEG-75 was tested in rats. The LD_{50} for a 50% solution was 13.0 g/kg. Eighty-percent of the deaths occurred within 30 h of the injection, and the surviving rats were observed for 14 days. No PEG-75 remained in the peritoneal cavity at the end of this period (Smyth et al. 1950).

Groups of 2 rabbits received 5% solutions of PEGs -32, -75, and -150 by slow intravenous injection (10 g/kg) via the ear vein. The infusion rate was 2.5 mI/min. All animals survived to termination (day 14). One rabbit given PEG-150 had renal tubular cell swelling (Smyth et al. 1947).

Dermal

Triethylene Glycol

Union Carbide (1990c) dosed five male and five female rabbits with a single percutaneous dose of 16 mg/kg Triethylene Glycol. No signs of dermal irritation were observed, but one female was emaciated on the fourth day after dosing. Two females showed abdominal distention four and 14 days after dosing, and one of them died. Necropsy of the dead rabbit showed a gas-filled intestine. Necropsy on day 14 revealed slight skin vascularization of the treated skin in one male. In one surviving female the lungs were tan, and the stomach was filled with liquid.

PEG-6 and PEG-8

The acute dermal toxicity of undiluted PEG-6 and PEG-8 was tested on New Zealand white rabbits using modified FDA cuff testing. Six rabbits had 20 ml/kg of either PEG applied to their skin. No deaths resulted from this treatment (Smyth et al. 1945).

PEG-75 and PEG-20M

Two groups of 4 male, albino, New Zealand rabbits had 20.0 ml/kg of 40% PEG-75 or 40% PEG-20M applied to their skin for 24 h. No deaths occurred during the 14-day observation period (Mellon institute of Industrial Research 1956).

Intratracheal

PEG-75

The pulmonary effects of PEG-75 on rats following endotracheal injection was investigated. Five male and five female Sprague-Dawley rats were lightly anesthetized and 1.0 g/kg of 50% PEG-75 (the highest nonlethal dose determined during initial tests) was injected endotracheally into their lungs. A positive control group was administered kerosine, and a negative control group was administered saline. Rats of each sex were killed on days 1, 2, and 3, and the remaining survivors were killed on day 14. No treatment-related deaths occurred during the study. A clear to light red discharge from the nose was observed 10-30 min following administration in the male rats only. The rats experienced an initial decrease in weight, but weight gain increased after 3 or 7 days. The absolute lung weights of both male and female rats were statistically increased. The lung weights relative to the body weights were increased for the females only. The only significant histologic change was alveolar histiocytosis in male rats. However, microscopic lesions in the rats killed on day 14 were not statistically different from the negative control group (Bushy Run Research Center 1988a).

In another study, groups of 10 male and female Sprague-Dawley rats were slightly anesthetized and had 2.0 ml/kg of 7.5% (w/v) PEG-75 (0.15 g/kg PEG-75) injected into their lungs endotracheally. A control group of rats was treated with 2.0 ml/kg of saline. The rats were monitored regularly for toxic effects. Two rats per gender were killed on days 1, 2, and 3, and the remaining survivors were killed on day 14. Necropsies were performed on all of the animals. There were no treatment-related deaths or signs of toxicity during the study. The rats experienced an initial decrease in body weights, but gained weight steadily after day 3. The lung weights of the treated animals (in terms of both absolute weight and weight relative to body weight) were normal. A few of the lungs had a change in color, which was not observed in the control rats, but the incidence of these changes was not statistically significant. A

few of the rats also had interstitial pneumonitis, but the incidence was not statistically significant compared to the controls (Bushy Run Research Center 1988b).

SHORT-TERM TOXICITY

Oral

Triethylene Glycol

Lauter and Vrla (1940) reported a study in which albino rats received daily doses of Triethylene Glycol via stomach tube for 30 consecutive days. The dosing groups were 0.1 mg/kg of a 5% aqueous solution, 3.0 mg/kg of a 30 % aqueous solution, 10.0 mg/kg of undiluted Triethylene Glycol, and 20.0 mg/kg of undiluted Triethylene Glycol (n = five rats per group; sex unspecified). Animals in the lower two dose groups had normal weight gains and no signs of toxicity. Animals in the 10 mg/kg dose group had decreased weight gains, hair loss and diarrhea. Of the animals in the 20 mg/kg dose group, three died within the first 24 hours after the first dose, and the remaining two died before the third day of the study.

In another study, mature albino rats received drinking water containing 5 or 10% by volume of Triethylene Glycol for 30 days (n = 5 rats per group; sex unspecified). All animals in the 5% dose group had signs of severe toxicity, and one animal died on day 8, 21, and 28. The remaining two animals in the group survived to study completion and recovered after exposure ended. All animals in the 10% dose group had signs of toxicity and died by day 12.

In the last study, young (3-week-old) rats were exposed to drinking water containing 3 or 5% by volume of Triethylene Glycol for 30 days (n = 5 rats per group; sex unspecified). All animals in the 3% dose group survived to study completion without signs of toxicity. Animals in the 5% dose group had signs of toxicity in the first two weeks of exposure but showed improvement thereafter. Body weight gains were decreased, but weights returned to normal after the exposure period ended. One animal in the 5% dose group died on day 25 (Lauter and Vrla 1940).

Preliminary to a subchronic exposure reported later in this report, Van Miller and Ballantyne (2001) conducted a probe 14-d study using rats given dietary concentrations of 0 ppm (control), 10,000, 20,000 or 50,000 ppm Triethylene Glycol daily. Triethylene Glycol consumptions were determined to be 1132, 2311 or 5916 mg/kg with males, and 1177, 2411 or 6209 mg/kg with females for the treatment groups, respectively. There were no mortalities or adverse clinical signs, and no effects on body weight, hematology, serum chemistry, organ weights, and gross or microscopic pathology. Feed consumption was increased at the high dosage. Urinalysis showed increased urine volume and decreased pH with high dose males and females, and increased volume with mid-dose males.

PEG-4

Union Carbide Corp. (1994) exposed male Fischer 344 rats to 0, 5000, 25,000, or 50,000 ppm PEG-4 (as tetraethylene glycol) in drinking water for five consecutive days in a Dominant Lethal Assay. The respective daily consumption levels of PEG-4 were 425 ± 45, 2441 ± 328, and 5699 ± 1341 mg/kg. Males were observed for clinical toxicity, and urine was collected on the fifth day of PEG-4 exposure. At the end of the five-day exposure period, the PEG-4 drinking water was replaced with regular water. The males were then mated with ten naive females (reproductive results of the dominant lethal assay are described in the Genotoxicity section later in this report). Ten weeks after the end of dosing the males were killed and necropsied. Males in the 50,000 ppm group had decreased body weights on the fifth day of treatment, but at one week after removal of PEG-4 body weights were similar to controls. Water consumption was increased in males of the 25,000 and 50,000 ppm groups during the treatment period, and urinalysis indicated increased urine volume and decreased urine pH in all PEG-4 dose groups. Males of the 50,000 ppm group also had decreased urine osmolarity. Necropsy of the males revealed no treatment-related gross or histological effects.

Schladt et al. (1998) dosed Wistar rats at 0, 220, 660, or 2000 mg/kg/day PEG-4 (as tetraethylene glycol) (n = 10/sex/dose) by oral gavage for 33 days. The dosing volume was 5 ml/kg. Animals were observed daily for clinical signs of toxicity. Body weights, feed and water consumption were recorded weekly. Blood was collected for hematology and clinical chemistry at week 4. Urine was collected for urinalysis at weeks 2 and 5. Urine was collected for determination of oxalic acid on days 2 and 25 of dosing. Animals were killed for necropsy and histology at the end of the dosing period. There were no treatment-related effects on clinical signs, mortality, feed and water consumption, body weights, hematology parameters, gross necropsy, or histopathology. There were no toxicologically relevant effects on serum chemistry. Urine pH was decreased and urine osmolarity was increased in the 660 mg/kg males and 2000 mg/kg females, however, these findings were considered not toxicologically relevant. The content of urine oxalic acid was not affected by the PEG-4 doses tested. The NOAEL of PEG-4 in this study was the highest oral dose, 2000 mg/kg/day.

PEG-75

A 5-week study of the effects of PEG-75 on the kidneys of rabbits was conducted (Smyth et al. 1942). Groups of five rabbits were given 5, 10, or 20 g/kg PEG-75 by stomach tube 6 days per week. Blood urea concentrations monitored throughout the study were normal, and at necropsy and microscopic examination, no abnormalities were found in the kidneys. Slightly retarded growth was

reported in the animals receiving 20 g/kg, but the authors attributed this to appetite reduction as a result of the large volume of inert material in the stomach.

Inhalation

Triethylene Glycol

Union Carbide (1992) exposed Sprague-Dawley rats to Triethylene Glycol by aerosol inhalation for six hours a day for nine days over a two-week period. The target Triethylene Glycol exposure levels were 0 (filtered air control), 500, 2000, and 5000 mg/m^3. The actual Triethylene Glycol exposure levels were 494, 2011, and 4842 mg/m^3 (n = 10/sex/group). Five additional rats were added to the control and 5000 mg/m^3 group for planned postexposure recovery observations. The mean particle size for aerosolized Triethylene Glycol was 2.48 microns. All rats in the 5000 mg/m^3 dose group died or were euthanized moribund on or before exposure day 5. Prior to their deaths, clinical observations of the animals in this group included ataxia, prostration, unkempt fur, labored respiration (males only), ocular discharge, swollen periocular tissue, perinasal and perioral encrustation, blepharospasm, and reduced body weights.

Necropsies of the high-dose animals revealed hyperinflation of the lungs (failure of the lungs to collapse when the chest cavity was opened), ocular opacity, congestion and hemorrhage of many organs and tissues (pituitary gland, brain, nasal mucosa, kidney, thymus and lungs). Rats exposed to 2011 or 494 mg/m^3 Triethylene Glycol survived to the study's completion, and the only clinical observations noted were swollen periocular tissue and perinasal encrustation. After the fifth exposure the males in the 2011 mg/m^3 group had decreased body weights. Feed (females only) and water consumption were increased in the mid- and low-dose groups. Hematological analysis showed increased erythrocyte counts (females only), decreased red corpuscle volume, increased albumin aminotransferase activity, increased alkaline phosphatase activity, and increased blood urea nitrogen in rats of the 2011 and 494 mg/m^3 groups. Analysis of the urine revealed increased urine volume, decreased urine osmolarity and pH, and decreased N-acetyl-β-D-glucoseaminidase activity in the 2011mg/m^3 group.

At necropsy the mid-dose rats had increased relative and absolute liver and kidney weights. The only remarkable microscopic finding was minimal to mild alveolar histiocytosis. The authors stated that these findings indicate impaired liver function without morphological evidence of organ injury. The threshold exposure concentration for hepatotoxicity from inhalation of aerosol Triethylene Glycol was approximately 494 mg/m^3. There were no consistent findings to suggest renal injury. Because exposed animals ingested (preened) Triethylene Glycol from wet fur, contributing (unknown quantity) to the total dose received by the animals, a nose-only study was conducted. Male and female CR rats (n=10/sex/group) were exposed to aerosols of Triethylene Glycol for 6 hours/day for 9 days over an 11-day period by nose-only exposure. Mean exposure concentrations were 0, 102, 517, or 1036 mg/m^3. No exposure-related clinical signs were observed. Non-statistically significant decreases in female body weight gains were reported in the mid and high concentration groups. The apparent decrease in the mid dose group was determined to be due to the inclusion of an outlier in the control group with a much higher weight. When this animal was excluded, no decrease in weight gains was observed for the mid dose group. No changes in feed and water consumption were noted. No clinical pathology findings were related to Triethylene Glycol exposure, and no exposure-related organ weight changes were noted in any group (Union Carbide 1992).

Intravenous

PEG-6, PEG-8, PEG-32, PEG-75 and PEG-150

Three of eight chronically epileptic monkeys given intravenous infusions of 60% PEG-8 in water (1 ml/h) for 3 weeks had decreased appetites, a greasy texture to their lower extremities, edema of their genitals and legs, and deteriorating infusion sites (Lockard and Levy 1978). Similar reactions occurred in other epileptic monkeys and normal monkeys treated with 60% and 65% PEG-8 (Lockard and Levy 1978; Lockard et al. 1979).

Smyth et al. (1947) studied the effects of intravenous injections of PEGs -6, -8, -32, -75, and -150 in rabbits. The animals were given 1 g injections via the ear vein of 5% PEG solutions in 0.85% sodium chloride 6 days a week for 5 weeks. The average dose was 350 mg/kg/day. No deaths occurred in the groups receiving PEG-6 and PEG-32, but 1 of 5 rabbits died in the PEG-8 group, 1 of 9 died in the PEG-75 group, and 1 of 5 died in the PEG-150 group. One PEG-8 rabbit and four PEG-75 rabbits had hepatic cell and renal tubular cell swelling.

Dermal

Groups of 8 male albino rabbits had 0.4 or 0.8 g/kg PEG-75 or PEG-20M applied to their clipped abdomens for 1 h a day for 30 days. A control group of rabbits was treated with distilled water. All of the rabbits were weighed weekly and observed for signs of toxicity. No treatment-related deaths occurred. Mean body weight gains were greater in treatment groups receiving 0.8 g/kg (735.1 g for PEG-75; 701.0 g for PEG-20M) than in the control group (671.8 g). Mild, transient erythema was observed at the application sites (Mellon Institute of Industrial Research 1956).

Herold et al. (1982) developed an animal model to study the potential toxicity of repeated applications of a PEG-based antimicrobial cream to burn patients. The hair of New Zealand white rabbits was removed, and 2 paravertebral skin excisions (2.5 **x** 15 cm) were made on their backs. The experimental rabbits had either the antimicrobial cream or the PEG-vehicle (63% PEG-6, 5% PEG-20, and 32% PEG-75) alone applied to their lesions. The dressings of all the rabbits were changed every 12 h for 7 days. In the control group only the bandaging procedures were used.

Seven of the 8 rabbits treated with the antimicrobial cream and 3 of the 4 rabbits treated with the PEG-vehicle died during the study. They had increased total serum calcium, increased osmolality gap, high anion gap metabolic acidosis, and renal failure. These alterations were consistent with that seen in burn patients treated with the antimicrobial cream. All six of the control animals survived. The authors suggested that the syndrome observed in the experimental animals was a form of systemic toxicity as a result of the absorption of the PEGs, which were metabolized into nephrotoxic compounds, acid alcohols, and diacids (Herold et al.1982).

SUBCHRONIC TOXICITY

Oral Studies

Triethylene Glycol

Van Miller and Ballantyne (2001) studied the potential for Triethylene Glycol to produce nephrotoxicity, or other organ/tissue injury, in a subchronic (90-d) study conducted by continuous inclusion of Triethylene Glycol in the diet of Fischer 344 rats (20 males and 20 females). The dietary concentrations were 0 ppm (control), 10,000, 20,000 or 50,000 ppm Triethylene Glycol, daily. Triethylene Glycol consumption was determined to be 748, 1522 or 3849 mg/kg (males), and 848, 1699 or 4360 mg/kg (females).

There was neither mortality nor signs of toxicity, and no dose-response effects in serum chemistry, gross and microscopic pathology. Body weights were decreased during the dosing period with both males and females at the high dose. Body weight gains were decreased at all dosages with males and females. No hematological effects were seen with females, but males of the mid- and high-dose groups had slightly decreased erythrocyte counts and hematocrits, and high-dose males had decreased hemoglobin concentration with increased mean corpuscular volumes. These were considered to reflect a mild hemodilution related to the absorption of large Triethylene Glycol doses. Urinalysis showed dosage-related decreased pH, and increased urine volume mainly at the high dose. These were probably related to the renal excretion of absorbed Triethylene Glycol and/or metabolites. Kidney weights were increased for high-dose females, and increased relative (to body) weight of kidneys for males and females from the mid- and high-dose groups were observed, probably related to the renal excretion of the absorbed Triethylene Glycol and/or its metabolites. These findings indicate that the subchronic continuous oral dosing of Triethylene Glycol to rats does not result in local or systemic specific organ or tissue toxicity. These findings contrast with the known repeated oral toxicity, notably nephrotoxicity, produced by ethylene and diethylene glycols. Therefore, Triethylene Glycol had significantly lesser potential for systemic toxicity by the oral route than its lower molecular weight homologues (Van Miller and Ballantyne 2001).

PEG-6 and PEG-8

Groups of 5 male albino rats received either PEG-6 or PEG-8 in their drinking water at concentrations of 0.06, 0.25, 1, 4, and 16 g/100 ml for 90 days. Ten control rats received untreated water. The rats were observed for 90 days. All animals drinking 4% solutions (5.4 g/kg/day PEG-6 and 4.8 g/kg/day PEG-8) or less survived to termination.

The rats given 16% solutions (20.5 g/kg/day PEG-6 and 16.4 g/kg/day PEG-8) drank 25-75% less than the control rats. Three rats died from both treatment groups before termination; the rats drinking PEG-6 died within 9 days, and the rats consuming PEG-8 died in 80-84 days. At necropsy, swollen livers were found in all of the PEG-6 treated rats, and microscopic examination showed dilated renal glomeruli, which the authors attributed to low water intake. Animals that died before termination of the study (from both treatment groups) also had necrosis of epithelial cells of the convoluted renal tubules. No organ abnormalities were reported in the PEG-8 rats surviving to termination (Smyth et al. 1945). A similar study confirmed these results (Smyth et al. 1950).

Hermansky et al. (1995) studied the effects of PEG-8 following 13 weeks (65 doses) of gavage treatment in Fischer 344 rats (10/group/sex) at doses of 1.0, 2.5 or 5.0 ml/kg (1.1, 2.8 and 5.6 g/kg, respectively) body weight/day for 5 days/week. The control animals received water by gavage (5.0 ml/kg b.w./treatment day). An additional 10 rats/sex/group were assigned to the control and high-dose groups for a 6-week recovery period. Potential renal toxicity was evaluated; there was no mortality or changes in hematology or clinical chemistry measurements attributed to PEG-8 toxicity.

Loose feces in the mid- and/or high-dose group of both sexes were attributed to bulk cathartic effects of PEG-8. Slight decreases in feed consumption and body weights in the mid- and/or high-dose group of male and female rats were attributed to the physical presence of PEG-8 in the intestinal tract. The authors noted, however, that a direct effect of PEG-8 on the intestinal tract was not ruled out. Increased water consumption occurred as a result of a possible increase in serum osmolality due to the absorption of the PEG-8 or a reflection of the water dosing received by the control animals. Increased urinary concentration and decreased urinary pH were at least partially attributed to absorption, possible metabolism, and urinary excretion of PEG-8.

Small increases in absolute and/or relative kidney weights, observed in various dose groups, were attributed to the osmotic effect of the test substance and/or metabolites in the urine. The significance of a slight increase in relative kidney weights in female rats following the recovery period was unknown. Although no microscopic changes were observed in the kidneys or urinary bladder, a slight, reversible renal toxicity may have resulted in male rats treated by gavage with 2.5 ml/kg/day and rats of both sexes treated by gavage with 5.0 ml PEG-8 kg/day (Hermansky et al. 1995).

PEG-6, PEG-8, PEG-32, PEG-75, and PEG-150

Smyth et al. (1942) conducted a 90-day oral toxicity study of PEG-6, PEG-32 and PEG-75. Groups of five rats were given 1-16% (0.88-22.9 g/kg/day) PEG-6, PEG-32 or 0.05-16% (0.04-19.0 g/kg/day) PEG-75 in their drinking water. No deaths were caused by any of the dosages, and blood cytology and hemoglobin were normal. The animals drinking PEG-6 and PEG-32 grew normally, and at necropsy the only abnormality found was in the kidneys. Microscopically, the Bowman's capsule was dilated in one rat in each of the following PEG-6 dosage groups: 4.05, 8.1, and 22.9 g/kg/day. Lower doses did not cause such changes. The growth of rats drinking 7.0 and 19.0 g/kg/day PEG-75 was reduced 25% compared to controls. A PEG-75 dose of 19.0 g/kg/day caused renal lesions, such as distension of the Bowman's capsule, granular detritus, secretion of albuminoid, and cloudy swelling of the convoluted tubules.

Smyth et al. (1950) reported that 0.04 g/kg/day PEG-75 in drinking water could be administered to rats without causing adverse effects. These authors noted that the safe oral dose of PEG-75 for rats was 1.6 g/kg. The authors noted that the PEG-75 used in the study was from a later year of production, and explained that the discrepancy in results was probably due to better manufacturing methods.

Smyth et al. (1955) investigated the relationship between the molecular weight of PEGs and subacute toxicity. Groups of 10 rats (5 of each sex) were given 2, 4, 8, 16, and 24% PEGs ranging in molecular weight from 200 to 6000 (which includes PEGs -6, -8, -32, -75, and -150) in drinking water for 90 days. For PEGs -6, -8, -32, and -75, toxicity was dose dependent. The rats had reduced body weight gain and increased renal and hepatic weights. In the group receiving PEG-150, only the rats fed a concentration of 24% had signs of toxicity. For PEGs ranging from 200 to 4000 in molecular weight, there was no relationship between molecular weight and toxicity. PEG-150 was distinctly less toxic than the lower molecular weight PEGs.

PEG-20M

PEG-20M was tested for toxicity in a 90-day study using CT-Wistar albino rats. Groups of 10 rats were fed PEG-20M as 0.5, 1.0, 2.0, 4.0, and 10.0% of their diets. A control group of rats was fed the diet alone. The rats were weighed weekly, and their kidneys and livers were weighed at necropsy. No treatment-related deaths occurred. The only sign of toxicity caused by the diet of 10.0% PEG-20M was decreased liver weights. No signs of toxicity were observed in the 4.0% PEG-20M treatment group. In the lower-dose groups, scattered, barely significant differences in body weight gain, appetite, and organ weights were associated, but not correlated, with dose (Mellon Institute of Industrial Research 1956).

Intravenous

PEG-75

Three groups of 9 Beagle dogs were given intravenous injections of 10% PEG-75 in 0.85% aqueous sodium chloride at dosages of 10, 30, and 90 mg/kg/day. A corresponding group of dogs, injected with the sodium chloride vehicle alone, served as a control. Two dogs from each group were killed after 43 daily injections, and another two dogs were killed after 99 daily injections. The remaining dogs were killed after 178 injections. During the course of the study, no changes were observed in the general behavior, appetite, body weight, or bodily functions of the dogs. At necropsy, none of the dogs had gross lesions or microscopic changes in any of their tissues or organs that could be attributed to PEG-75. No statistically significant differences were found between the experimental and control animals either in the organ weights or biochemical tests (Carpenter et al. 1971).

Dermal Studies

PEG-6, PEG-8, PEG-20, PEG-32, PEG-75, PEG-150, and PEG-20M

Fifteen female Sprague-Dawley rats received 886 mg/kg of a formulation containing 3% PEG-8 applied to the shaved skin of their backs for 13 weeks. The treatment site was 10 - 15% of the total surface area, and the site was shaved once a week throughout the study. Daily applications were made 5 times a week. All of the animals survived the test period, and no changes in body weight gains, appearance, or behavior were observed. Most of the animals had moderate irritation and a brown discoloration of the skin at the treatment site, and hyperkeratosis and parakeratosis was found upon histopathologic examination. Serum chemistry, hematology, and urinalysis parameters taken during the study were similar to those seen in the untreated control group, or fell between the range of normal values established in this laboratory for the Sprague-Dawley rat. At necropsy, no gross abnormalities or changes in organ

weights were found. The rats had a pulmonary infection, but this was not considered treatment-related since the formulation was not volatile (CTFA 1981).

In another study, Sprague-Dawley rats (number unspecified) were given daily dermal applications (2400 mg/kg) of a formulation containing 5% PEG-8 for 13 weeks. All of the animals survived to the end of the study and no change in their behavior was noted. There was a significant decrease in body weight gains of the treated rats compared to the untreated controls, and minimal irritation and desquamation and scabbing were observed at the application sites. There were statistically significant changes in the various hematology parameters investigated. However, the authors noted that these changes were within the historical limits for untreated control rats. The only toxicologically significant changes were an increased neutrophiI/lymphocyte ratio for male rats, and increased activities of serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase (SAP), and serum glutamic oxaloacetic transaminase (SGOT) for male rats, and SGPT and SGOT for female rats.

At necropsy, both male and female rats had hyperemia of the stomach and small and large intestines, and an apparent smoothing of the gastric mucosa. The relative weights of the brain, heart, and testes of the male rats were increased, and the absolute weights of the spleens from male rats was decreased. Histopathologic alterations included acanthosis, hyperkeratosis, sebaceous gland hyperplasia, and chronic inflammation in the dermis; all were indicative of dermal irritation. Submucosal edema and inflammation, and mucosal hyperemia were observed, but these changes were also present in the female rats of the control group. The presence of a black material subsequently determined to be iron, was detected in the connective tissue of the denuded tips of the villi of the small intestine of the experimental male rats.

The authors suggested that the decreased body weights of the treated animals and the increased neutrophil to lymphocyte ratios in male rats were related to the skin changes, since there were no significant gross or microscopic changes in the brain, heart, testes, or spleen. The changes in their weight were not considered to be evidence of toxicity. Similarly, the livers had no microscopic lesions to indicate that the increased enzyme activities were treatment related. The changes in the gastrointestinal tract were thought to be related to the ingestion of the formulation, since the applications were not made under occlusive patches. The authors concluded that the formulation containing 5% PEG-8 did not produce cumulative systemic toxic effects (CTFA 1985a).

An 18-week toxicity study of skin absorption conducted by Smyth et al. (1945), two groups of six albino white rabbits received dermal applications (2 ml/kg/day) of PEG-6 or PEG-8 on their clipped abdomens 5 days a week. All animals survived to termination, and no evidence of toxicity was observed during the study or at necropsy.

Undiluted PEG-6, PEG-32 and 50% aqueous PEG-75 also were nontoxic when applied to the skin for prolonged periods of time. Dosages of 10 g/kg of the “Carbowax” compounds 1500 and 4000 (the latter in the form of a 50% aqueous solution), placed on thin cotton pads, were applied to the abdominal skin of rabbits 5 days a week for 13 weeks. Control animals were given applications of petrolatum or water. Very little or none of the experimental compounds was absorbed, and no interference with renal function or microscopic renal changes were observed (Smyth et al. 1942).

Tusing et al. (1954) evaluated the dermal toxicity of PEGs -6, -8, -75, and -150 using albino white rabbits. Groups of 10 rabbits were given the following treatments for 12-13 weeks: two groups had 2.0 ml/kg PEG-6 and PEG-8 bound to the skin of their clipped abdomens 5 times a week; and two groups had 10 g/kg PEG-75 and PEG-150 applied to their abdominal skin for 5 consecutive days. Two groups of 5 animals served as controls, and were subjected to the bandaging procedures without the PEGs. No significant skin reactions or evidence of systemic toxicity were caused by any of the PEGs. Although 14 test animals died before study termination and all of the control animals survived, the authors noted that the deaths appeared to be due to an incidental coccidial infection. A parasitic infection was also found among the control and surviving test animals.

CHRONIC TOXICITY

Oral

Triethylene Glycol

Fitzhugh and Nelson (1946) fed Osborne-Mendel rats diet (ground commercial rat biscuits with 1 % added cod liver oil) containing 0, 1, 2, or 4 % Triethylene Glycol for two years (n = 12/group). Body weights and feed consumption were measured weekly. There were no toxic effects observed in the Triethylene Glycol group. Feed consumption, growth rate, mortality, incidence of bladder stones, incidence of bladder tumors, and incidence of kidney and liver damage were all similar between the Triethylene Glycol and control groups. The same doses of diethylene glycol produced dose-dependent toxicity in all parameters noted above.

PEG-6, PEG-8, PEG-32, and PEG-75

A 2-year oral toxicity study of PEG-6 and PEG-32 and PEG-75 was conducted using Wistar albino rats (Smyth et al. 1947). Four groups of 16 rats (8 of each gender) were given solutions of PEG-6 or PEG-32 in place of their water supply at concentrations of 0.02, 0.08, 0.4, and 2%. An identical set of rats was given 0.00125, 0.005, 0.02, and 0.08% solutions of PEG-75. The control group of rats were given untreated water. The animals were monitored for adverse behavioral or physiological changes throughout the study, and were killed and examined at the end of 2 years.

The weighted mean dosages during the study were calculated to be 0.015, 0.059, 0.27, and 1.69 g/kg/day for PEG-6 and PEG-32, and 0.00085, 0.0036, 0.017, and 0.062 g/kg/day for PEG-75. Fifty-five percent of the rats died before termination of the study. The only sign of toxicity was a decreased rate of growth in the animals given the two highest doses of PEG-6 and PEG-32 (1.69 and 0.27 g/kg/day), and the high dose of PEG-75 (0.062 g/kg/day). After 1 year, a 9% difference was found between the weights of the treated animals and that of the controls (including the animals given smaller doses of the PEG). At necropsy, the treated rats had several neoplasms and soft aggregates of protein in the urinary bladder, but these changes were also found in the control rats and were considered typical manifestations of aging (Smyth et al. 1947).

The results of this study were reinterpreted by Smyth et al. (1950), who pointed out that only one untreated control rat survived the 1947 experiment, so a synthetic control group consisting of this rat and the rats receiving the lowest dosages was established for comparative purposes. They compared the weights of the dosed rats with untreated animals and noted a trend of effect associated with dosage; however, they could find no direct indication that PEGs caused a decrease in growth. The authors concluded that the greatest doses of PEG-6 and PEG-32 (1.69 g/kg/day) and PEG-75 (0.062 g/kg/day) did not cause any toxic effects in rats (Smyth et al. 1950).

Smyth et al. (1955) conducted 2 year toxicity studies of PEGs -8, -32, and -75. Groups of Wistar-derived rats (20 of each gender) were administered 0, 1, 2, 4, and 8% PEG-8, or 0, 0.5, 1, 2, 4, and 8% PEG-75 in their feed. PEG-32 was administered to Sherman strain rats (35 of each sex) in their feed at concentrations of 0, 0.02, 0.08, 0.4, 2, 4, and 8%. Evidence of toxicity was minor. PEG-8 at concentrations of 4% and 8% caused a slight reduction in the growth rate of male rats, and rats of both sexes fed 8% PEG-75 grew slightly less than control rats. PEG-32 administered at 8% slightly increased the incidence of renal cell swelling (Smyth et al. 1955).

The chronic toxicity of these PEGs was also investigated using dogs. Groups of 4 dogs were given 2% dietary concentrations of PEG-8, PEG-32, and PEG-75 for 1 year. Body weight, blood cytology, bromsulfalein retention, and prothrombin time were evaluated throughout the study. There was no significant difference between these measurements in treated dogs and those of controls; at necropsy, no abnormalities or microscopic lesions were observed in any of the major organs (Smyth et al. 1955).

OCULAR IRRITATION

Triethylene Glycol

Union Carbide (1990c) reported that ocular exposure to 0.1 ml Triethylene Glycol in six rabbits did not produce corneal injury, however all rabbits displayed acute iritis and minor transient conjunctival irritation. The affected tissues returned to normal within 24 hours after exposure.

PEG-6, PEG-8, PEG-32, PEG-75

Smyth et al. (1945) reported that 20% PEG-6 and undiluted PEG-8 were slightly more or equally irritating to the conjunctiva of rabbits than a 10% solution of glycerine in saline. An investigation of corneal necrosis produced by contact with undiluted PEG-6 or PEG-8 was also conducted. The PEGs (amount not specified) were instilled into the conjunctival sac of rabbits, and 18-24 h later fluorescein staining was used to determine corneal changes. Traces of diffuse corneal necrosis were found in one to two of the five eyes tested for each ingredient. No corneal necrosis was observed when 15% solutions of either PEG were administered (Smyth et al. 1945).

Carpenter and Smyth (1946) reported that 0.5 ml undiluted PEG-6, PEG-8, PEG-32, and PEG-75 did not cause corneal injuries to the eyes of rabbits 24 h after application. A 35% solution of PEG-8 (0.1 ml) was instilled into the conjunctival sac of four albino rabbits 1, 3, 6, 7, and 13 times over 2, 4, 7, 26, and 50 h. The eyes were monitored for corneal and conjunctival edema, serum extravasion in conjunctivae, and blood/aqueous humor barrier disruption. PEG-8 caused little or no irritation to the eyes (Laillier et al. 1975).

Guillot et al. (1982) conducted ocular tolerance tests of PEG-8 following official French methods (Journal Officiel de la Republique, Francaise 1973). Two different production lots of PEG-8 were tested using the eyes of rabbits. Evaluations were made 1 h after administration, after 24 h, and on days 2, 3, 4, and 7. Fluorescein staining was used to detect corneal ulceration. The ocular irritation indices were 8.50 and 9.83, and no corneal opacity was observed. PEG-8 was not an ocular irritant.

Laillier et al. (1976) instilled a 35% solution of PEG-8 (0.1 ml) into the conjunctival sac of four albino rabbits 1, 3, 6, 7, and 13 times over 2, 4, 7, 26, and 50 h. The eyes were monitored for corneal and conjunctival edema, serum extravasion in conjunctivae, and blood/aqueous humor barrier disruption. PEG-8 caused little or no irritation to the eyes.

When 0.1 ml PEG-32 (melted in a water bath) was instilled into the conjunctival sac of six rabbits, mild conjunctival irritation was observed in all of the eyes and iritis was observed in three rabbits. All signs of irritation disappeared by 48 h (Bushy Run Research Center 1987).

A 2% solution of PEG-75 caused congestion of the lower eye lid of rabbits for 5 min. The length of irritation increased with concentration. Solutions of 28% and 42% caused congestion for 30 min and 60 min, respectively. It was reported that a 10% solution

of PEG-75 was as irritating as 2% glycerol, 2% boric acid, or 5% ethyl alcohol. The irritancy of a 50% solution was equal to 5% sodium chloride. The authors attributed the irritancy to hypotonicity (Smyth et al. 1942).

DERMAL IRRITATION/SENSITIZATION

Triethylene Glycol

Triethylene Glycol did not produce any erythema, edema, or other dermal reactions in six rabbits that had been exposed to 0.5 ml Triethylene Glycol for four hours in an occluded patch test (Union Carbide 1990c).

PEG-6, PEG-8, PEG-32, PEG-75, and PEG-20M

When undiluted PEG-6 and PEG-8 (amount not specified) were applied to the clipped abdomens of albino rabbits (six rabbits for each PEG) for 4 h, no signs of irritation were found in 24 h (Smyth et al. 1945).

No irritation was observed during the acute dermal toxicity study (described earlier in this report), in which 20 ml/kg of undiluted PEG-6 and PEG-8 were applied to the skin of six rabbits (Smyth et al. 1945).

Cutaneous tolerance tests of PEG-8 were conducted by Guillot et al. (1982) following official French methods (Journal Officiel de la Republique Francaise 1980). Two different production lots of PEG-8 were tested using rabbits and occlusive patch testing. The primary irritation indices were 0.04 and 0 for the two lots, respectively. These authors also reported that PEG-8 was nonirritating to rabbits during a 6 -week cutaneous study. The mean maximum cutaneous index for both production lots of PEG-8 was 0.67. No significant lesions were found during macroscopic and microscopic.

Smyth et al. (1942) applied 3 g PEG-6 and PEG-32 or 6 ml 50% PEG-75 to the clipped abdomens of guinea pigs (10 animals per treatment group) for 4 days. The PEGs did not irritate the skin. In the 13 week dermal toxicity study described earlier in this report, the investigators reported that repeated applications (5 days per week) of 20 g undiluted PEG-6 and PEG-32 was irritating to the abdominal skin of rabbits, but was less irritating than petrolatum. Fifty percent PEG-75 (40 ml) caused no irritation.

Six rabbits had 0.5 ml of PEG-32 (melted in a water bath) applied under occlusive patch to their skin for 4 h. No irritation was observed during the 7 day observation period (Bushy Run Research Center 1987).

In a 30 day dermal toxicity study (described earlier in this report), PEG-75 and PEG-20M at doses of 0.4 and 0.8 g/kg/day caused mild erythema. All signs of irritation disappeared by the last application (Mellon Institute of Industrial Research 1956).

Carpenter et al. (1971) used a modified Landsteiner intradermal sensitization test to determine the parenteral sensitization potential of PEG-75. Twenty male albino guinea pigs were given eight doses (0.1 ml) of 0.1% PEG-75 in 0.85% NaCl on alternate days (3 per week). A challenge of 0.05 ml was administered after 3 weeks of no treatment. None of the animals were sensitized.

INHALATION TOXICITY

Triethylene Glycol

Robertson et al. (1947) placed 24 male and 12 female rats in a chamber containing supersaturated Triethylene Glycol vapor. Four male and two female control rats were kept in a separate chamber containing normal air. Animals remained in the respective chambers for six to 13 months. Triethylene Glycol exposure by inhalation of saturated vapor in 24 hours was 0.004 cc/kg/day. The growth rates of adult and offspring rats in the Triethylene Glycol inhalation group was similar to growth in the control group. General health of the rats were not affected by the Triethylene Glycol as vapor. Hematology was likewise similar between control and treated animals. Necropsies showed no treatment-related lesions.

Five male and five female Sprague-Dawley rats were exposed to a single 6-hour inhalation treatment of saturated Triethylene Glycol vapor at 21°C. None of the rats died or had any signs of toxicity as a result of the treatment (Union Carbide 1986a).

Union Carbide (1990b) exposed four groups of Sprague-Dawley rats, five of each sex per group, to an aerosol atmosphere of Triethylene Glycol for four hours. The aerosol concentrations were 2.6, 3.9, 5.0, and 6.7 mg/L Triethylene Glycol. The median aerosol particle diameters per group ranged from 4.4 to 9.3 μm. Animals were observed for signs of toxicity after exposure and for several days following. Immediately after exposure, all rats had wet/oily fur and perinasal and periocular encrustation. In the 6.7 and 5.0 mg/L groups clinical signs included bright red discoloration of the eyes, ears, and feet, blepharospasm, and an absence of toe and tail pinch reflexes. Audible respiration and decreased motor activity were observed in the 5.0 mg/L group on post-exposure day 1. For the first 2 to 5 days after exposure periocular and perinasal encrustation and discolored and unkempt fur were observed. In the 5.0 mg/L group three females died on the second day after exposure, and two females died on the third day. The cause of death for these rats could not be determined upon necropsy and microscopic examinations. The treatment of 5.0 mg/L Triethylene Glycol exposure was repeated in five additional female rats. While these additional rats exhibited the same clinical signs observed in the other exposure conditions, none died prematurely. The only treatment-related gross lesions found in necropsy were brown discoloration of the kidneys (two males in the 5.0 mg/L group) and discoloration of the caudate lobe of the liver (1 female in the 3.9 mg/L group). The authors determined that the LC_{50} for Triethylene Glycol aerosol in Sprague-Dawley rats is greater than 3.9 mg/L.

PEG-75

Groups of 10 male and 10 female Fischer 344 rats were exposed to aerosols of PEG-75 (20% w:w in water) at 0, 109, 567, or 1008 mg/m^3 for 6 h five times per week for 2 weeks (total of nine exposures) (Klonne et al. 1989). The approximate mass median aerodynamic diameters of the particles for each of the treatment groups were 6.1, 5.0, and 3.8 μm, respectively. The rats were necropsied after nine exposures. Separate groups of control rats and high-dose rats were necropsied after a 2-week recovery period.

All of the rats survived to termination of the study. Parameters of ophthalmology, serum chemistry, urinalysis, and gross lesions of the experimental rats were comparable to those of the control animals. Male rats exposed to 567 or 1008 mg/m^3 PEG-75 had decreased body weight gains, and the latter group also had a 50% increase in neutrophil counts. These changes did not occur in the male rats killed after a 2 week recovery period or in any of the female rats killed at either interval. For both sexes, there was a 10% and 18% increase in absolute weights of the lungs for the 567 and 1008 mg/m^3 groups, respectively. The only microscopic changes were in the lungs. There was a concentration-dependent increase in the number of macrophages in the alveoli of rats of both treatment schedules (Klonne et al. 1989).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In a special report on the reproductive and developmental toxicity of ethylene glycol and its ethers, the CIR Expert Panel noted that metabolites of ethylene glycol monoalkyl ethers, such as methoxyethanol and ethoxyethanol (but not butoxyethanol) are reproductive and developmental toxicants, but not ethylene glycol monoalkyl ethers themselves (Andersen 1999c). NTP (2004) concluded that ethylene glycol itself was not a reproductive/developmental toxicant.

Triethylene Glycol

Triethylene glycol and two of its derivatives were evaluated for reproductive toxicity in a continuous breeding protocol with Swiss CD-1 mice (Bossert et al. 1992). Triethylene Glycol (0, 0.3, 1.5, and 3%) was administered in drinking water to breeding pairs (20 pairs per treatment group, 40 control pairs) during a 98-day cohabitation period. Reproductive function was assessed by the number of litters per pair, live pups per litter, proportion of pups born alive, and pup weights. There were no apparent effects on reproductive function in the animals receiving Triethylene Glycol at doses up to 3% in the drinking water. However, some developmental toxicity was demonstrated for Triethylene Glycol. Continuous exposure of dams to 1.5 or 3% Triethylene Glycol significantly decreased live pup weights at birth compared to control and 0.3% Triethylene Glycol. Reproductive toxicity was not demonstrated in mice receiving Triethylene Glycol at doses up to 6.78 g/kg.

Union Carbide (1990d) dosed pregnant CD-1 mice with Triethylene Glycol by oral gavage daily on gestation days 6 through 15. The Triethylene Glycol doses were 0, 0.5, 5, or 10 ml/kg/day (n = 30 mice per group). The Triethylene Glycol doses were of neat undiluted Triethylene Glycol, calculated based on most recent body weight measurements, and the negative control dose was 10 ml/kg/day deionized water. Feed and water consumption as well as body weights and clinical observations were recorded throughout the study. Dams were killed on gestation day 18. At this time uteri containing fetuses were removed for evaluation, and the dams underwent gross necropsy and microscopic evaluation of certain tissues. Measures of pregnancy outcome were evaluated. Live fetuses were counted, sexed, and weighed before being fixed and stained for evaluations of visceral and skeletal morphology. Half of the live fetuses were examined by serial sections for soft-tissue craniofacial malformations. There were no treatment-related maternal deaths, and no dams aborted. Maternal body weights and body weight gains were similar between all dose groups. There were no affects of treatment on feed or water consumption.

Maternal toxicity observed in the 10 ml/kg/day group included hyperactivity with audible and rapid respiration. Necropsy revealed no differences between the treated and control groups, except that relative (but not absolute) kidney weights were increased in the high dose group. Pregnancy outcomes (number of corpora lutea, viable and non-viable implantations, and sex ratio) were not affected by Triethylene Glycol treatment. The sum of fetal body weights per litter were significantly decreased in the 5 and 10 ml/kg/day groups. There were no treatment related malformations noted in the external or visceral examinations.

The lowest observable effect level for skeletal abnormalities seen at gestation day 18 (cervical centra #1, #2, #3, or #4 poorly ossified; reduced number of caudal segments; unossifed proximal phlalanges of hindlimb; and poorly ossified proximal phlalanges of hindlimb) was 10 ml/kg/day and for poorly ossified frontal and supraoccipital bones was 5 ml/kg/day.

The authors concluded that Triethylene Glycol exposure during organogenesis resulted in evidence of slight maternal toxicity at 10 ml/kg/day and consistent evidence of developmental delay at 5 and 10 ml/kg/day (Union Carbide 1990d).

Union Carbide (1991) dosed pregnant Sprague-Dawley rats with Triethylene Glycol by oral gavage on gestation days 6 through 15. The doses were 0, 1, 5, or 10 ml/kg/day (n = 55 rats per group). The Triethylene Glycol doses were of neat undiluted Triethylene Glycol, calculated based on most recent body weight measurements, and the negative control dose was 10 ml/kg/day deionized water. Feed and water consumption as well as body weights and clinical observations were recorded throughout the study. Dams were killed on gestation day 21. At this time uteri containing fetuses were removed for evaluation, and the dams underwent gross necropsy and microscopic evaluation of certain tissues. Measures of pregnancy outcome were evaluated. Live fetuses were counted, sexed, and weighed before being fixed and stained for evaluations of visceral and skeletal morphology. Half of the live fetuses were examined by serial sections for soft-tissue craniofacial malformations.

There were no maternal deaths and no aborted pregnancies. In the 10 ml/kg/day group maternal body weights were decreased on gestation days 9 through 18, feed consumption was decreased on gestation days 6 through 15, and water consumption was increased on gestation days 6 through 18. Clinical observations in the 10 mg/kg/day group included audible respiration, urine stains, periocular encrustation, and perioral wetness. Dams in the 5 ml/kg/day group had decreased body weights on gestation day 18, decreased feed consumption on gestation days 6 through 9, and increased water consumption on gestation days 6-15. Animals treated with 1 ml/kg/day had no observations different from controls. At necropsy maternal body weights (adjusted for gravid uterine weight) were decreased and relative (but not absolute) kidney weights were increased in the high-dose group compared to controls. There were no treatment-related effects on pregnancy outcome with the exception of a decrease in the sum of fetal body weights per litter in the 10 ml/kg/day. There were no significant increases in the incidence of external, visceral or skeletal malformations. There was an increase in the incidence of one skeletal variation (bilobed thoracic centrum # 10) in the high-dose group. While there was some evidence of maternal toxicity, no biologically significant embryotoxiciy or teratogenicity was observed at the doses administered in this study (Union Carbide 1991).

PEG-6, PEG-32, and PEG-75

Smyth et al. (1947) investigated the reproductive toxicity of PEG-6, PEG-32 and PEG-75 during the 2-year oral toxicity studies (described earlier in this report). The animals at each dose (0.015, 0.059, 0.27, and 1.69 g/kg/day PEG-6, PEG-32; and 0.00085, 0.0036, 0.017, and 0.062 g/kg/day PEG-75) were allowed to breed during the study and records were kept of the F_1 and F_2 generations. No changes or adverse responses to either compound occurred in the three generations.

In the 90-day oral toxicity study conducted by Smyth et al. (1942) described earlier, the authors reported that rats drinking dosages of 0.23 g/kg/day or more of PEG-75 had testicular tubule degeneration and scant or degenerated sperm. They noted that although none of their control rats had these conditions, historical control rats have had such changes.

GENOTOXICITY

Triethylene Glycol

Union Carbide (1986b) evaluated Triethylene Glycol in a bacterial mutagenicity assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. Triethylene Glycol at concentrations of 1 to 112.6 mg/plate was not mutagenic in any of the strains tested with or without the presence of S9 microsomal activation.

Triethylene Glycol at doses of up to 50 mg/ml tested negative for genotoxicity in the Chinese Hamster Ovary Mutation (Union Carbide, 1986c) and Sister Chromatid Exchange (Union Carbide 1986d) assays in CHO cells.

PEG-4

Mortelmans et al. (1986) reported that PEG-4 (concentrations up to 10000 μg/plate) was negative for mutagenicity in *Salmonella typhimurium* strains TA100, TA 1535, TA 1537, and TA 98 with and without S9 rat or hamster liver microsome activation.

Union Carbide Corp. (1988) used an *in vivo* bone marrow chromosome aberration assay was used to evaluate the clastogenic (chromosome breaking) potential of PEG-4. Sprague-Dawley rats received a single 10 ml/kg oral dose of 0, 1250, 2500, or 5000 mg/kg PEG-4 (n = 5/sex/group) diluted in water. The dose levels were selected based on a preliminary test in which PEG-4 was non-toxic up to 5000 mg/kg. A positive control group received an i.p. injection of 30 mg/kg cyclophosphamide to demonstrate the responsiveness of the animals to a recognized clastogenic agent. Animals were killed at 12, 24, or 48 hours after dosing. Bone marrow tissue from the femur of each rat was isolated and prepared for staining of the chromosomes of mitotic cells on slides. Cells were evaluated for chromosome number, specific type of chromosome- or chromatid-type aberrations, and further classified for deletions and exchanges.

None of the three dose levels of PEG-4 tested produced statistically significant or dose-related increases in relative numbers of chromosome aberrations compared to negative control values. Simple chromatid breaks and fragments were observed, but the frequencies were within the range of spontaneous incidence for the test system. The positive control (cyclophosphamide) group exhibited significant increases in the numbers and types of chromosomal damage in both male and female rats, demonstrating the effectiveness of the test system in detecting clastogenic agents (Union Carbide Corp. 1988).

Union Carbide Corp. (1994) exposed male Fischer 344 rats (n = 20 rats per group) to 0, 5000, 25,000, or 50,000 ppm PEG-4 in drinking water for five consecutive days in a dominant lethal assay. The respective daily consumption levels of the three doses of PEG-4 were 425 ± 45, 2441 ± 328, and 5699 ± 1341 mg/kg. At the end of the five-day dosing period, the PEG-4 drinking water was replaced with regular water. Beginning 24 hours after the last PEG-4 exposure, the males were mated with two naive (nontreated) virgin females. When those females showed evidence of copulation, they were replaced with two more females, until each male had mated with ten females or until ten weeks had passed. At the end of the tenth week after PEG-4 exposure, males were killed for necropsy (observations of male toxicity are described in the Short-Term Toxicity section earlier in this report). The females were

observed and killed on gestation day 15, at which time corpora lutea and implantation sites (resorptions and live embryos) were counted.

Reproductive parameters, including number of fertile males and number of gravid females with viable implants, were not affected by PEG-4 treatment. There were no significant preimplantation losses or dominant lethal effects observed. A concurrent positive control group of males receiving an i.p. injection of 0.5 mg/kg triethylenemelamine (TEM) were bred with naive females in a similar manner described above. The TEM group showed increased pre- and postimplantation loss, increased early resorptions, and significant dominant lethal effects, verifying the validity of the test system (Union Carbide Corp. 1994).

PEG-8

CHO cells were incubated with PEG-8 at concentrations ranging from 1.0 to 0.0625% (by volume) for 5 h without metabolic activation, or for 2 h using S9 metabolic activation. EMS was used as a positive control. In the absence of metabolic activation, no statistically significant increases occurred in the SCE frequency at any of the doses of PEG-8. In the presence of a metabolic activation system, the only SCE value that was statistically significant from the solvent control group occurred at the 0.5% dose level. However, there was no indication of a correlation between dose and SCE induction (Bushy Run Research Center 1980).

Rat hepatocytes were treated with PEG-8 in DMSO at concentrations ranging from 0.0001% to 0.1% (by volume) for 2 h in a culture medium containing [^{3}H]thymidine and hydroxyurea. UDS activity was determined by analyzing radioactive incorporation into isolated hepatocyte nuclei or in precipitated DNA. The positive controls used were DMN and 4-nitroquinoline oxide. While there was a trend to elevated levels of UDS measured in the nuclei and DNA of the hepatocytes, the only statistically significant increase in radioactive thymidine incorporation was measured in the precipitated DNA of the cells treated with the highest concentration. No dose-response relationship was apparent in the precipitated DNA measurement and there was no significant elevation of UDS levels measured in the nuclei (Bushy Run Research Center 1980).

PEG-150

PEG-150 was tested in the mouse lymphoma TK+/-+TK-/- forward mutation assay without metabolic activation at concentrations of 50.1, 75.2, 100.0, 125.0, and 150.0 μm/l. The mutation frequencies (mutants/10^6 surviving cells) at these concentrations were 46, 65, 61, 60, and 126, respectively. Two control cultures had mutation frequencies of 51 and 60. The mutation index (mutation frequency of treated culture/average mutation frequency of control cultures) ranged from 0.8 to 2.3 (Wangenheim and Bolcsfoldi 1988).

CARCINOGENICITY

PEG-8

The following carcinogenicity data on PEG-8 were obtained from experiments testing the carcinogenicity of other materials, in which PEG-8 was used as a solvent control. Twenty Swiss male mice fed 0.30 ml PEG-8 weekly for 30 weeks did not have tumors (Berenblum and Haran 1955).

PEG-8 (0.05 ml) was injected into the ventral wall of the gastric antrum of 12 guinea pigs. The animals were killed for necropsy after 8 months. No gastric lesions were found (Zaldivar 1963).

Male CB stock rats were injected intraperitoneally with 0.25 ml PEG-8 once a week for 6 months. Among the 24 animals, one case of hepatoma was reported (Boyland et al. 1968).

Twenty Chester Beatty Stock mice were given weekly subcutaneous injections of PEG-8 (0.2 ml) for 1 year. No neoplasms developed in these animals (Roe et al. 1966).

Subcutaneous injections of PEG-8 (0.25 ml) were administered weekly to 20 male and 20 female Sprague-Dawley rats for 20 weeks. The mice were killed for necropsy after 106 weeks. No sarcomas or fibromas developed in the subcutaneous tissues. Mammary fibroadenomas and carcinomas were observed. However, the incidence of these neoplasms did not differ significantly from that of the untreated control rats (Carter 1969).

TUMOR GROWTH INHIBITION

PEG-75

Hartveit (1969a) reported that oral administration of PEG-75 significantly decreased subcutaneous tumor growth in female mice. Thirteen mice were injected with Ehrlich's ascites carcinoma and given drinking water containing 20% PEG-75 for 8 days. Control animals were given untreated water after injection. The treated rats had a marked reduction in the inflammatory response around the tumor transplants, and tumor growth was reduced by 84%. These tumors were not infiltrative. Lymph node hypertrophy and splenic atrophy also occurred. Female control animals had inflammatory responses and tumor growth was infiltrative. Since in vitro studies indicated that PEG-75 was not directly toxic to these tumor cells (Hartveit 1967), the author suggested that PEG-75 ". . .upset the immunological balance in host-tumor relationship and that subsequent changes in response may be ultimately responsible for the difference in the subcutaneous growth of the tumor transplants."

In similar studies using male rats, 20% PEG-75 reduced subcutaneous tumor growth by 48% compared to that seen in untreated controls. However, the tumor growth in male mice treated with 10% PEG-75 was not inhibited and was similar to that seen in the control rats (Hartveit 1969a).

PEG-150

lntraperitoneal injection (1 ml) of 10% PEG-75 in physiological saline inhibited the growth of Ehrlich's ascites carcinoma transplants in female mice. The mean tumor diameter was reduced by 15% in short-term studies (9-12 days), and by 30% in studies of greater duration (3-7 weeks) compared to untreated control mice (Hartveit 1969a).

In *vitro* studies of PEG-150 indicated that PEG-150 augmented the generation of antitumor cytotoxicity by MOPC-315 tumor-bearer splenic cells (Mokyr et al. 1982), and potentiated mitogen-induced lymphocyte stimulation (Bessler et al. 1977). PEG-150 also enhanced the murine T-cell proliferative response against autologous non-T stimulator cells (Ponzio 1980).

CLINICAL ASSESSMENT OF SAFETY

Hammer et al. (1989) reported that PEG ingestion induces diarrhea in normal human volunteers.

DERMAL IRRITATION AND SENSITIZATION

PEG-6, PEG-8, PEG-20, PEG-32, PEG-75, and PEG-150

In a Draize test, one of 200 individuals was sensitized to an experimental bar of soap. PEG-6 (3% in petrolatum) was determined to be the component in the soap causing this reaction. Challenges with 1% and 3% PEG-75 and PEG-150 also produced positive results. However, the individual was not sensitive to an open test with 3% PEG-6 (Maibach 1975).

The irritation potential of a formulation containing 3.0% PEG-8 was determined using 10 volunteers. Each of the panelists had two 0.3 ml samples of the formulation applied to their back under an occlusive patch for 23 h, the sites were scored at 24 h, and new patches were applied to the same sites. Applications were made daily for 3 weeks. The 3.0% PEG-8 formulation caused evidence of a moderate potential for mild cumulative irritation. Composite scores for this panel were 208 and 411 out of a maximum possible score of 630, and the average end point day (the day patching was discontinued because of maximum irritation) was 14.90 and 8.80, respectively, for the two samples tested (Hill Top Research, Inc. 1979).

In a number of repeat insult patch tests, PEG-8 did not exhibit a potential for inducing allergic contact dermatitis. These studies, completed on products containing PEG-8, are detailed in Table 7. In general, the following procedures were used: a formulation containing PEG-8 was applied under an occlusive patch to the backs of the panelists for 24 h every Monday, Wednesday, and Friday for 3 weeks. The sites were scored 48 or 72 h after application, and new samples were applied to the same site. After a 3 week non-treatment period, a challenge patch was applied to a previously untreated site for 24 h. The sites were scored 24 and 48 h after the patch removal (CTFA 1980, 1982a, b, c, d, 1983b, c, 1984, 1985b).

Smyth et al. (1942) applied undiluted PEG-6 and PEG-32 and 50% aqueous PEG-75 to the backs of 100 men for 7 days. After 10 days, the patients were reapplied with the PEGs for 2 days. Three cases of irritation occurred during the initial 7 day exposure. The authors attributed these reactions to previous hypersensitivity or to direct irritation of the compound. During the 2 day re-application period, PEG-6 and PEG-32 caused 3 sensitization reactions, and PEG-75 caused four reactions. All reactions were mild.

Smyth et al. (1945) reported that undiluted PEG-6 and PEG-8 caused mild sensitization reactions. Using the same method as above, PEG-6 and PEG-8 were applied to the backs of 23 men. PEG-6 and PEG-8 caused erythema in 9% and 4% of the subjects, respectively.

Later production lots of PEG-8 and PEG-75 were also tested using patch tests and human subjects. No reactions occurred in the 100 male and 100 female subjects tested (Smyth et al. 1950).

Hannuksela et al. (1975) tested 1,556 eczema patients with PEG-8 using the chamber test method. Testing was done throughout the year. PEG-8 was applied for 20-24 h and readings were made 1, 2, and 4-5 days later. Positive reactions occurred in 0.3% of the patients.

When 92 dermatologic patients were tested with PEG-6, 4% had positive reactions. Of 12 sensitized patients, five reacted to PEG-8, and only one reacted to PEG-6, PEG-32 and PEG-150. The author concluded that group sensitization of the PEGs only occurred with polymers of similar molecular weight (Braun 1969).

A human repeat insult patch test with challenge of masque containing 66% PEG-8 was conducted in 54 subjects (44 males and 19 females; 18-65 years of age) (TKL Research, Inc. 2007). During the induction phase, the test material was applied to 1 side of the infrascapular area of the back. The application sites were assessed for erythema, edema and other signs of cutaneous irritation. Following induction, subjects had a 2-week rest period, after which they entered the challenge phase that consisted of one 48-h patch application to the original site and a naive site on the opposite side of the back. Observations at the naive site during challenge and the

patterns of reactivity during the induction period were analyzed for contact allergic response. Under the conditions of this study, there was no evidence of sensitization or significant irritation.

A cytotoxicity study was performed on an Episkinc reconstructed human epidermis model (MTT conversion assay) on a mask containing 66% PEG-8 (Episkin SNC 2007). The negative control in the study was the untreated epidermis, solvent control was 150 μL of water used to dilute the products, and the positive control was 150 μL of an aqueous solution of sodium dodecyl sulfate at a concentration of 20 mg/mL. Based on the the conditions of this study, it was concluded that on a reconstructed human epidermis model, the product was a non-irritant.

A cutaneous study was conducted using a purifying mask (containing 66% PEG-8) following a single dermal application (Peritesco 2007). Fifty female subjects (19 - 67 years of age) participated in the study. No signs of irritation were observed in any of the subjects. The authors concluded that this product was non-irritating.

RENAL TOXICITY

PEG-6, PEG-20, and PEG-75

Sturgill et al. (1982) reported cases of renal tubular necrosis resulting in the death of burn patients treated with topical ointments containing PEGs. Over a 2-year period, 40 patients with burns over 20-70% of their bodies were treated with a PEG-based antimicrobial cream. The active ingredient in the dressing was 0.2% nitrofurazone, and the PEG-base consisted of 63% PEG-6, 5% PEG-20, and 32% PEG-75. Nine patients died from a syndrome of renal failure, metabolic acidosis, and osmolal gaps. The ointment was identified as the toxic agent. PEG and its metabolites were present in the serum of the patients and, at autopsy, six of the patients had extremely swollen kidneys, with hydropic degeneration and necrosis of proximal tubules. Two individuals had oxalate crystals. Such changes were not present in 14 comparable burn patients not treated with the PEG-based ointment. The investigators noted that the renal changes were similar to that seen in ethylene glycol poisoning.

The same syndrome as described in the patients above occurred in three other burn patients who died from renal failure after being treated with the same antimicrobial cream. These patients also had a markedly decreased ratio of ionized calcium to total calcium in their serum. These changes were linked to the presence of PEGs and their metabolites in the circulation (Bruns et al. 1982).

These data formed the basis for the "damaged skin" caveat discussed in the introduction. The nephrotoxicity seen in burn patients presumably resulted because no intact skin barrier remained to prevent the entry of PEGs into the circulation. The question remained about the degree of dermal penetration of PEGs (and concern regarding nephrotoxicity) with less severely damaged skin.

DERMAL PENETRATION OF PEGs

Raabe and Norman (2009) at the Institute for In Vitro Sciences developed an in vitro model of damaged skin representative of the degree of damage that would be seen in the consumer population. Levels of skin damage and disease states from published studies were correlated with increases in transepidermal water loss (TEWL). Increases in TEWL of 3.5 to 6.5 were determined to reflect moderate skin damage.

A clinical study was performed to determine the degree of skin damage (as measured using TEWL) from either sodium lauryl sulfate (SLS) at 1, 5, and 10% or 1, 20 or 30 successive tape-strippings. Tape-stripping produced more reproducible results and more of a defined dose-response. SLS again was compared to tape-stripping in a pilot study of cadaver skin using $^{3}H_2O$ penetration to assess barrier function disruption. The use of 20 successive tape-strips was chosen as indicative of moderate skin damage and clear disruption of barrier function in a reproducible manner.

PEG-4 was selected as the test article because its low molecular weight range (120-210) would maximize dermal penetration and because [^{14} C] PEG-4 was readily available. A rinse-off (surfactant based) and a leave-on (water in oil emulsion) formulation were used as vehicles in which PEG-4 was tested using cadaver skin mounted in flow-through diffusion cells and samples of receptor fluid taken each 1.5 h. For the rinse-off formulation, exposure was 5 min followed by rinsing. For leave-on formulations, the material was left on the skin sample for 24 h. Three cadaver skin donors were used, with two minimum replicate tissues from each donor per group. The integrity of the skin samples was determined using $^{3}H_2O$.

Absorption of PEG-4 from the rinse-off formulation was 0.37 ± 0.22% in intact skin and 2.30 ± 4.21% for skin that had been tape-stripped 20 times. The absorption of PEG-4 from the leave-on formulation was 8.42 ± 1.56% for intact skin and 33.72 ± 20.11% for skin that had been tape-stripped 20 times. Study results are summarized in Table 8. These data were used in a risk assessment for PEG renal toxicity.

RENAL TOXICITY RISK ASSESSMENT

The Personal Care Products Council (2009b) provided a risk assessment for Kidney Effects of PEGs. In addition, the Council (2009c) summarized the data from the Raabe and Norman study above.

The Council stated that the best available oral NOEL for renal toxicity for PEGs is 1.1 g/kg (Hermansky et al. 1995).

Highest Exposure from a Leave-On Product

Of the reported uses of PEGs, the product type potentially applied to the largest body surface at the highest concentration contains 12% PEG-6 in the "body and hand creams, lotions and powders" category. Assuming this is a whole body product (resulting in higher exposure than a hand-only product), the amount of product used per day from Loretz et al. (2005) is 7.63 g (50^{th} percentile body lotion use) or 14.39 g (90^{th} percentile body lotion use).

Using data from the dermal penetration study by Raabe and Norman (2009), the average total absorption of PEG-4 from a leave-on formulation in a) intact and b) damaged skin, with exposure expressed as a percentage of the applied dose using data from all acceptable trials, is a) 8.42% and b) 33.72%, respectively. Resulting exposure from the leave-on product (amount of cosmetic applied ***x*** concentration of PEG-6 ***x*** units conversion factor ***x*** PEG-4 penetration percent ÷ body weight) would be:

- ***50% percentile:***
  Intact skin: 7.63 g/day x 0.12 x 1000 mg/g x 0.0842 ÷ 60 kg = 1.3 mg/kg/day
  Damaged skin: 7.63 g/day x 0.12 x 1000 mg/g x 0.3372 ÷ 60 kg = 5.1 mg/kg/day
- ***90% percentile:***
  Intact skin: 14.39 g/day x 0.12 x 1000 mg/g x 0.0842 ÷ 60 kg = 2.4 mg/kg/day
  Damaged skin: 14.39 g/day x 0.12 x 1000 mg/g x 0.3372 ÷ 60 kg = 9.7 mg/kg/day

Highest Exposure from a Rinse-off Product

Of the reported uses of PEGs, the rinse-off product type with potentially the highest exposure is a shampoo (noncoloring) containing 62% PEG-8. The amount of product used per day from Loretz et al. (2006) is 10.75 g (50 th percentile shampoo use) or 23.63 (90th percentile shampoo use).

The average total absorption of PEG-4 from a rinse-off formulation in a) intact and b) damaged skin was a) 0.37% and b) 2.30%, respectively (Raabe and Norman 2009),. Resulting exposure from the rinse-off product would be:

- ***50% percentile:***
  Intact skin: 10.75 g/day x 0.62 x 1000 mg/g x 0.0037 ÷ 60 kg = 0.41 mg/kg/day
  Damaged skin: 10.75 g/day x 0.62 x 1000 mg/g x 0.023 ÷ 60 kg = 2.6 mg/kg/day
- ***90% percentile:***
  Intact skin: 23.63 g/day x 0.62 x 1000 mg/g x 0.0037 ÷ 60 kg = 0.90 mg/kg/day
  Damaged skin: 23.63 g/day x 0.62 x 1000 mg/g x 0.023 ÷ 60 kg = 5.4 mg/kg/day

The Council noted that these calculations overestimate exposure because 1) PEG-4 was used in the dermal penetration studies but PEG-6 and PEG-8 were used in the reported products; due to their larger size, penetration of PEG-6 and PEG-8 is likely to be lower than PEG-4; and 2) for damaged skin, 100% of exposed skin is assumed to be damaged.

Comparison of Exposure to NOEL (Margin of Safety)

Leave-on, 50th percentile:

Assuming PEG-6 is 100% metabolized to ethylene glycol, comparison of the highest exposure product in intact (1.3 mg/kg/day) and damaged (5.1 mg/kg/day) skin to the NOEL for kidney toxicity (1.1 g/kg/day) results is Margins of Safety of 846 and 216, respectively.

Leave-on, 90th percentile:

Assuming PEG-6 is 100% metabolized to ethylene glycol, comparison of the highest exposure product in intact (2.4 mg/kg/day) and damaged (9.7 mg/kg/day) skin to the NOEL for kidney toxicity (1.1 g/kg/day) results is Margins of Safety of 458 and 113, respectively.

Rinse-off, 50th percentile:

Assuming PEG-8 is 100% metabolized to ethylene glycol, comparison of the highest exposure product in intact (0.41 mg/kg/day) and damaged (2.6 mg/kg/day) skin to the NOEL for kidney toxicity (1.1 g/kg/day) results is Margins of Safety of 2,683 and 423, respectively.

Rinse-off, 90th percentile:

Assuming PEG-8 is 100% metabolized to ethylene glycol, comparison of the highest exposure product in intact (0.90 mg/kg/day) and damaged (5.4 mg/kg/day) skin to the NOEL for kidney toxicity (1.1 g/kg/day) results is Margins of Safety of 1,222 and 204, respectively.

The Council noted that these calculations underestimate the MOS because 1) it is assumed that 100% of PEG is metabolized to ethylene glycol; and 2) exposure is overestimated.

CASE REPORTS

PEG-6, PEG-8, PEG-20, and PEG-75

A commercial solution for treatment of tinea infection of the toe webs containing PEG-8 as a solvent caused immediate urticaria in a 50-year-old man. A similar product also containing PEG-8 also caused the same symptoms. The two solutions and PEG-8 caused contact urticaria within 15 min when tested for immediate reactions on the patient's forearms. Five control subjects treated with PEG-8 did not have this reaction. The irritation was not a result of delayed type hypersensitivity, since patch test results after 48 h for both products and PEG-8 were negative (Fisher 1977).

Two cases of delayed allergic eczematous contact dermatitis caused by PEGs used in a soluble dressing to treat patients with second-degree burns was reported (Fisher 1978). The dressing contained the active ingredient nitrofurazone in a base composed of PEGs -6, -20, and -75. In one case, a woman treating burns on her leg suffered from erythema and edema 48 h after application. After a patch test, she had strong reactions to the dressing, PEG-6, and PEG-8. No reactions occurred in six control patients. PEG-20 and PEG-75 were negative for sensitization in patch tests. In another case, a man receiving treatment for burns on his chest suffered severe, edematous, vesicular, and crusted contact dermatitis on his burns. Patch tests of the dressing, PEG-6, and PEG-8 were strongly positive. PEG-20 and PEG-75 did not cause any reactions.

Another case of immediate urticarial reaction was linked to PEG-6 in an ear medication. Patch tests of the medication and PEG-6 were negative, but when they were tested for immediate reactions on this patient's forearms urticarial reaction occurred within 20 min. Five control patients did not have this reaction (Fisher 1978).

SUMMARY

Polyethylene Glycols (PEGs) are condensation polymers of ethylene oxide that perform a wide variety of functions in cosmetics depending on molecular weight. Ingredients in this safety assessment include: Triethylene Glycol and Polyethylene Glycols (PEGs) -4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEG $\geq$ 4 that may become a cosmetic ingredient in the future.

The physical and biological properties of the individual PEGs are dependent on their molecular weight. PEGs may also contain trace amounts of 1,4-dioxane, a by-product of ethoxylation and small quantities of ethylene oxide.

In metabolism studies with rats, rabbits, dogs, and humans, the lower molecular weight PEGs were absorbed by the digestive tract and excreted in the urine and feces. The greater molecular weight PEGs were absorbed more slowly or not at all. For example, PEG-8 is rapidly absorbed by the GI tracts of several mammalian species and excreted primarily in the urine with less excretion in the feces and PEG-150 in water was not absorbed from the gastrointestinal tract of humans.

PEGs are used in the pharmaceutical industry as vehicles for drugs and as ointment bases.

The following are reported to be in use to the FDA's VCRP or reported in an industry survey of use concentrations: Triethylene Glycol and PEGs -4, -6, -8, -9, -10, -12, -14, -20, -32, -40, -75, -90, -150, -180, -220, -240, -350, -400, -450, -2M, -5M, -7M, -14M, -23M, -45M, -90M, and -180M, with the highest reported use (299) in PEG-8 at concentrations up to 85%.

Several studies reported effects of minimal toxicological significance, including crenation and clumping of rabbit erythrocytes. In a study of PEGs radioprotection, low molecular weight were effective, while PEG-20 and above were not. In a study of the biochemical effects of a series of commonly used drug carrier vehicles, PEG-6 was bioactive in its own right, increasing urine concentrations of dicarboxylic acids, creatinine, taurine, and sugars.

In general, PEGs had low acute oral toxicity. The higher-molecular-weight PEGs appeared to be less toxic than the lower PEGs in oral studies. Oral LD_{50} values in rodents ranged from 15 to 22 g/kg, and the intravenous LD_{50} in rodents ranged from 7.3 to 9.5 g/kg. The LC_{50} of aerosolized Triethylene Glycol in rats was greater than 3.9 mg/L.

PEG-8 administered for 13 weeks of gavage treatment in Fischer 344 rats at doses of 1.1, 2.8 and 5.6 g/kg/day for resulted in no mortality or changes in hematology or clinical chemistry measurements attributed to PEG-8 toxicity.

Dermal exposure to PEGs was not irritating in rabbits in several studies. Overall, PEGs were not irritating to the skin of rabbits and guinea pigs. PEG-75 was not a sensitizer in guinea pigs.

Ocular exposure to Triethylene Glycol in rabbits produced no corneal injury, however all rabbits displayed acute iritis and minor transient conjunctival irritation. Overall, PEGs cause mild, transient ocular irritation in rabbits.

Inhalation of aerosolized PEG-75 at concentrations up to 1008 mg/m^3 caused little or no toxicity in rats.

In reproductive and developmental toxicity studies in rats and mice, PEGs did not produce biologically significant embryotoxicity or teratogenicity.

PEGs were not mutagenic or genotoxic in the Ames assay, a Chinese Hamster ovary cell mutation assay, an *in vivo* bone marrow assay, a dominant lethal assay, the mouse TK+/-+TK-/- forward mutation assay, or a sister chromosome exchange assay. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to various test animals.

In clinical studies, PEG-6 and PEG-8 caused mild cases of immediate hypersensitivity. Extensive clinical studies of patients with normal skin demonstrate that PEG-8 was not a sensitizer and one large study in patients with eczematous skin, only 0.3% positive reactions were seen to PEG-8. Cases of delayed allergic contact dermatitis have been reported in burn patients treated with antimicrobial creams with a PEG vehicle.

Use of antimicrobial creams with a PEG vehicle have been associated with renal toxicity when applied to burned skin. Measured values for dermal penetration of PEG-4 as a function of number of tape strippings demonstrated that tape stripping can increase dermal penetration. Exposure estimates that combined type and use quantity of cosmetic product, concentration of PEGs, and dermal penetration were used to determine exposures to skin in which tape stripping had removed the stratum corneum. These exposures were used with the renal toxicity NOEL to develop a margin of safety calculation, with values ranging from 113 to over 2,600.

DISCUSSION

The available acute, short-term, and chronic toxicity data support the safety of PEGs at the concentrations used in cosmetic products. Likewise, these ingredients are not genotoxic or carcinogenic, nor are they reproductive or developmental toxicants. While there is some suggestion of minor ocular irritation, these ingredients are not dermal irritants or sensitizers in individuals with normal skin. While there are case reports of allergic contact dermatitis in burn patients treated with an antimicrobial agent in a PEG vehicle, there also one clinical study of over 1,500 patients with eczematous skin in which positive reactions were seen in less than one-third of one percent of individuals, suggesting that sensitization is not a significant concern for individuals with damaged skin.

The CIR Expert Panel has further considered one issue of concern --- that PEGs use on severely damaged skin, as in burned skin, can be associated with renal toxicity. Clearly, the available data demonstrate an absence of renal toxicity when PEGs are applied to normal skin. The Panel then considered the newly available dermal penetration data for normal skin and for skin in which the stratum corneum substantially has been removed. These data demonstrated that the dermal penetration of lower molecular weight PEGs is increased when the stratum corneum barrier is removed. The question the Panel then addressed was the significance of that finding. Using assumptions that would maximize the risk (e.g., whole body use of a hand lotion containing 12% PEG-6), a margin of safety of over 100 was maintained between the renal toxicity no observable effect level (the level at which no adverse effects are seen) and the exposure that could result from use of leave-on cosmetics. Even higher margins of safety were found for rinse-off cosmetics, suggesting no reason for concern for PEGs use in rinse-off products in the current practices of use and concentration.

The CIR Expert Panel further reasoned that the almost total removal of the stratum corneum was not unlike the damaged skin seen in certain skin diseases such as atopic dermatitis. Were a user to have such a condition and use a cosmetic product containing PEGs (e.g. the hand lotion containing 12% PEGs noted above), even at the 90th percentile of use quantities, the Panel was reassured that there is a large margin of safety between exposure to PEGs from use of leave-on cosmetics and any concern about adverse effects.

The Panel did note that, were the stratum corneum and the epidermis both absent (as in partial and full thickness burns), then penetration of PEGs into the dermis is likely, leading to systemic exposure and possible renal toxicity as seen with burn patients. The Expert Panel strongly asserted that it is inappropriate to apply cosmetic products containing high concentrations of PEGs to individuals exhibiting barrier skin disruption through both the stratum corneum and the epidermis, or greater.

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

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration and the duration of the exposure and their site of deposition within the respiratory system. In practice, aerosols should have at least 99% of their particle diameters in the 10 – 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm. Particles with an aerodynamic diameter of $\leq$ 10μm are respirable. In addition to inhalation toxicity data, the panel determined that PEGs can be used safely in hair sprays, because the product particle size is not respirable.

The CIR Expert Panel also acknowledged that the "damaged skin" caveat from the original safety assessment of PEGs was carried over to safety assessments of PEGs and PEG esters in which it appeared in either the discussion or the conclusion, including:

- PEG-2, -3, -5, -10, -15, and -20 Cocamine;
- PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate and PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate;
- PEG-2, -3, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150 and -175 Distearate;
- PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate;
- PEG-5, -10, -24, -25, -35, -55, -100, and -150 Lanolin; PEG-5, -10, -20, -24, -30, and -70 Hydrogenated Lanolin; PEG-75 Lanolin Oil; and PEG-75 Lanolin Wax;
- PEG-10 Propylene Glycol; PEG-8 Propylene Glycol Cocoate; PEG-55 PropyleneGlycol Oleate; and PEG-25, -75, and -120 Propylene Glycol Stearate;

- PEG-20 Sorbitan Cocoate, PEG-40 Sorbitan Diisostearate, PEG-2, -5, -20 Sorbitan Isostearate, PEG-40 and -75 Sorbitan Lanolate, PEG-10, -40, -44, -75, and -80 Sorbitan Laurate, PEG-3 and -6 Sorbitan Oleate, PEG-80 Sorbitan Palmitate, PEG-40 Sorbitan Perisostearate, PEG-40 Sorbitan Peroleate, PEG-3, -6, -40, and -60 Sorbitan Stearate, PEG-20, -30, -40, and -60 Sorbitan Tetraoleate, PEG-60 Sorbitan Tetrastearate, PEG-20 and -160 Sorbitan Triisostearate, PEG-18 Sorbitan Trioleate, PEG-40 and -50 Sorbitan Hexaoleate, PEG-30 Sorbitol Tetraoleate Laurate, and PEG-60 Sorbitol Tetrastearate;
- PEG-5, -10, -16, -25, -30, and -40 Soy Sterol; and
- PEG-6, -8, and -20 Sorbitan Beeswax

Accordingly, conforming changes in each of these safety assessments are made to remove the "damaged skin" caveat from each of them.

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concluded that Triethylene Glycol and Polyethylene Glycols (PEGs))-4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEG $\geq$ 4 are safe in the present practices of use and concentration.[1]

[1]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 the group. This conclusion effectively amends the safety assessments of PEG derivatives and removes the caveat regarding use on damaged skin for those ingredients as listed in the discussion.

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Table 1. CAS numbers, cosmetic ingredient definitions and functions, and technical/other names as given in the International Cosmetic Ingredient Dictionary and Handbook (Gottschalck and Bailey 2008) for Triethylene Glycol (1a) and Polyethylene Glycols (1b)

Table 1a

Ingredient	CAS No.	Definition - aliphatic alcohol[a]	Function	Technical/Other Names
Triethylene Glycol	112-27-6	n equals 3	fragrance ingredient; viscosity decreasing agent	2,2'-[1,2-ethanediylbis(oxy)] bisethanol ethanol, 2,2'-[1,2-ethanediylbis(oxy)] bis

Table 1b

Ingredient		Polymers of ethylene oxide where n has an average value[a]	Function	Technical/Other Names[c]
PEG-4	112-60-7	average value of 4	humectant; solvent	2,2'-[oxybis(2,1-ethanediyloxy)] bisethanol ethanol, 2,2'-[oxybis(2,1-ethanediyloxy)] bis polyethylene glycol 200 polyoxyethylene (4) tetraethylene glycol
PEG-6	2615-15-8	average value of 6	humectant; solvent	3,6,9,12,15-pentaoxaheptadecane-1,17-diol polyethylene glycol 300 polyoxyethylene (6) hexaethylene glycol
PEG-7	25322-68-3[b]	average value of 7	humectant; solvent	polyethylene glycol (7) polyoxyethylene (7)
PEG-8	5117-19-1	average value of 8	humectant; solvent	3,6,9,12,15,18,21-heptaoxatricosane-1,23-diol octaethylene glycol polyethylene glycol 400 polyoxyethylene (8)
PEG-9	-[b]	average value of 9	humectant; solvent	3,6,9,12,15,18,21,24-octaoxahexacosane-1,26-diol nonaethylene glycol polyoxyethylene (9)
PEG-10	5579-66-8	average value of 10	humectant; solvent	decaethylene glycol 3,6,9,12,18,21,24-nonaoxahexacosane-1,29-diol polyoxyethylene (10)
PEG-12	6790-09-6	average value of 12	humectant; solvent	dodecaethylene glycol 3,6,9,12,15,18,21,24,27,30,33-undecaoxapentatriacontane-1,35-diol 3,6,9,12,15,18,21,24,27,30,33-undecaoxapentatricontane-1,35-diol polyethylene glycol (12) polyethylene glycol 600
PEG-14	-[b]	average value of 14	humectant; solvent	polyoxyethylene (14) polyethylene glycol (14)
PEG-16	-[b]	average value of 16	humectant; solvent	polyethylene glycol (16) polyoxyethylene (16)
PEG-18	-[b]	average value of 18	humectant; solvent	polyethylene glycol (18) polyoxyethylene (18)
PEG-20	-[b]	average value of 20	humectant; solvent	polyethylene glycol 1000 polyoxyethylene (20)
PEG-32	-[b]	average value of 32	binder; humectant; solvent	polyethylene glycol 1540 polyoxyethylene (32)
PEG-33	-[b]	average value of 33	binder; humectant; solvent	polyoxyethylene (33) polyethylene glycol (33)
PEG-40	-[b]	average value of 40	binder; humectant; solvent	polyethylene glycol 2000 polyoxyethylene (40)
PEG-45	-[b]	average value of 45	binder; humectant; solvent	polyethylene glycol (45) polyoxyethylene (45)
PEG-55	-[b]	average value of 55	binder; humectant; solvent	polyethylene glycol (55) polyoxyethylene (55)
PEG-60	-[b]	average value of 60	binder; humectant; solvent	polyethylene glycol 3000 polyoxyethylene (60)
PEG-75	-[b]	average value of 75	binder; humectant; solvent	polyethylene glycol 4000 polyoxyethylene (75)
PEG-80	-[b]	average value of 80	binder; humectant; solvent	polyethylene glycol 4000

				polyoxyethylene (80) polyethylene glycol (80)
PEG-90	-[b]	average value of 90	binder; humectant; solvent	polyoxyethylene (90) polyethylene glycol (90)
PEG-100	-[b]	average value of 100	binder; humectant; solvent	polyoxyethylene (100) polyethylene glycol (100)
PEG-135	-[b]	average value of 135	binder; humectant; solvent	polyoxyethylene (135) polyethylene glycol (135)
PEG-150	-[b]	average value of 150	binder; humectant; solvent	polyoxyethylene (150) polyethylene glycol 6000
PEG-180	-[b]	average value of 180	binder; humectant; solvent	polyoxyethylene (180) polyethylene glycol (180)
PEG-200	-[b]	average value of 200	binder; humectant; solvent	polyoxyethylene (200) polyethylene glycol 9000
PEG-220	-[b]	average value of 220	binder; humectant; solvent	polyoxyethylene (220) polyethylene glycol (220)
PEG-240	-[b]	average value of 240	binder; humectant; solvent	polyoxyethylene (240) polyethylene glycol (240) polyethylene glycol 11000
PEG-350	-[b]	average value of 350	binder; emulsion stabilizer; solvent	polyoxyethylene (350) polyethylene glycol 20000
PEG-400	-[b]	average value of 400	binder; emulsion stabilizer; solvent	polyoxyethylene (400) polyethylene glycol (400)
PEG-450	-[b]	average value of 450	binder; emulsion stabilizer; solvent	polyoxyethylene (450) polyethylene glycol 20000
PEG-500	-[b]	average value of 500	binder; emulsion stabilizer; solvent	polyoxyethylene (500) polyethylene glycol (500)
PEG-800	-[b]	average value of 800	anticaking agent; binder; humectant; plasticizer; viscosity increasing agent-aqueous	polyoxyethylene (800) polyethylene glycol (800)
PEG-2M	-[b]	average value of 2000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (2000) polyethylene glycol (2000) PEG-2000
PEG-5M	-[b]	average value of 5000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (5000) polyethylene glycol (5000) PEG-5000
PEG-7M	-[b]	average value of 7000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (7000) polyethylene glycol (7000) PEG-7000
PEG-9M	-[b]	average value of 9000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (9000) polyethylene glycol (9000) PEG-9000
PEG-14M	-[b]	average value of 14000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (14000) polyethylene glycol (14000) PEG-14000
PEG-20M	-[b]	average value of 20000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (20000) polyethylene glycol (20000) PEG-20000
PEG-23M	-[b]	average value of 23000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (23000) polyethylene glycol (23000) PEG-23000
PEG-25M	-[b]	average value of 25000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (25000) polyethylene glycol (25000) PEG-25000
PEG-45M	-[b]	average value of 45000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (45000) polyethylene glycol (45000) PEG-45000
PEG-65M	-[b]	average value of 65000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (65000) polyethylene glycol (65000) PEG-65000
PEG-90M	-[b]	average value of 90000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (90000) polyethylene glycol (90000) PEG-90000
PEG-115M	-[b]	average value of 115000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (115000) polyethylene glycol (115000) PEG-115000
PEG-160M	-[b]	average value of 160000	binder; emulsion stabilizer;	polyoxyethylene (160000)

			viscosity increasing agent-aqueous	polyethylene glycol (160000)
PEG-180M	-[b]	average value of 180000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyethylene glycol (180000)

[a] The formula for all PEGs is: $H(OCH_2CH_2)_nOH$. This column gives the value/average value for "n."

[b] The generic CAS No. for PEGs is 25322-68-3.

[c] The *International Nonproprietary Names for Pharmaceutical Substances* for PEGs is macrogol.

Table 2. Ingredient names, molecular weight names as given in the International Cosmetic Ingredient Dictionary and Handbook (Gottschalck and Bailey 2008) and corresponding average molecular weights (Personal Care Products Council 2009).

Ingredient name	Molecular weight name	Calculated average molecular weight ((n x 44) +18)
Triethylene Glycol		150
PEG-4	polyethylene glycol 200	194
PEG-6	polyethylene glycol 300	282
PEG-7		326
PEG-8	polyethylene glycol 400	370
PEG-9		414
PEG-10	polyethylene glycol 500	458
PEG-12	polyethylene glycol 600	546
PEG-14		634
PEG-16		722
PEG-18		810
PEG-20	polyethylene glycol 1000	898
PEG-32	polyethylene glycol 1540	1426
PEG-33		1470
PEG-40	polyethylene glycol 2000	1778
PEG-45		1998
PEG-55		2438
PEG-60	polyethylene glycol 3000	2658
PEG-75		3318
PEG-80	polyethylene glycol 4000	3538
PEG-90		4068
PEG-100		4418
PEG-135		5958
PEG-150	polyethylene glycol 6000	6618
PEG-180	polyethylene glycol 8000	7938
PEG-200	polyethylene glycol 9000	8818
PEG-220		9698
PEG-240	polyethylene glycol 11000	10578
PEG-350	polyethylene glycol 20000	15418
PEG-400		17618
PEG-450	polyethylene glycol 20000	19818
PEG-500		22018
PEG-800		35218
PEG-2M (2000)		88018
PEG-5M (5000)		220018

Ingredient name	Molecular weight name	Calculated average molecular weight ((n x 44) +18)
PEG-7M (7000)		308018
PEG-9M (9000)		396018
PEG-14M (14000)		616018
PEG-20M (20000)		880018
PEG-23M (23000)		1012018
PEG-25M (25000)		1100018
PEG-45M (45000)		1980018
PEG-65M (65000)		2860018
PEG-90M (90000)		3960018
PEG-115M (115000)		5060018
PEG-160M (160000)		7040018
PEG-180M (180000)		7920018

Table 3. Chemical and Physical Properties of PEGs -6, -8, -32, -75, -150, -14M, and -20M (Patty 1963, Sax 1979, FAO 1983, Hunting 1983, Windholz 1983, Silverstein et al. 1984).

Property	PEG-6	PEG-8	PEG-32	PEG-75	PEG-150	PEG-14M	PEG-20M
Physical Description	Colorless, odorless, hygroscopic liquid	Viscous, slightly hygroscopic liquid with a slight odor	Odorless solid	White, free-flowing powder, or creamy white flakes	White, waxy solid, powder, or creamy, white flakes	White powder	Solid
Soluble in:	Water	Water	-	-	Water	Water	-
Molecular Weight	260 - 315	285 - 420	1,300 - 1,600	3,000 - 4,800	6,000 - 9,000	600,000	-
Melting Point	-	-	-	-	58 - 62°C	65°C	-
Flash Point	385 - 415°F	435 - 460°F, 471°F	510°F	515 - 520°F	515 - 520°F	-	-
Freezing Point	-15 to -6°C	4 - 10°C	43 - 46°C	53 - 58°C	56 - 63°C	-	-
Viscosity at 210°F	-	7.3[a]	-	76 – 110[a]	470 – 900[a]	-	-

[a] centistokes

Table 4. Chemical and physical properties of Triethylene Glycol and PEG-4 (Budavari 1989, Union Carbide 1990a, Ashford 1994, NTP 2001a).

Property	Triethylene Glycol (Reference)	PEG-4 (Reference)
Molecular Weight	150.17	190 - 210
Relative Density	1.1274	1.127
Specific Gravity	1.126	1.125
Freezing Point	-4.3 C	
Boiling Point	285 C (283 C @ 760 mmHg)	327 C
Flash Point	330 to 342 F	171.1 to 182.2 C
Refractive Index	1.4578 @ 15 C	1.459 @ 25 C
Viscosity	47.8 cp @ 20 C	4.3 centistrokes @ 210 C
Vapor Pressure	< 0.01 mmHg @ 20 C	low
Vapor Density (air = 1)	5.2	

Table 5. Frequency of use and use concentration for Triethylene Glycol and PEGs -4, -6, -8, -9, -10, -12, -14, -20, -32, -40, -75, -90, -150, -180, -220, -240, -350, -400, -450, -2M, -5M, -7M, -14M, -20M, -23M, -45M, -90M, and -180M as a function of cosmetic product category.

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
	Triethylene Glycol	
Shaving Products		
Aftershave lotions	-	0.2%
Shaving creams	3	-
Skin Care Products		
Cleansers	-	0.0006%
Face and neck creams, lotions, powders and sprays	-	0.03%
Body and hand creams, lotions powders and sprays	-	0.2%
Bath Products		
Oils, tablets and salts	1	-
Bubble baths	1	-
Others	4	-
Noncoloring Hair Products		
Conditioners	1	-
Hair Products (coloring)		
Tints	1	-
Bath Products		
Soaps and detergents	1	-
Personal Hygiene Products		
Others	19	-
Total uses/ranges for Triethylene Glycol	**31**	**0.0006 - 0.2%**
	PEG-4	
Bath products		
Oils, tablets, and salts	-	67%
Soaps and detergents	2	0.2 - 2%
Others	1	-
Eye makeup		
Eye shadows	2	3 - 5%
Eye lotions	-	0.1%
Eye makeup removers	1	0.2 - 2%
Fragrance products		
Others	3	-
Noncoloring hair care products		
Conditioners	6	-
Shampoos	2	5%
Tonics, dressings, etc.	2	-
Wave sets	-	0.5 - 2%
Makeup		
Blushers	-	7
Foundations	3	-
Lipsticks	-	0.3%
Nail care products		
Cuticle softeners	-	20%
Others	-	0.3%
Oral hygiene products		
Dentifrices	-	1 - 8%
Personal hygiene products		
Underarm deodorants	3	20%
Shaving products		
Aftershave lotions	6	1%
Preshave lotions	1	-
Shaving creams	-	0.03 - 17%
Others	2	-
Skin care products		
Cleansers	4	1 - 8%
Face and neck creams, lotions, powders and sprays	1	2 - 3%
Body and hand creams, lotions, powders and sprays	21	3 - 4%
Moisturizers	8	4 - 5%
Night creams, lotions, powders and sprays	1	5%
Skin fresheners	1	5%
Others	2	-
Suntan products		
Suntan gels, creams, liquids and sprays	-	0.01%
Indoor tanning preparations	-	6%
Others	-	2%

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Total uses/ranges for PEG-4	**72**	**0.01 - 67%**
	PEG-6	
Baby products		
Others	1	-
Bath products		
Oils, tablets, and salts		11%
Soaps and detergents	18	0.01 - 23%
Bubble baths	1	
Others	1	1%
Eye makeup		
Eyeliners	-	3%
Mascara	-	0.03%
Eye lotions	1	0.2%
Eye makeup removers	1	-
Others[a]	-	0.2 - 0.6%
Fragrance products		
Colognes and toilet waters	-	2 - 3%
Others	1	-
Nail care products		
Nail creams and lotions	-	1%
Noncoloring hair care products		
Shampoos	-	2%
Conditioners	1	3 - 4%
Hair sprays (aerosol fixatives)	-	0.2%
Tonics, dressings, etc.	1	1 - 51%
Others	1	-
Makeup		
Face powders	-	4%
Foundations	-	0.8 - 2%
Makeup bases	-	3%
Makeup fixatives	2	-
Others	3	-
Shaving products		
Aftershave lotions	1	0.8 - 2%
Shaving creams	-	0.5%
Others[b]	-	5%
Oral hygiene products		
Dentifrices	-	3%
Personal hygiene products		
Underarm deodorants	1	2%
Feminine hygiene products	-	0.2%
Others	2	-
Skin care products		
Cleansers	26	5 - 10%
Face and neck creams, lotions, powders and sprays	20	3 - 45%[j]
Body and hand creams, lotions, powder and sprays	5	2 - 12%
Moisturizers	32	2 - 14%
Night creams, lotions, powders and sprays	1	2%
Paste masks/mud packs	2	6 - 10%
Skin fresheners	1	-
Foot powders and sprays	-	1%
Others	9	-
Suntan products		
Suntan gels, creams, liquids and sprays	5	2%
Indoor tanning preparations	2	-
Others	1	-
Total uses/ranges for PEG-6	**140**	**0.01 - 51%**
	PEG-8	
Baby products		
Baby lotions, oils, powders and creams	-	5%
Others	1	-
Bath products		
Oils, tablets, and salts	1	-
Soaps and detergents	5	2 - 15%
Others	4	30%
Fragrance products		
Colognes and toilet waters	-	2 - 10%
Eye makeup		
Eyebrow pencils	1	-
Eye shadows	2	0.5%
Eye lotions	-	0.1 - 3%

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Eye makeup removers	4	3%
Others	1	1%
Noncoloring hair care products		-
Conditioners	12	3 - 12%
Rinses	-	10%
Shampoos	1	62%
Tonics, dressings, etc.	6	0.0002 - 62%
Others	2	10 - 85%
Makeup		
Blushers	1	-
Face powders	-	8%
Foundations	14	0.03 - 10%
Lipsticks	16	0.1%
Makeup bases	56	-
Others	9	0.1%
Oral hygiene products		
Dentifrices	3	3%
Personal hygiene products		
Underarm deodorants	14	2 - 13%
Others	2	4 - 46%
Shaving products		
Aftershave lotions	4	2 - 5%
Shaving creams	2	-
Others[c]	1	10%
Skin care products		
Cleansers	41	0.5 - 66%
Face and neck creams, lotions, powders and sprays	14	0.002 - 10%[k]
Body and hand creams, lotions, powders and sprays [i]	26	0.3 - 6%[l]
Moisturizers	17	2 - 6%
Depilatories	-	0.9%
Foot powders and sprays	-	20%
Night creams, lotions, powders and sprays	7	0.01 - 6%
Paste masks/mud packs	10	0.003 - 59%
Skin fresheners	5	-
Others[d]	-	0.01 - 46%
Suntan products		1 - 5%
Indoor tanning preparations	1	-
Suntan gels, creams and liquids	-	0.5 - 5%
Others	16	-
Total uses/ranges for PEG-8	**288**	**0.0002 - 85%**

PEG-9

Noncoloring Hair Products		
Conditioners	10	-
Others	-	0.9%
Makeup Products		
Foundations	2	0.04%
Makeup bases	-	0.02%
Total uses/ranges for PEG-9	**12**	**0.02% - 0.9%**

PEG-10

Makeup Products		
Foundations	-	0.2%
Lipsticks	-	0.1%
Suntan Products		
Suntan gels, creams and liquids	-	0.2%
Total uses/ranges for PEG-10	**-**	**0.1 - 0.2%**

PEG-12

Makeup Products		
Mascara		4%
Foundations		8%
Eye Makeup Products		
Eye makeup removers	4	-
Fragrance Products		
Colognes and toilet waters	-	4%
Others	1	-
Noncoloring Hair Products		
Tonics, dressings, etc.	3	4%
Others	1	9 - 56%
Oral Hygiene Products		
Dentifrices	2	
Bath Products		

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Soaps and detergents	12	-
Personal Hygiene Products		
Others	1	-
Skin Care Products		
Face and neck creams, lotions, powders and sprays	1	-
Moisturizers	5	
Foot powders and sprays		30%
Others	1	0.04%
Suntan Products		
Indoor tanning preparations	1	-
Total uses/ranges for PEG-12	**32**	**0.04 - 56%**

PEG-14

Bath Products		
Bubble baths	-	0.3%
Others	-	2%
Fragrance Products		
Perfumes	-	2%
Others	2	-
Eye Makeup Products		
Others	1	-
Noncoloring Hair Products		
Shampoos	1	0.3%
Shaving Products		
Shaving creams	1	-
Bath Products		
Bath oils, tablets and salts	1	-
Skin Care Products	-	-
Cleansers	-	0.3%
Face and neck creams, lotions, powders and sprays	1	-
Body and hand creams, lotions, powders and sprays	-	0.1 - 2%[m]
Moisturizers	1	-
Night creams, lotions, powders and sprays	1	-
Total uses/ranges for PEG-14	**10**	**0.1 - 2%**

PEG-20

Bath products		
Soaps and detergents	-	0.02 - 2%
Eye makeup		
Eyeliners	-	1 - 18%
Eye lotions	-	2%
Eye makeup removers	-	2%
Noncoloring hair care products		
Tonics, dressings, etc.	-	18%
Others	-	27%
Makeup		
Blushers	-	2%
Foundations	-	2%
Makeup bases	-	2%
Personal hygiene products		
Underarm deodorants	-	0.8%
Shaving products		
Aftershave lotions	-	20%
Skin care products		
Face and neck creams, lotions, powders and sprays	-	4 - 8%
Body and hand creams, lotions, powders and sprays	-	2%
Moisturizers	-	5%
Night creams, lotions, powders and sprays	-	3%
Paste masks/mud packs	-	6%
Others[f]	-	0.4 - 8%
Suntan products		
Suntan gels, creams, liquids and sprays	-	3 - 4%
Total uses/ranges for PEG-20	-	**0.02 - 27%**

PEG-32

Baby products		
Shampoos	1	-
Bath products		
Oils, tablets, and salts		11%
Soaps and detergents	4	11%
Bubble baths	1	-
Eye makeup		
Eyeliners	1	-

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Eye lotions	1	1 - 4%
Eye makeup removers	1	2 - 3%
Mascara	2	0.03 - 2%
Fragrance products		
Colognes and toilet waters	-	2%
Others	1	-
Noncoloring hair care products		
Shampoos	-	2%
Hair conditioners	-	3%
Hair sprays (aerosol fixatives)	-	0.2%
Tonics, dressings, etc.	3	2%
Others	1	15%
Makeup		
Face powders	-	4%
Foundations	2	2%
Makeup bases	-	3%
Makeup fixatives	2	-
Others	1	-
Nail care products		
Cuticle softeners	-	2%
Nail creams and lotions	-	1%
Others	1	-
Shaving products		
Aftershave lotions	-	0.8%
Shaving creams	-	0.1%
Others[b]	-	5%
Oral Hygiene products		
Dentifrices	-	2%
Skin care products		
Cleansers	35	0.8 - 11%
Face and neck creams, lotions, powders and sprays	17	0.5 - 12%
Body and hand creams, lotions, powders and sprays	4	2 - 12%
Moisturizers	31	0.5 - 14%
Night creams, lotions, powders and sprays	2	0.5 - 10%
Paste masks/mud packs	4	2 - 6%
Skin fresheners	-	0.5 - 4%
Others	10	0.5 - 1%
Suntan products		
Indoor tanning preparations	1	-
Suntan gels, creams and liquids	-	2%
Others	1	-
Total uses/ranges for PEG-32	**127**	**0.03 - 15%**

PEG-40

Noncoloring hair care products		
Conditioners	1	-
Tonics, dressings, etc.	3	-
Others	21	-
Makeup		
Foundations	-	0.2%
Oral hygiene products		
Dentifrices	-	6%
Mouthwashes and breath freshener sprays	1	-
Shaving products		
Aftershave lotions	1	-
Skin care products		
Cleansers	-	0.001 - 6%
Face and neck creams, lotions, powders and sprays	-	3%
Body and hand creams, lotions, powders and sprays	-	3%
Moisturizers	1	-
Night creams, lotions, powders and sprays	-	0.001 - 3%
Paste masks/mud packs	-	0.001 - 3%
Skin fresheners	-	0.6%
Others	-	0.005%
Total uses/ranges for PEG-40	**28**	**0.001 - 6%**

PEG-75

Bath products		
Oils, tablets, and salts	1	-
Soaps and detergents	-	2 - 5%
Makeup products		
Foundations	-	7%
Eye makeup		

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Eyeliners	4	11%
Mascara	10	-
Others	1	-
Noncoloring hair care products		
Tonics, dressings, etc.	1	2 - 16%
Rinses	-	3%
Others	1	29%
Personal hygiene products		
Underarm deodorants	-	0.5 - 0.8%
Shaving products		
Aftershave lotions	-	6%
Shaving creams	-	3%
Others	1	-
Skin care products		
Cleansers	4	0.5 - 7%
Face and neck creams, lotions, powders and sprays	2	0.4 - 4%
Body and hand creams, lotions, powders and sprays	1	0.2 - 36%
Foot powders and sprays	-	0.5 - 7%
Moisturizers	6	4 - 7%
Night creams, lotions, powders and sprays	1	-
Paste masks/mud packs	8	3%
Skin fresheners	1	-
Other	7	0.4%
Total uses/ranges for PEG-75	**49**	**0.2 - 36%**
	PEG-90	
Bath Products		
Soaps and detergents	6	-
Others	-	0.05%
Noncoloring Hair Products		
Tonics, dressings, etc.	1	0.2%
Others	-	21%
Personal Hygiene Products		
Underarm deodorants	7	-
Shaving Products		
Aftershave lotions	-	0.2%
Skin Care Products		
Face and neck creams, lotions, powders and sprays	5	-
Body and hand creams, lotions, powders and sprays	5	-
Paste masks	1	-
Total uses/ranges for PEG-90	**25**	**0.05 - 21%**
	PEG-150	
Bath products		
Oils, tablets, and salts	9	2 - 5%
Soaps and detergents	-	1%
Bubble baths	-	2%
Capsules	1	-
Others	1	1 - 4%
Eye makeup		
Eye lotions	1	-
Noncoloring hair care products		
Conditioners	2	1%
Hair sprays (aerosol fixatives)	-	0.3%
Rinses	-	0.5%
Tonics, dressings, etc.	3	0.5%
Others	1	-
Makeup		
Makeup bases	1	2%
Foundations	-	0.0009 - 2%
Lipsticks	-	1%
Personal hygiene products		
Underarm deodorants	3	-
Others	2	-
Nail Products		
Nail creams and lotions	-	1%
Skin care products		
Cleansers	-	0.03 - 3%
Face and neck creams, lotions, powders and sprays	5	0.009 - 6%
Body and hand creams, lotions, powders and sprays	1	2%
Foot powders and sprays	1	-
Moisturizers	5	0.009 - 6%
Night creams, lotions, powders and sprays	1	-

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Paste masks/mud packs	1	1%
Skin fresheners	1	-
Others	4	0.009 - 3%
Suntan products		
Suntan gels, creams and liquids	-	2%
Total uses/ranges for PEG-150	**43**	**0.0009 - 6%**
	PEG-180	
Baby Products		
Shampoos	-	2%
Bath Products		
Oils, tablets, and salts	-	4%
Others	-	6
Eye Makeup Products		
Eyeliners	-	4%
Noncoloring Hair Products		
Conditioners	-	0.5 - 3%
Tonics, dressings and other hair grooming aids	-	1%
Others	-	5%
Makeup Products		
Lipsticks	-	4%
Nail Products		
Nail cream and lotions	-	2%
Shaving Products		
Shaving creams	-	0.05%
Skin Care Products		
Cleansers	-	5%
Face and neck creams, lotions, powders and sprays	-	1 - 2%
Skin fresheners	-	0.5%
Total uses/ranges for PEG-180	**-**	**0.05 - 5%**
	PEG-220	
Bath Products		
Others	1	-
Personal Hygiene Products		
Others[g]	-	0.4%
Skin Care Products		
Cleansers	-	0.3%
Total uses/ranges for PEG-220	**-**	**0.3 - 0.4%**
	PEG-240	
Makeup Products		
Face powders	-	10%
Bath Products		
Soaps and detergents	-	5%
Skin Care Products		
Face and neck creams, lotions, powders and sprays	-	4%
Moisturizers	1	
Total uses/ranges for PEG-240	**1**	**4 - 10%**
	PEG-350	
Makeup Products		
Foundations	-	1%
Eye makeup products	-	-
Eye lotions	1	-
Skin Care Products		
Face and neck creams, lotions, powders and sprays	3	1%
Body and hand creams, lotions, powders and sprays	2	1%
Moisturizers	2	-
Night creams, lotions, powders and sprays	1	-
Skin fresheners	1	-
Total uses/ranges for PEG-350	**10**	**1%**
	PEG-400	
Makeup Products		
Foundations	-	1%
Makeup bases	-	3%
Eye Makeup Products		
Eye lotions	3	-
Bath Products		
Soaps and detergents	-	2%
Shaving Products		

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Aftershave lotions	-	3%
Skin Care Products		
Face and neck creams, lotions, powders and sprays	2	3%
Body and hand creams, lotions, powders and sprays	-	3%
Moisturizers	1	2%
Paste masks	-	2%
Suntan Products		
Suntan gels, creams and liquids	-	2%
Total uses/ranges for PEG-400	**6**	**1 - 3%**

PEG-450

Noncoloring Hair Products		
Others	1	-
Skin Care Products		
Face and neck creams, lotions, powders and sprays	-	1%
Body and hand creams, lotions, powders and sprays	2	1%
Moisturizers	2	1%
Total uses/ranges for PEG-450	**5**	**1%**

PEG-2M

Fragrance Products		
Others	1	-
Noncoloring Hair Products		
Conditioners	3	0.5%
Tonics, dressings, etc.	3	-
Skin Care Products		
Others	1	-
Total uses/ranges for PEG-2M	**8**	**0.5%**

PEG-5M

Noncoloring Hair Products		
Conditioners	-	0.01%
Tonics, dressings, etc.	1	0.01%
Skin Care Products		
Cleansers	1	-
Total uses/ranges for PEG-5M	**2**	**0.01%**

PEG-7M

Bath Products		
Oils, Tablets and salts	2	0.5%
Noncoloring Hair Products		
Conditioners	1	-
Shampoos	41	-
Others	-	0.2%
Shaving Products		
Shaving creams	1	0.2 - 0.5%
Shaving soaps	1	-
Skin Care Products		
Moisturizers	1	0.05 - 0.1%
Face and neck creams, lotions, powders and sprays	-	0.1%
Total uses/ranges for PEG-7M	**47**	**0.05 - 0.5%**

PEG-14M

Baby products		
Shampoos	1	0.1%
Lotions, oils, powders, and creams	-	0.05%
Others	5	-
Bath products		
Oils, tablets, and salts	-	0.1%
Soaps and detergents	8	0.05 - 0.5%
Bubble baths	-	0.1%
Others	2	0.1%
Noncoloring hair care products		
Conditioners	6	0.2%
Shampoos	10	0.03%
Tonics, dressings, etc.	3	0.5%
Others	2	-
Hair coloring products		
Shampoos	1	-
Bleaches	1	-
Makeup		
Makeup bases	-	0.2%

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Shaving products		
Shaving creams	6	0.2 - 0.3%
Others[e]	13	0.1%
Skin care products		
Cleansers	13	0.05 - 0.5%
Face and neck creams, lotions, powder and sprays	-	0.05%
Body and hand creams, lotions, powder and sprays	-	0.1%
Skin fresheners	1	-
Others	3	-
Total uses/ranges for PEG-14M	**75**	**0.05 - 0.5%**
	PEG-20M	
Noncoloring hair care products		
Conditioners	-	1%
Makeup		
Face powders	-	3%
Personal hygiene products		
Underarm deodorants	-	0.4%
Skin care products		
Cleansers	-	0.4%
Total uses/ranges for PEG-20M	**-**	**0.4 - 3%**
	PEG-23M	
Eye Makeup Products		
Others	1	-
Noncoloring Hair Products		
Shampoos	1	0.05%
Tonics, dressings, etc.	1	-
Shaving Products		
Others	13	-
Total uses/ranges for PEG-23M	**16**	**0.05%**
	PEG-45M	
Baby Products		
Others	2	
Noncoloring Hair Products		
Conditioners	1	0.03 - 0.3%
Shampoos	2	0.05%
Tonics, dressing, etc.	3	0.1 - 0.3%
Bath Products		
Soaps and detergents	1	0.05 - 0.08%
Personal Hygiene Products		
Others	3	-
Shaving Products		
Shaving creams	1	0.2%
Shaving soaps	1	-
Skin Care Products		
Body and hand creams, lotions, powders and sprays	-	0.1%
Total uses/ranges for PEG-45M	**14**	**0.03 - 0.3%**
PEG-90M		
Noncoloring Hair Products		
Conditioners	4	0.05 - 0.1%
Shampoos	3	0.0002%
Rinses	-	0.08%
Tonics, dressings, etc.	22	0.3 - 1%
Others	19	-
Hair Products (Coloring)		
Hair dyes and colors	-	0.5%
Others[h]	-	0.02 - 0.05%
Makeup Products		
Foundations	-	0.01%
Bath Products		
Soaps and detergents	14	0.05%
Personal Hygiene Products		
Others	-	0.3%
Shaving Products		
Shaving creams	2	0.01 - 0.2%
Shaving soaps	1	2%
Others	24	-
Skin Care Products		
Cleansers	-	0.05%
Face and neck creams, lotions, powders and sprays	3	0.1%

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Moisturizers	2	-
Total uses/ranges for PEG-90M	**94**	**0.0002 - 0.3%**
	PEG-180M	
Noncoloring Hair Products		
Conditioners	-	0.05%
Shampoos	-	0.08%
Total uses/ranges for PEG-180M	**-**	**0.05 - 0.08%**

[a] 0.2% in an eye gel, 0.6% in an eye mask
[b] 5% in a shaving gel
[c] 10% in a shaving gel
[d] 10% in a foot/leg massage gel, 40% in a body peel
[e] 0.1% in a shaving gel
[f] 0.4% in a bronzer
[g] 0.4% in a body scrub
[h] 0.02% in a hair color remover
[i] a prototype body and hand product containing 20% PEG-8 is not currently on the market
[j] includes a face and neck spray at 3%
[k] includes a face and neck spray at 0.002%
[l] includes body and hand sprays in the 1 - 3% range
[m] includes a body and hand spray at 2%

Table 6. Acute Oral LD_{50} values for Triethylene Glycol and PEGs.

Ingredient (concentration)	Species (No.)	LD_{50} (g/kg)	Reference
Triethylene Glycol	Rat	22.06	Smyth et al (1941)
	Guinea pig	14.66	Smyth et al (1941)
	Mouse	18.5	Smyth et al (1941)
	Rat	15 - 22	Budavari (1989)
	Rat	>16 ml/kg	Union Carbide (1990c)
PEG-4 (100%)	Mouse	6.4	Shaeffer and Schellenberg (1984)
	Rat	32.77	Smyth et al. (1941)
PEG-6 (100%)	Albino Wistar rat	31.7	Smyth et al. (1945)
	Rabbit	17.3	Smyth et al. (1950)
PEG-6 (50%)	White rat	45.6	Smyth et al. (1960)
	White rat	38.9	Smyth et al. (1950)
	White rat (10)	31.6	Smyth et al. (1941)
	Albino rabbit	20.7	Smyth et al. (1945)
	Guinea pig (10)	19.6	Smyth et al. (1941)
PEG-8 (100%)	Albino Wistar rat	32.8	Smyth et al. (1945)
PEG-8 (50%)	White rat	43.6	Smyth et al. (1950)
	White rat (10)	37.4	Smyth et al. (1941)
	Albino rabbit	26.8	Smyth et al. (1945)
PEG-32 (50%)	White rat	51.2	Smyth et al. (1950)
	Rat	>16	Bushy Run Research Center (1987)
PEG-75 (100%)	Rabbit	76	Smyth et al. (1950)
PEG-75 (50%)	White rat	>50	Smyth et al. (1950)
	White rat	59	Smyth et al. (1950)
PEG-150 (50%)	White rat	>50	Smyth et al. (1950)
PEG-20M (30%)	Rat	31.6	Mellon Institute of Industrial Research (1956)

Table 7. Results of Human Repeat Insult Patch Tests with Formulas Containing PEG-8.

No. of test subjects	Dose delivery	Results	References
90	Induction patches (0.1 ml of test material) 1 and 2 had 3.0% in formulation, and the rest of the patches contained a 50% aq. dilution of the formulation containing 3%	Based on irritant reactions with the first two patches, the formulation was diluted for the remainder of the patches. Minimal to mild irritation was noted in over 75% of the panelists during induction. Twenty-two of the panelists had a response at the 24 h challenge reading. Some of these individuals also had reactions at the 48 h reading. The most severe reaction was mild erythema.	CTFA 1980
84	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Seventeen individuals had minimal to mild erythema at least once during the induction phase. One panelist had barely perceptible erythema at the 24 h challenge reading. No reactions were observed at 48 h.	CTFA 1982a
84	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Minimal to mild irritation was observed in 25 panelists at least once during induction. Minimal erythema was observed in one panelist during the 24 h challenge reading. No reactions were observed at 48 h.	CTFA 1982b
98	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Three subjects had minimal to mild reactions during the induction phase. No reactions were evoked during the challenge phase.	CTFA 1982c
109	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Four panelists had barely perceptible erythema at least once during induction. No sensitization reactions were observed.	CTFA 1982d
100	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Four panelists had minimal erythema once during induction. None of the panelists had reactions during the challenge phase.	CTFA 1983a
102	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Minimal irritation was observed in 18 panelists during induction. No reactions were evoked during the challenge phase.	CTFA 1983b
106	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Thirty-eight panelists had minimal erythema at least once during the induction phase. Only one case of mild erythema was observed at the 24 h challenge reading. In a follow-up study, this subject showed no signs of sensitization.	CTFA 1984
97	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Twenty subjects had minimal to mild erythema during induction. Five subjects had minimal responses during the challenge phase. Reactivity was not confirmed in three subjects tested in a follow-up study.	CTFA 1985

Table 8. Dermal penetration of PEG-4 in rinse-off and leave-on formulation for intact skin samples and skin samples tape-stripped 20 times. (Raabe and Norman 2009).

Treatment Group	Parameter		Line Purge	Upper stratum corneum	Lower stratum corneum	Epidermis	Dermis	Cumulative in Receptor Fluid (24h)	Tissue Handling Residues	Total Absorption
PEG-4 in rinse-off formulation in intact skin	% [a]	Mean	0.00%	0.06%	0.01%	0.14%	0.09%	0.06%	0.01%	0.37%
		s.d.	0.00%	0.04%	0.01%	0.14%	0.16%	0.03%	0.01%	0.22%
	µg/cm^2	Mean	0.00	0.15	0.03	0.35	0.23	0.14	0.02	0.93
		s.d.	0.01	0.10	0.03	0.35	0.41	0.07	0.02	0.55
PEG-4 in rinse-off formulation in tape-stripped skin	% [a]	Mean	0.00%	ND [b]	ND	0.18%	0.06%	2.03%	0.02%	2.30%
		s.d.	0.00%	ND	ND	0.13%	0.07%	4.26%	0.02%	4.21%
	µg/cm^2	Mean	0.01	ND	ND	0.45	0.16	5.07	0.05	5.74
		s.d.	0.01	ND	ND	0.33	0.17	10.64	0.04	10.52
PEG-4 in leave-on formulation in intact skin	% [a]	Mean	0.04%	3.02%	1.52%	1.80%	0.34%	1.44%	0.26%	8.42%
		s.d.	0.02%	0.96%	0.70%	0.69%	0.26%	0.54%	0.24%	1.56%
	µg/cm^2	Mean	0.10	7.54	3.80	4.51	0.85	3.61	0.64	21.05
		s.d.	0.04	2.39	1.76	1.74	0.65	1.34	0.61	3.89
PEG-4 in leave-on formulation in tape-stripped skin	% [a]	Mean	0.45%	ND	ND	10.68%	1.27%	20.27%	1.06%	33.72%
		s.d.	0.43%	ND	ND	3.90%	0.84%	21.24%	0.42%	20.11%
	µg/cm^2	Mean	1.12	ND	ND	26.70	3.18	50.66	2.65	84.31
		s.d.	1.07	ND	ND	9.75	2.10	53.10	1.05	50.29

[a] % applied dose

[b] not determined

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Final Report on the Safety Assessment of Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate[1]

The oil derived from the seed of the Ricinus communis plant and its primary constituent, Ricinoleic Acid, along with certain of its salts and esters function primarily as skin-conditioning agents, emulsion stabilizers, and surfactants in cosmetics, although other functions are described. Ricinus Communis (Castor) Seed Oil is the naming convention for castor oil used in cosmetics. It is produced by cold pressing the seeds and subsequent clarification of the oil by heat. Castor oil does not contain ricin because ricin does not partition into the oil. Castor oil and Glyceryl Ricinoleate absorb ultraviolet (UV) light, with a maximum absorbance at 270 nm. Castor oil and Hydrogenated Castor Oil reportedly were used in 769 and 202 cosmetic products, respectively, in 2002; fewer uses were reported for the other ingredients in this group. The highest reported use concentration (81%) for castor oil is associated with lipstick. Castor oil is classified by Food and Drug Administration (FDA) as generally recognized as safe and effective for use as a stimulant laxative. The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives established an acceptable daily castor oil intake (for man) of 0 to 0.7 mg/kg body weight. Castor oil is hydrolyzed in the small intestine by pancreatic enzymes, leading to the release of glycerol and Ricinoleic Acid, although 3,6-epoxyoctanedioic acid, 3,6-epoxydecanedioic acid, and 3,6-epoxydodecanedioic acid also appear to be metabolites. Castor oil and Ricinoleic Acid can enhance the transdermal penetration of other chemicals. Although chemically similar to prostaglandin E_1, Ricinoleic Acid did not have the same physiological properties. These ingredients are not acute toxicants, and a National Toxicology Program (NTP) subchronic oral toxicity study using castor oil at concentrations up to 10% in the diet of rats was not toxic. Other subchronic studies of castor oil produced similar findings. Undiluted castor oil produced minimal ocular toxicity in one study, but none in another. Undiluted castor oil was severely irritating to rabbit skin in one study, only slightly irritating in another, mildly irritating to guinea pig and rat skin, but not irritating to miniature swine skin. Ricinoleic Acid was nonirritating in mice and in one rabbit study, but produced well-defined erythema at abraded and intact skin sites in another rabbit study. Zinc Ricinoleate was not a sensitizer in guinea pigs. Neither castor oil nor Sodium Ricinoleate was genotoxic in bacterial or mammalian test systems. Ricinoleic Acid produced no neoplasms or hyperplasia in one mouse study and was not a tumor promoter in another mouse study, but did produce epidermal hyperplasia. Castor oil extract had a strong suppressive effect on S_{180} body tumors and ARS ascites cancer in male Kunming mice. No dose-related reproductive toxicity was found in mice fed up to 10% castor oil for 13 weeks. Female rats injected intramuscularly with castor oil on the first day after estrus had suppressed ovarian folliculogenesis and anti-implantation and abortive effects. Castor oil used as a vehicle control in rats receiving subcutaneous injections had no effect on spermatogenesis. A methanol extract of *Ricinus communis* var. *minor* seeds (ether-soluble fraction) produced anti-implantation, anticonceptive, and estrogenic activity in rats and mice. Clinically, castor oil has been used to stimulate labor. Castor oil is not a significant skin irritant, sensitizer, or photosensitizer in human clinical tests, but patients with occupational dermatoses may have a positive reaction to castor oil or Ricinoleic Acid. The instillation of a castor oil solution into the eyes of nine patients resulted in mild and transient discomfort and minor epithelial changes. In another study involving 100 patients, the instillation of castor oil produced corneal epithelial cell death and continuity breaks in the epithelium. Because castor oil contains Ricinoleic Acid as the primary fatty acid group, the Cosmetic Ingredient Review (CIR) Expert Panel considered the safety test data on the oil broadly applicable to this entire group of cosmetic ingredients. The available data demonstrate few toxic effects. Although animal studies indicate no significant irritant or sensitization potential, positive reactions to Ricinoleic Acid in selected populations with identified dermatoses did suggest that sensitization reactions may be higher in that population. Overall, however, the clinical experience suggests that sensitization reactions are seen infrequently. In the absence of inhalation toxicity data on these ingredients, the Panel determined that these ingredients can be used safely in aerosolized cosmetic products because the particle sizes produced are not respirable. Overall, the CIR Expert Panel concluded that these cosmetic ingredients are safe in the practices of use and concentrations as described in this safety assessment.

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel.

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INTRODUCTION

The safety of the following ingredients in cosmetics is reviewed in this report: Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate. For the sake of brevity, Ricinus Communis (Castor) Seed Oil will be referred to as castor oil.

Glyceryl Ricinoleate and Glyceryl Ricinoleate SE are esters of glycerin and Ricinoleic Acid (component of castor oil). A Cosmetic Ingredient Review (CIR) safety assessment (Elder 1988) of Glyceryl Ricinoleate in cosmetics was published with the conclusion that the available data are insufficient to support the safety of this ingredient as used in cosmetics. The following data were needed for completion of this safety assessment: (1) 28-day chronic dermal toxicity (guinea pigs) and (2) clinical sensitization and photosensitization studies (or an appropriate ultraviolet spectrum instead of the photosensitization data).

Glyceryl Ricinoleate and Glyceryl Ricinoleate SE are included in the present safety assessment in the expectation that the available data on castor oil, Ricinoleic Acid, salts of Ricinoleic Acid, and other esters of Ricinoleic Acid will contribute to a resolution of the CIR Expert Panel's data needs for Glyceryl Ricinoleate and Glyceryl Ricinoleate SE.

CHEMISTRY

Definition and Structure

Ricinus Communis (Castor) Seed Oil

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Ricinus Communis (Castor) Seed Oil (CAS no. 8001-79-4) is defined as the fixed oil that is obtained from the seeds of *Ricinus communis*. Other names for this oil include: Castor Oil, Castor Oil (Ricinus communis L.), Castor Seed Oil, Ricinus Communis, and Ricinus Communis Oil (Gottschalck and McEwen 2004), and Ricinus Oil (TNO BIBRA International Ltd. 1999). As given by TNO BIBRA International Ltd. (1999), the structural formula is:

where R represents a fatty acyl group [$CH_3(CH_2)_5CH(OH)CH_2CH{=}CH(CH_2)_7COOH$] that is typically derived from Ricinoleic Acid. Ricinoleic Acid accounts for 87% to 90% of the fatty acyl groups, and the following other fatty acids comprise the remaining fatty acyl groups: oleic acid (2% to 7%), linoleic acid (3% to 5%), palmitic acid (1% to 2%), stearic acid (1%), dihydrostearic acid (1%), and trace amounts of other fatty acyl groups (not specified) (TNO BIBRA International Ltd. 1999).

According to other sources, Castor Oil contains 2.4% lauric acid (Larsen et al. 2001), 2% to 5% linoleic acid (Maier et al. 1999), and globulin, cholesterol, lipase, vitamin E, and β-sitosterol (Scarpa and Guerci 1982).

Hydrogenated Castor Oil

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Hydrogenated Castor Oil (CAS no. 8001-78-3) is defined as the end product of controlled hydrogenation of Ricinus Communis (Castor) Seed Oil. Castor Oil, Hydrogenated is another technical name for this ingredient, and Castor Wax (trade name) and Montane 481 (trade name mixture) are other names under which Hydrogenated Castor Oil is marketed (Gottschalck and McEwen 2004).

Ricinoleic Acid, Its Salts, and Simple Esters

Table 1 includes the structures, definitions, and cosmetic ingredient functions of Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate.

Chemical and Physical Properties

Properties of castor oil and Hydrogenated Castor Oil are summarized in Table 2 and properties of the following ingredients are summarized in Table 3: Ricinoleic Acid, Ethyl Ricinoleate, Methyl Ricinoleate, Sodium Ricinoleate, Potassium Ricinoleate, and Zinc Ricinoleate.

Composition/Impurities

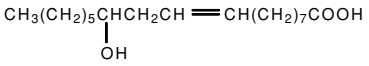
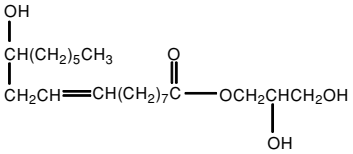
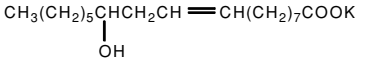
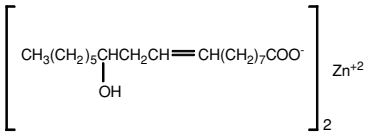
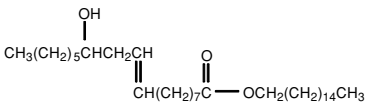
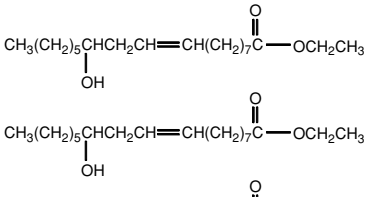
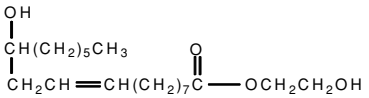
Castor Oil

The following three peaks were observed in a gas-liquid chromatogram on castor oil: palmitic acid (1.7%), C18 acids (stearic, oleic, and linoleic acids) (15.9%), and Ricinoleic Acid (82.4%) (Kato and Yamaura 1970).

According to the *Food Chemicals Codex* (National Academy of Sciences 1996), the requirements for castor oil are as follows: free fatty acids (passes test), heavy metals, as Pb (not more than 10 mg/kg), hydroxyl value (between 160 and 168), iodine value (between 83 and 88), saponification value (between 176 and 185), and specific gravity (between 0.952 and 0.966). The test for free fatty acids is described as follows: free fatty acids (10 g) are dissolved in 50 ml of a mixture of equal volumes of alcohol and ether (which has been neutralized to phenolphthalein with not more than 7 ml of 0.1 N sodium hydroxide). Phenolphthalein (1 ml) is added, followed by titration with 0.1 N sodium hydroxide until the solution remains pink (after shaking).

Similarly, the United States Pharmacopeia (Committee of Revision of the United States Pharmacopeial Convention 2004a)

TABLE 1
Structures, definitions, and functions of ricinoleic acid, its salts, and esters (Gottschalck and McEwen 2004)

Structure	Definition	Function
	**Ricinoleic Acid** (CAS nos. 141-22-0 and 7431-95-0) is an unsaturated fatty acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid; 9-Octadecenoic Acid, 12-Hydroxy-; Ricinic Acid; and Ricinolic Acid	Surfactant–cleansing agent
	**Glyceryl Ricinoleate** (CAS nos.141-08-2, 1323-38-2, and 5086-52-2) is the monoester of glycerin and ricinoleic acid. Other names include: Glycerin Monoricinoleate; Glycerol Monoricinoleate; Glyceryl Monoricinoleate, 12-Hydroxy-9-Octadecenoic Acid, Monoester with 1,2,3-Propanediol; Ricinoleic Acid Monoglyceride; and Ricinolein, 1-Mono-	Skin-conditioning agent—emollient and surfactant–emulsifying agent
See above	**Glyceryl Ricinoleate SE** is a self-emulsifying grade of Glyceryl Ricinoleate containing sodium and/or potassium stearate	Skin-conditioning agent—emollient and surfactant–emulsifying agent
	**Potassium Ricinoleate** (CAS no. 7492-30-0) is the potassium salt of Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, Monopotassium Salt and 9-Octadecenoic Acid, 12-Hydroxy-, Monopotassium Salt	Surfactant–cleansing agent and surfactant–emulsifying agent
See above, except with Na in place of K	**Sodium Ricinoleate** (CAS no. 5323-95-5) is the sodium salt of Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, Sodium Salt; 9-Octadecenoic Acid, 12-Hydroxy, Sodium Salt; and Sodium Ricinate	Surfactant–cleansing agent and surfactant–emulsifying agent
	**Zinc Ricinoleate** (CAS no. 13040-19-2) is the zinc salt of Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, Zinc Salt and 9-Octadecenoic Acid, 12-Hydroxy-, Zinc Salt	Anticaking agent, deodorant agent, and opacifying agent
	**Cetyl Ricinoleate** (CAS no.10401-55-5) is the ester of cetyl alcohol and Ricinoleic Acid. Other names include: Hexadecyl 12-Hydroxy-9-Octadecenoate; 12-Hydroxy-9-Octadecenoic Acid, Hexadecyl Ester; 9-Octadecenoic Acid, 12-Hydroxy-, Hexadecyl Ester; and Ricinoleic Acid, Hexadecyl Ester	Skin-conditioning agent—occlusive
	**Ethyl Ricinoleate** (CAS no. 55066-53-0) is the ester of ethyl alcohol and Ricinoleic Acid. Other names include: Ethyl 12-Hydroxy-9-Octadecenoate; 12-Hydroxy-9-Octadecenoic Acid-, Ethyl Ester; 9-Octadecenoic Acid, 12-Hydroxy-, Ethyl Ester; and Ricinoleic Acid, Monoethyl Ester	Fragrance ingredient and skin-conditioning agent—emollient
	**Glycol Ricinoleate** (CAS nos. 106-17-2 and 40275-40-9) is the ester of ethylene glycol and Ricinoleic Acid. Other names include: 1,2-Ethanediol Monoricinoleate; Ethylene Glycol Monoricinoleate; Glycol Monoricinoleate; 2-Hydroxyethyl 12-Hydroxy-9-Octadecenoate; 9-Octadecenoic Acid, 12-Hydroxy-, 2-Hydroxyethyl Ester; and Ricinoleic Acid, 2-Hydroxyethyl Ester	Emulsion stabilizer and skin-conditioning agent—emollient

(Continued on next page)

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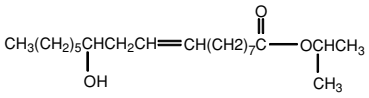
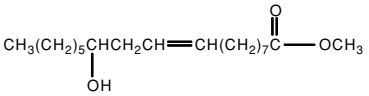
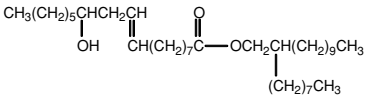
TABLE 1
Structures, definitions, and functions of ricinoleic acid, its salts, and esters (Gottschalck and McEwen 2004) *(Continued)*

Structure	Definition	Function
	**Isopropyl Ricinoleate** (CAS no. 71685-99-9) is the ester of isopropyl alcohol and Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, 1-Methylethyl Ester; 1-Methylethyl, 12-Hydroxy-9-Octadecenoate; 9-Octadecenoic Acid, 12-Hydroxy-, 1-Methylethyl Ester; and Ricinoleic Acid, Isopropyl Ester	Skin-conditioning agent—emollient
	**Methyl Ricinoleate** (CAS nos. 141-24-2 and 23224-20-6) is the ester of methyl alcohol and ricinoleic acid. Other names include: Castor Oil Acid, Methyl Ester; 12-Hydroxy-9-Octadecenoic Acid, Methyl Ester; Methyl Castor Oil Fatty Acid; Methyl 12-Hydroxy-9-Octadecenoate; 9-Octadecenoic Acid, 12-Hydroxy-, Methyl Ester; and Ricinoleic Acid, Methyl Ester	Skin-conditioning agent—emollient
	**Octyldodecyl Ricinoleate** (CAS nos. 79490-62-3 and 125093-27-8) is the ester of Octyldodecanol and Ricinoleic Acid. Other names include: 12-Hydroxy-9-Octadecenoic Acid, 2-Octyldodecyl Ester; 9-Octadecenoic Acid, 12-Hydroxy-, 2-Octyldodecyl Ester; 2-Octyldodecyl 12-Hydroxy-9-Octadecenoate; and 2-Octyldodecyl Ricinoleate	Skin-conditioning agent—occlusive

has published the following requirements for castor oil: free fatty acids ("the free fatty acids in 10 g require for neutralization not more than 3.5 ml of 0.10 N sodium hydroxide") heavy metals (0.001%), hydroxyl value (between 160 and 168), iodine value (between 83 and 88), saponification value (between 176 and 182), and specific gravity (between 0.957 and 0.961).

Hydrogenated Castor Oil

According to Nikitakis and McEwen (1990), Hydrogenated Castor Oil consists primarily of glyceryl-tri-hydroxystearate. An earlier source (Binder et al. 1970) indicates that 12-hydroxystearic acid is the principal constituent of Hydrogenated Castor Oil.

The National Formulary (Committee of Revision of the United States Pharmacopeial Convention 2004b) has published the following requirements for Hydrogenated Castor Oil: free fatty acids (free fatty acids in 20 g require for neutralization not more than 11.0 ml of 0.1 N sodium hydroxide), heavy metals (0.001%), hydroxyl value (between 154 and 162), iodine value (not more than 5), and saponification value (between 176 and 182).

Methods of Production

Castor Oil

According to Kathren et al. (1959), castor oil is extracted from the bean of the tropical plant, *Ricinus communis*, by either of the following two methods: (1) use of a solvent [not stated] or (2) mechanical crushing, grinding, and pressing. The former method is more efficient, leaving a more dessicated residue. This residue, known as pomace, contains ricin and a separate allergen (Ratner and Gruehl 1929). Following extraction from the castor bean, neither of these two fractions is present in castor oil (Ordman 1955).

According to a more recent reference (Cornell University 2001), ricin does not partition into the oil because of its water solubility. Therefore, castor oil does not contain ricin, provided that cross-contamination does not occur during its production.

Other sources indicate that castor oil is produced via the cold pressing of the seeds of *Ricinus communis* (Hui 1996) and by cold expression and subsequent clarification of the oil by heat (Gennaro 1990).

Hydrogenated Castor Oil

According to Nikitakis and McEwen (1990), Hydrogenated Castor Oil is obtained by the controlled hydrogenation of pure Castor Oil. Another source (Campbell & Co. 2002) indicates that Hydrogenated Castor Oil (hard, brittle wax) results from the addition of hydrogen to Castor Oil in the presence of a nickel catalyst.

Ricinoleic Acid

One of the simplest methods for obtaining Ricinoleic Acid is the hydrolysis of castor oil. Ricinoleic acid may then be separated from hydrolyzed castor Oil by successive additions of urea (i.e., urea complexing) (Chakravarty and Bose 1963). According to a more recent source, Ricinoleic Acid results from the saponification of castor oil (Lewis 1997).

TABLE 2
Chemical and physical properties of Castor Oil and Hydrogenated Castor Oil

Property	Value	Reference
	Castor Oil	
Color/Form	Colorless to pale-yellow viscous liquid	Lewis 2000
Taste	Slightly acrid	National Toxicology Program (NTP) 2003
Specific gravity	0.945 to 0.965 at 25°/25°C; 0.961 to 0.963 at 15.5°/15.5°C	NTP 2003
Density	0.953 to 0.965 g/ml at 20°C	NTP 2003
Viscosity	6 to 8 poises at 25°C	NTP 2003
	283 cP at 37°C	Fredholt et al. 2000
Solubility	In water (<1 mg/ml at 20°C); in DMSO (≥100 mg/ml at 20°C); In 95% ethanol (≥ 100 mg/ml at 20°C); in methanol (miscible); In acetone (≥100 mg/ml at 20°C)	NTP 2003
	Miscible in absolute alcohol, glacial acetic acid, chloroform, and ether	Lewis 2000
Surface tension	39.0 dynes/cm at 20°C; 35.2 dynes/cm at 80°C	NTP 2003
Refractive index	1.4784 at 20°C; 1.473 to 1.477 at 25°C; 1.466 to 1.473 at 40°C	NTP 2003
Optical rotation	Not less than +3.5°	NTP 2003
Flash point	229°C (445°F)	NTP 2003
Autoignition temperature	448°C (840°F)	NTP 2003
Melting point	−12°C	NTP 2003
Boiling point	313°C	NTP 2003
Freezing point	−10°C	NTP 2003
Saponification value	178	NTP 2003
Iodine value	85	NTP 2003
Acid value	<4	NTP 2003
Reichert-Meissl value	<0.5	NTP 2003
Polenske value	<0.5	NTP 2003
Acetyl value	144 to 150	NTP 2003
Hydroxyl value	161 to 169	NTP 2003
	Hydrogenated Castor Oil	
Color/Form	White to cream waxy solid	Nikitakis and McEwen 1990
Odor	As specified by the buyer	Nikitakis and McEwen 1990
	Slight characteristic odor	Allegri et al. 1981
Taste	Tasteless	Allegri et al. 1981
Identification	Positive: Close match to a standard IR spectrum with no indication of foreign materials	Nikitakis and McEwen 1990
Specific gravity	0.98 to 1.04 at 25°/25°C	Nikitakis and McEwen 1990
Melting range	78° to 90°C	Nikitakis and McEwen 1990
Acid value	5.0 maximum	Nikitakis and McEwen 1990
Saponification value	175 to 185	Nikitakis and McEwen 1990
Iodine value	As specified by the buyer	Nikitakis and McEwen 1990
	<5.0	Budavari 1989
Hydroxyl value	155 max	KIC Chemicals, Inc. 2004

(Continued on next page)

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TABLE 2
Chemical and physical properties of Castor Oil and Hydrogenated Castor Oil *(Continued)*

Property	Value	Reference
Density	0.98 g/cm^3	Physical & Theoretical Chemistry Lab 2004
Solubility	Insoluble in water and organic solvents.	Lewis 1997
	Soluble in chloroform; very slightly soluble in benzene; virtually insoluble in alcohol, ethyl ether, carbon disulfide, and water	Allegri et al. 1981
Drying loss	When dried under vacuum in presence of phosphoric acid anhydride, should lose no more than 0.1% of weight	Allegri et al. 1981
Sulfuric ash	Not more than 0.01%	Allegri et al. 1981

Methyl Ricinoleate

According to Masri et al. (1962), Methyl Ricinoleate has been obtained by alcoholysis of castor oil, followed by fractional distillation of the crude esters and further purification by low temperature crystallization. According to a more recent source, Methyl Ricinoleate is a product of either the esterification of Ricinoleic Acid or the alcoholysis of castor oil; the product is purified by vacuum distillation (Lewis 1997).

Ultraviolet Absorption

Castor Oil

A ultraviolet (UV) absorption spectrum on castor oil indicates maximum absorbance at 270 nm; absorption peaks at 280 and 260 nm were also observed (Sasol North America, Inc. no date).

Glyceryl Ricinoleate

A UV absorption spectrum on Glyceryl Ricinoleate indicates maximum absorbance at 270 nm and an absorption peak at 280 nm (Sasol North America, Inc. no date).

Analytical Methods

Castor Oil

Castor oil has been analyzed using the following methods: mass spectroscopy (Ayorinde et al. 2000), gas-liquid chromatography (Kato and Yamaura 1970; Ramsey et al. 1980), thin-layer chromatography (Srinivasulu and Mahapatra 1973), and nonaqueous reverse-phase high-performance liquid chromatography–mass spectrometry (Stübiger et al. 2003).

Methyl Ricinoleate

Methyl Ricinoleate has been analyzed by nuclear magnetic resonance (NMR) spectroscopy (Wineburg and Swern 1973) and gas-liquid chromatography (Paulus and Champion 1972).

Reactivity

Castor Oil

Castor oil is combustible when exposed to heat, and spontaneous heating may occur (Lewis 2000).

According to Gunstone (1989), Castor Oil is a precursor of octadeca-9,11-dienoic acid (dehydration reaction); 12-hydroxystearic acid (hydrogenation); heptanol and undec-10-enoic acid (pyrolysis); and sebacic acid, 10-hydroxydecanoic acid, octan-2-ol, and octan-2-one (alkaline fusion).

According to Achaya (1971), the hydrogenation of Castor oil produces 12-hydroxystearate, stearate, 12-ketostearate, and ricinoleyl alcohol. Dehydrated castor oil is a dehydration product of castor oil, and contains a fair proportion of conjugated dienes.

Hydrogenated Castor Oil

Hydrogenated Castor Oil is combustible and is incompatible with strong oxidizing agents (Physical and Theoretical Chemistry Lab 2004).

USE

Purpose in Cosmetics

Ricinus Communis (Castor) Seed Oil functions as a fragrance ingredient and a skin-conditioning agent—occlusive in cosmetic products, and Hydrogenated Castor Oil functions as a skin-conditioning agent—occlusive and a viscosity increasing agent—nonaqueous (Gottschalck and McEwen 2004). The cosmetic ingredient functions of Ricinoleic Acid and some of its salts and esters are included in Table 1. Except for the anticaking, deodorant, and opacifying agent functions of Zinc Ricinoleate and the surfactant function of Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Glyceryl Ricinoleate, and Glyceryl Ricinoleate SE, these ingredients function as skin-conditioning agents in cosmetic products. In addition to functioning as a skin-conditioning agent, Ethyl Ricinoleate also functions as a fragrance ingredient. Glycol Ricinoleate also functions as an emulsion stabilizer, and Glyceryl Ricinoleate and Glyceryl Ricinoleate SE also function as surfactants in cosmetics.

Extent of Use in Cosmetics

Frequency of use data based on industry reports to the Food and Drug Administration (FDA) in 2002 indicate that Ricinus

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TABLE 3
Chemical and physical properties of Ricinoleic Acid, its salts, and esters

Property	Value	Reference
	Ricinoleic Acid	
Molecular weight	298.47	Lide and Frederikse 1993
Color/Form	Yellow fatty acid	Grant 1972
	Yellow, viscous liquid	Nikitakis and McEwen 1990
	Colorless to yellow, viscous liquid	Lewis 1997
Odor	As specified by the buyer	Nikitakis and McEwen 1990
Identification	Positive: Close match to a standard IR spectrum with no indication of foreign materials	Nikitakis and McEwen 1990
Specific gravity	0.940 at 25°/25°C	Nikitakis and McEwen 1990
Density	0.9450	Lide and Frederikse 1993
	0.940 at 27.4°/4°C	Lewis 1997
Solubility	Insoluble in water	Grant 1972
	Soluble in alcohol, acetone, ether, and chloroform	Budavari 1989
	Soluble in ethyl alcohol and diethyl ether	Lide and Frederikse 1993
	Soluble in most organic solvents; insoluble in water	Lewis 1997
Refractive index	1.4716 at 20°C	Nikitakis and McEwen 1990
	1.4716	Lide and Frederikse 1993
	1.4697 at 20°C	Lewis 1997
Optical rotation	$[\alpha]^{22/D}$ of +6.67°C	Budavari 1989
	+6.67° at 22°C	Nikitakis and McEwen 1990
	$[\alpha]^{12/D}$of +5.05	Lide and Frederikse 1993
	Dextrorotatory	Lewis 1997
Melting point	5.5°C	Nikitakis and McEwen 1990
	α : 7.7°C; β: 16°C; γ: 5.5°C	Lide and Frederikse 1993
	5.5°C	Lewis 1997
Boiling point	226.8°C	Lide and Frederikse 1993
	226°C at 10 mm Hg	Lewis 1997
Combustibility	Combustible	Lewis 1997
Neutralization value	187.98	Budavari 1989
	188	Nikitakis and McEwen 1990
Iodine value	85.05	Budavari 1989
	85	Nikitakis and McEwen 1990
	Potassium Ricinoleate	
Color/Form	White paste	Lewis 1997
Solubility	Soluble in water	Lewis 1997
Combustibility	Combustible	Lewis 1997
	Sodium Ricinoleate	
Color/Form	White or slightly yellow powder	Lewis 1997
Odor	Nearly odorless	Lewis 1997
Solubility	Soluble in water or alcohol	Lewis 1997
Combustibility	Combustible	Lewis 1997
	Zinc Ricinoleate	
Color/Form	Fine white powder	Lewis 1997
Odor	Faint fatty acid odor	Lewis 1997
Density	1.10 at 25°/25°C	Lewis 1997

(Continued on next page)

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TABLE 3
Chemical and physical properties of Ricinoleic Acid, its salts, and esters *(Continued)*

Property	Value	Reference
Melting point	92°C to 95°C	Lewis 1997
Combustibility	Combustible	Lewis 1997
	Methyl Ricinoleate	
Color/Form	Colorless liquid	Lewis 1997
Solubility	Insoluble in water; soluble in alcohol and ether	Lewis 1997
Density	0.9236 at 22°/4°C	Lewis 1997
Refractive index	1.4628	Lewis 1997
Boiling point	245°C at 10 mm Hg	Lewis 1997
Flash point	−4.5°C	Lewis 1997
Combustibility	Combustible	Lewis 1997
	Ethyl Ricinoleate	
Molecular weight	326.52	Lide and Frederikse 1993
Density	0.9045	Lide and Frederikse 1993
Refractive index	1.4618	Lide and Frederikse 1993
Optical rotation	$[\alpha]^{22/D}$ of +5.3	Lide and Frederikse 1993
Boiling point	258°C	Lide and Frederikse 1993

Communis (Castor) Seed Oil and Hydrogenated Castor Oil are being used in a total of 769 and 202 cosmetic products, respectively. Glyceryl Ricinoleate (16 cosmetic products), Ricinoleic Acid (6 cosmetic products), Sodium Ricinoleate (12 cosmetic products), Zinc Ricinoleate (3 cosmetic products), and Cetyl Ricinoleate (55 cosmetic products) were also reported. These data are given in Table 4 (FDA 2002).

Use concentration data obtained from an industry survey by the Cosmetic, Toiletry, and Fragrance Association (CTFA 2004) indicate that Ricinus Communis (Castor) Seed Oil and Hydrogenated Castor Oil are being used in cosmetics at concentrations up to 81% and 39%, respectively (see Table 4).

Other maximum ingredient use concentrations reported in Table 4 are as follows: Glyceryl Ricinoleate (up to 12%), Zinc Ricinoleate (up to 2%), Cetyl Ricinoleate (up to 10%), and Octyldodecyl Ricinoleate (up to 5%). Of the product categories listed in Table 4, the highest reported use concentration for Ricinus Communis (Castor) Seed Oil is associated with lipsticks. Two other sources indicate that lipstick contains 44% *w/w* castor oil (Hui 1996) and 10% to 67% castor oil (Smolinske 1992).

Certain ingredients in this group are reportedly used in a given product category, but the concentration of use is not available. For other ingredients in this group, information regarding use concentration for specific product categories is provided, but the number of such products is not known. In still other cases, an ingredient is not in current use, but may be used in the future. For example, Potassium Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, and Methyl Ricinoleate are not currently reported to FDA as in use, nor are there industry survey data indicating a current use concentration.

Cosmetic products containing Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, and Ricinoleic Acid and its salts and esters are applied to most areas of the body, and could come in contact with the oral, ocular, or nasal mucosae. These products may be used on a daily basis, and could be applied frequently over a period of several years.

Product categories for Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, and salts and esters of Ricinoleic Acid include potential aerosol applications. Bower (1999) characterized the typical diameter of anhydrous hair spray particles in the 60- to 80-μm range (typically, <1% are below 10 μm). Pump hair sprays, in contrast, have typical particle diameters of ≥80 μm. Johnsen (2004) reported that the mean particle diameter is around 38 μm in a typical aerosol spray. In practice, he stated that aerosols should have at least 99% of particle diameters in the 10- to 110-μm range. For comparison, Jensen and O'Brien (1993) reported a mean aerodynamic diameter of 4.25 ± 1.5 μm for respirable particles, which is smaller than any of the cosmetic product particle sizes given above.

Noncosmetic Use

Castor Oil, Hydrogenated Castor Oil, and Ricinoleic Acid Salts and Esters

According to Aplin and Eiseo (1997), castor oil is used as an industrial lubricant and as a medicinal purgative; the authors noted that medicinal Castor Oil does not contain ricin. McKeon et al. (2000) confirmed lubricant and anti-fungal uses and additional uses in paints, coatings, and plastics.

The following uses have been reported for Hydrogenated Castor Oil (Budavari 1989): in water-repellent coatings, candles,

TABLE 4
Current uses and concentrations of Ricinus Communis (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
	Ricinus Communis (Castor) Seed Oil	
Baby products		
Shampoos (29)	—	—
Lotions, oils, powders, and creams (60)	1	—
Other (34)	2	—
Bath products		
Oils, tablets, and salts (143)	1	22
Soaps and detergents (421)	—	0.008
Bubble baths (215)	—	—
Capsules (2)	—	—
Other (196)	10	—
Eye makeup		
Eyebrow pencils (102)	10	3
Eyeliners (548)	11	4–8
Eye shadow (576)	9	2–5
Eye lotions (25)	—	—
Eye makeup remover (100)	1	—
Mascara (195)	16	0.4–3
Other (152)	11	13
Fragrance products		
Colognes and toilet waters (684)	—	0.1
Perfumes (235)	—	0.3–1
Powders (273)	—	—
Sachets (28)	—	—
Other (173)	—	—
Noncoloring hair care products		
Conditioners (651)	20	0.0002–5
Sprays/aerosol fixatives (275)	1	—
Straighteners (63)	—	—
Permanent waves (207)	—	—
Rinses (42)	5	19
Shampoos (884)	—	0.005
Tonics, dressings, etc. (598)	34	0.005–52
Wave sets (53)	—	16
Other (277)	6	—
Hair—coloring products		
Dyes and colors (1690)	27	2
Tints (49)	—	—
Rinses (20)	—	0.0005
Shampoos (32)	—	—
Color sprays (5)	—	—
Lighteners with color (5)	—	—
Bleaches (120)	1	0.04
Other (55)	—	—
Makeup		
Blushers (245)	10	0.08–45
Face powders (305)	1	1

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TABLE 4
Current uses and concentrations of Ricinus Communis (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics
(Continued)

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
Foundations (324)	5	0.05–6
Leg and body paints (4)	—	—
Lipsticks (962)	492	15–81
Makeup bases (141)	4	0.002–20
Rouges (28)	1	38–48
Makeup fixatives (20)	—	—
Other (201)	25	40–49
Nail care products		
Basecoats and undercoats (44)	—	—
Cuticle softeners (19)	1	—
Creams and lotions (15)	1	—
Nail extenders (1)	—	—
Nail polishes and enamels (123)	—	69
Nail polish and enamel removers (36)	8	—
Other (55)	3	—
Personal hygiene products		
Bath soaps and detergents (421)	18	≤ 0.008
Underarm deodorants (247)	—	0.01–3
Douches (5)	—	—
Feminine deodorants (4)	—	—
Other (308)	1	0.003
Shaving products		
Aftershave lotions (231)	2	0.004–0.03
Beard softeners (0)	—	—
Mens talcum (7)	—	—
Preshave lotions (14)	—	—
Shaving creams (134)	—	—
Shaving soaps (2)	—	—
Other (63)	1	0.03
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (775)	4	0.004
Depilatories (34)	2	—
Face and neck creams, lotions, powders, and sprays (310)	1	1–7
Body and hand creams, lotions, powders, and sprays (840)	3	0.02–55
Body and hand sprays	—	0.004
Foot powders and sprays (35)	—	—
Moisturizers (905)	8	7
Night creams, lotions, powders, and sprays (200)	—	0.00004
Paste masks/mud packs (271)	2	—
Skin fresheners (184)	—	—
Other (725)	8	—
Suntan products		
Suntan gels, creams, liquids, and sprays (131)	1	6
Indoor tanning preparations (71)	—	—
Other (38)	1	10
Total uses/ranges for Ricinus Communis (Castor) Seed Oil	769	0.00004–81

TABLE 4
Current uses and concentrations of Ricinus Communis (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics *(Continued)*

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
	Hydrogenated Castor Oil	
Baby products		
Other (34)	—	5
Bath products		
Oils, tablets, and salts (143)	1	19
Soaps and detergents (421)	1	0.0003–0.7
Bubble baths (215)	—	4
Other (196)	—	3
Eye makeup		
Eyebrow pencils (102)	11	4–26
Eyeliners (548)	25	3–39
Eye shadow (576)	6	2–19
Eye lotions (25)	—	0.5
Eye makeup		
Eye makeup remover (100)	1	7
Mascara (195)	—	5
Other (152)	14	22–39
Fragrance products		
Colognes and toilet waters (684)	—	0.0003
Perfumes (235)	—	5
Other (173)	—	7
Noncoloring hair care products		
Shampoos (884)	—	0.02
Tonics, dressings, etc. (598)	—	3
Other (277)	1	—
Makeup		
Blushers (245)	2	3
Foundations (324)	4	0.9–5
Leg and body paints (4)	—	1
Lipsticks (962)	20	0.5–33
Makeup fixatives (20)	—	3–7
Other (201)	24	0.04–13
Nail care products		
Creams and lotions (15)	1	—
Oral hygiene products		
Other (6)	—	1–5
Personal hygiene products		
Underarm deodorants (247)	2	2–8
Feminine deodorants (4)	—	2
Other (308)	65	—
Shaving products		
Aftershave lotions (231)	2	—
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (775)	3	1
Face and neck creams, lotions, powders, and sprays (310)	—	1–2
Body and hand creams, lotions, powders, and sprays (840)	3	0.0003–1
Foot powders and sprays (35)	—	8

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TABLE 4

Current uses and concentrations of Ricinus Communis (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics *(Continued)*

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
Moisturizers (905)	3	1–5
Night creams, lotions, powders, and sprays (200)	1	1–3
Other (725)	9	0.1–1
Suntan products		
Suntan gels, creams, liquids, and sprays (131)	1	0.8–3
Other (38)	2	—
Total uses/ranges for Hydrogenated Castor Oil	202	0.0003–39
Glyceryl Ricinoleate		
Eyebrow pencil (102)	—	11
Eyeliner (548)	1	2
Eyeshadow (576)	5	—
Other eye makeup products (152)	1	2–12
Lipsticks (962)	5	—
Other shaving products (63)	1	—
Body and hand creams, lotions, powders, and sprays (840)	2	—
Night creams, lotions, powders, and sprays (200)	1	—
Total uses/ranges for Glyceryl Ricinoleate	16	12
Ricinoleic Acid		
Bath preparations		
Oils, tablets and salts (143)	1	—
Fragrance preparations		
Colognes and toilet waters (684)	1	—
Other fragrance preparations (173)	4	—
Total uses/ranges for Ricinoleic Acid	6	—
Sodium Ricinoleate		
Baby products		
Other baby products (34)	1	—
Bath Preparations		
Soaps and detergents (421)	10	—
Noncoloring Hair Preparations		
Shampoos (884)	1	—
Total uses/ranges for Sodium Ricinoleate	12	—
Zinc Ricinoleate		
Noncoloring hair preparations		
Hair sprays/aerosol fixatives (275)	—	1
Personal hygiene products		
Underarm deodorants (247)	2	2
Skin care preparations		
Skin cleansing creams, lotions, liquids, and pads (775)	1	—
Body and hand skin care preparations (sprays) (840)	—	1
Total uses/ranges for Zinc Ricinoleate	3	1–2
Cetyl Ricinoleate		
Makeup preparations		
Blushers (245)	—	3

TABLE 4
Current uses and concentrations of Ricinus Communis (Castor) Seed Oil and Ricinoleic Acid and its salts and esters in cosmetics *(Continued)*

Product category (total no. of formulations)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2004) (%)
Foundations (324)	3	2–3
Lipsticks (962)	26	0.5–10
Other makeup preparations (201)	1	—
Skin care preparations		
Skin cleansing creams, lotions, liquids, and pads (775)	2	0.1–0.5
Body and hand skin care preparations (840)	1	—
Moisturizers (905)	15	0.1–2
Paste masks (mud packs) (271)	3	—
Other skin care preparations (725)	3	4
Suntan preparations		
Other suntan preparations (38)	1	—
Total uses/ranges for Cetyl Ricinoleate	55	0.1–10
Octyldodecyl Ricinoleate		
Fragrance preparations		
Other fragrance preparations (173)	—	3
Makeup preparations		
Lipsticks (962)	—	3–5
Total uses/ranges for Octyldodecyl Ricinoleate	—	3–5

shoe polish, carbon paper, and ointments; for impregnating paper, wood, and cloth; for electrical condenser impregnation; as a solid lubricant; and as a pressure mold release agent in the manufacture of formed plastics and rubber goods. The use of Hydrogenated Castor Oil in waterproofing fabrics has also been reported (Lewis 1997).

According to FDA's *OTC (Over-the-Counter) Drug Review Ingredient Status Report* (FDA 2003a), castor oil is classified as generally recognized as safe and effective for use as a stimulant laxative, but not generally recognized as safe and effective for use as a wart remover. For use as a stimulant laxative, the single daily dose reported for one product ranges from 15 to 60 ml for adults and children ≥12 years (Drugstore.com, Inc. 2004).

FDA had issued a proposed rule in 1982 stating that Castor oil is generally recognized as safe and effective and not misbranded when used as an active ingredient (laxative) in OTC laxative drug products (FDA 1985) and a final rule is pending (FDA 2003a). FDA has concluded that castor oil does not meet monograph conditions and is not generally recognized as safe and effective for use as a wart remover in OTC wart remover drug products (FDA 1990).

Castor oil is included in the list of inactive ingredients (excipients) present in approved oral, intramuscular, and topical drug products or conditionally approved drug products that are currently marketed for human use (FDA 2003b).

FDA-approved direct/indirect food additive uses of Castor oil and the following Ricinoleic Acid salts and esters are summarized in Table 5: Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, and Methyl Ricinoleate.

The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (1980) established an acceptable daily intake (for man) of 0 to 0.7 mg/kg body weight for castor oil. The determination of range was based on consideration of the lack of adequate long-term studies.

Ricinoleic Acid

Noncosmetic uses of Ricinoleic Acid are as follows: turkey red oil, textile finishing, source of sebacic acid and heptanol, ricinoleate salts, and 12-hydroxystearic acid (Lewis 1997).

Zinc Ricinoleate

The following noncosmetic uses of Zinc Ricinoleate have been reported: fungicide, emulsifier, greases, lubricants, waterproofing, lubricating-oil additive, and stabilizer in vinyl compounds (Lewis 1997).

Methyl Ricinoleate

Noncosmetic uses of Methyl Ricinoleate include: plasticizer, lubricant, cutting oil additive, and wetting agent (Lewis 1997).

TABLE 5
Direct/indirect food additive uses of Castor Oil, Hydrogenated Castor Oil, and Ricinoleic acid salts and esters

Use	Specification/listing	Code of Federal Regulations (CFR)
Diluent	Not more than 500 ppm Castor Oil in the finished food may be used safely as a diluent in color additive mixtures for food use that are exempt from certification.	21 CFR 73.1
Release/antisticking agent	Provided that Castor Oil meets the specifications of the United States Pharmacopeia, it is permitted for use as a release agent and antisticking agent, not to exceed 500 ppm in hard candy.	21 CFR 172.876
Natural flavoring substance and adjuvant	Castor Oil is included in the list of natural flavoring substances and natural adjuvants that are permitted for direct addition to food for human consumption.	21 CFR 172.510
Plasticizer	Castor Oil is approved for use as a plasticizer (total not to exceed 30% by weight of rubber product, unless otherwise specified) in rubber articles that have been declared safe for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21 CFR 177.2600
Component of food-contact surface	Hydrogenated Castor Oil may be used safely as a component of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods.	21CFR176.170
Component of food-contact surface	Hydrogenated Castor Oil may be used safely as a component of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding dry food.	21CFR176.180
Component of defoaming agents	Castor Oil, Hydrogenated Castor Oil, Glycol Ricinoleate, Isopropyl Ricinoleate, and Methyl Ricinoleate are among the substances that are permitted for use in the formulation of defoaming agents that have been declared safe for use in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food.	21 CFR 176.210
Component of surface lubricants	Castor Oil is included in the list of substances permitted for use in surface lubricants that have been declared safe for use in the manufacture of metallic articles that contact food. May be used in surface lubricants employed to facilitate the drawing, stamping, or forming of metallic articles from rolled foil or sheet stock by further processing, provided that the total residual lubricant remaining in the metallic article in the form in which it contacts food does not exceed 0.2 mg per square inch of food-contact surface.	21 CFR 178.3910
Component of cellophane	Hydrogenated Castor Oil is included in the list of components of cellophane that may be safely used for packaging food.	21CFR 177.1200

TABLE 5
Direct/indirect food additive uses of Castor Oil, Hydrogenated Castor Oil, and Ricinoleic acid salts and esters *(Continued)*

Use	Specification/listing	Code of Federal Regulations (CFR)
Component of closure-sealing gaskets	Hydrogenated Castor Oil may be employed in the manufacture of closure-sealing gaskets that may be safely used on containers intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21CFR177.1210
Component of cross-linked polyester resins	Hydrogenated Castor Oil may be used in the production of or may be added to cross-linked polyester resins that may be safely used as articles or components of articles that are intended for repeated use in contact with food.	21CFR 177.2420
Textiles and textile fiber components derived from Castor Oil	Fats, oils, fatty acids, and fatty alcohols derived from Castor Oil are included in the list of substances that are permitted for use in textiles and textile fibers that have been declared safe for use as articles or components of articles that are intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21 CFR 177.2800
Component of adhesives	Polymeric esters of polyhydric alcohols and polycarboxylic acids prepared from glycerin and phthalic anhydride and modified with Castor Oil are permitted for use in adhesives that have been declared safe for use as components of articles intended for use in packaging, transporting, or holding food. Methyl Ricinoleate is also permitted for use in these adhesives.	21 CFR 175.105
Component of resinous and polymeric coatings	Castor Oil, Hydrogenated Castor Oil, Potassium Ricinoleate, Sodium Ricinoleate, and Zinc Ricinoleate are included in the list of substances employed in the production of resinous and polymeric coatings that have been declared safe for use as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21 CFR 175.300

BIOLOGICAL PROPERTIES

Absorption, Distribution, Metabolism, and Excretion

Castor Oil

In a study by Paul and McKay (1942), two rabbits (weight = 3 kg) were fed 6% castor oil in the diet for 18 days; fecal collection occurred during the last ten days. The utilization (uncorrected for metabolic fat) of castor oil was 92.1%, which the authors considered to be efficient utilization. For both rabbits, the percentage of fat in the feces was 2.2%.

In a study by Stewart and Sinclair (1945), adult rats (number, weights, and strain not stated) received a diet containing 48.4% castor oil for 4 to 6 weeks. Control rats received stock ration only. Feces were collected from three rats on the castor oil diet. At the end of the feeding period, excised organs/tissues were ground thoroughly and samples of phospholipid fatty acids were obtained from the liver, small intestine, and muscle; glyceride fatty acids were obtained from the liver and fat depots. There was no evidence of catharsis in any of the animals.

Average percentages of Ricinoleic Acid in the phospholipid fatty acids were as follows: liver (test: 1.3 ± 0.6% [9 analyses]; controls: 1.7 ± 1.1% [7 analyses]), small intestine (test: 4.9 ± 1.7% [8 analyses]; controls: 6.0 ± 4.4% [4 analyses]), and skeletal muscle (test: 3.6 ± 2.9% [8 analyses]; controls: 4.0 ± 1.7% [7 analyses]). The following values are average percentages of Ricinoleic Acid in glycerides and cholesterol esters: fat depots (test: 6.8 ± 4.2% [11 analyses]; controls: 0.5 ± 0.5% [7 analyses]) and liver (test: 7.2 ± 2.4% [8 analyses]; controls: 5.6 ± 4.1% [5 analyses]).

The authors concluded that the feeding of castor oil did not lead to the appearance of significant amounts of Ricinoleic Acid in phospholipids of the small intestine, liver, and skeletal muscle,

nor in glycerides of the liver. Additionally, they concluded that ricinoleic acid is a component acid of the glycerides in the fat depots, comprising 7% of the total fatty acids. The fatty acids excreted by each of three rats amounted to 2.1%, 2.2%, and 3.6% of those ingested. Total body fat in these three animals was also determined, and it was calculated that 1% to 2% of absorbed Ricinoleic Acid was deposited in the fat depots. The authors concluded that Ricinoleic Acid was rapidly metabolized (Stewart and Sinclair 1945).

Watson and Gordon (1962) studied the digestion, absorption, and metabolism of castor oil (medicinal grade) in eight male Sprague-Dawley rats (weights = 100 to 200 g). The composition of the castor oil was as follows: ricinoleic acid (90.0%), linoleic acid (4.7%), oleic acid (3.2%), stearic acid (1.0%), palmitic acid (1.0%), and palmitoleic acid (0.1%). In the first experiment, four rats were fed rat chow ad libitum, and the remaining four were fasted overnight. On the following morning, castor oil (1.0 ml) was dosed via stomach tube and chyle was collected over a 24-h period. The mean values for percent recovery of Ricinoleic Acid in fasted and fed rats were 6.8% and 24.2%, respectively ($p < .01$).

In the second experiment, seven weanling rats were fed a diet consisting of rat chow that had been mixed with castor oil (20% by weight). The control group was fed an olive oil-supplemented diet. After 4 and 8 weeks of feeding, an epididymal fat pad was removed from each rat in both groups, and fatty acid composition was determined using gas-liquid chromatography. Mean values for Ricinoleic Acid in the fat pad after 4 and 8 weeks of feeding were 9.1 ± 1.7 and $9.7 \pm 1.0\%$, respectively. Ricinoleic Acid was undetectable in the fat pads of control rats fed olive oil. For rats fed castor oil, random analyses of feces indicated a considerable fraction of hydroxystearic acid. However, hydroxystearic acid was undetectable in the feces of rats fed a normal diet. The authors suggested that hydrogenation of Ricinoleic Acid in the gut lumen by intestinal bacteria would be a likely explanation for this finding.

The relationship between dose and absorption of castor oil was studied in the final experiment. Polyethylene cannulae were inserted into the thoracic duct and duodenum of each of two rats, and the animals received 0.5 N saline overnight. On the following morning, one rat received 0.2 ml and one rat received 0.6 ml of castor oil, and the rats were killed 45 min post dosing. Only the high dose induced diarrhea. Intestines (small and large) were excised, homogenized, and tissue lipids were extracted. Chyle was also collected and extracted. Total lipid estimation and gas-liquid chromatography (GLC) analysis of fatty acids were performed on the extracts. For the rat dosed with 0.2 ml castor oil, the percentage of Ricinoleic Acid in the chyle was 18.1% and the percentage detected in the small bowel lipids was 6.2%. For the rat dosed with 0.6 ml Castor Oil, the percentage of Ricinoleic Acid in the chyle was 3.0% and the percentage in the small bowel was 3.1%. Ricinoleic Acid was undetectable in large bowel lipids from the rat with diarrhea. The result indicates a close correlation between the dose administered and the percentage of Ricinoleic Acid in the feces, i.e., greater absorption at the lower dose (Watson and Gordon 1962).

Castor oil is metabolized to Ricinoleic Acid by pancreatic lipase in hamsters (Gaginella and Bass 1978). Thompson (1980) reported that Castor Oil is a triglyceride that is hydrolyzed in the small intestine in humans by pancreatic enzymes, leading to the release of glycerol and Ricinoleic Acid.

In a study by Hagenfeldt et al. (1986), castor oil was administered intragastrically to germ-free and conventional rats (number not stated). Urine was collected at intervals over a 24-h period. The following epoxydicarboxylic acids were detected in the urine of both germ-free and conventional rats: 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid. These acids were not detected in urine collected from the rats prior to dosing with castor oil, and they also were not detected in steam-sterilized castor oil. The authors stated that results for the germ-free rat indicate that the cyclization of Ricinoleic Acid (hydroxy fatty acid in castor oil) to form an epoxy compound occurs endogenously and does not require the presence of intestinal bacteria.

In a study by Ihara-Watanabe et al. (1999), two groups of five male Wistar rats (3 weeks old) received 10% castor oil in the diet (cholesterol-enriched and cholesterol-free, respectively) for 20 days. In both dietary groups, a very small quantity of Ricinoleic Acid was present in perirenal adipose tissue, but not in the serum or hepatic tissue. It was also noted that the perirenal fatty acid profiles did not reflect those of the dietary fats, either in the absence or presence of dietary cholesterol. The fecal recovery of Ricinoleic Acid was approximately 0.5% of the total ingested. It was concluded that castor oil was readily absorbed and metabolized.

Hydrogenated Castor Oil

In a study by Binder et al. (1970), groups of 15 male albino rats (Slonaker substrain of Wistar strain, weights = 43 to 83 g) received diets containing the following oils: group 1 (fed 1% Hydrogenated Castor Oil (HCO) + 19% corn oil for 16 weeks), group 2 (1% HCO + 19% corn oil for 8 weeks, then 20% corn oil for 8 weeks), group 3 (10% HCO + 10% corn oil for 16 weeks), and group 4 (10% HCO + 10% corn oil for 8 weeks, then 20% corn oil for 8 weeks). The control group received 20% corn oil in the diet for 16 weeks. The sample of HCO that was incorporated into the diet contained 86.5% 12-hydroxystearic acid, 10.3% nonoxygenated acids, and 3.2% 12-ketostearic acid. Thus, the effective dietary concentrations of Hydrogenated Castor Oil in the 1% and 10% diets were 0.865% and 8.65%, respectively. Results relating to the toxicity of HCO are summarized in the section Subchronic Oral Toxicity later in the report.

After 4 weeks of feeding, some of the animals on the 1% HCO (three rats) and 10% HCO (three rats) diets were necropsied and excised abdominal adipose tissue from each group was pooled. At weeks 4 and 8, sets of three rats on the corn oil diet were used. At the end of the 16-week feeding period, adipose tissue from rats in the various dietary groups was analyzed. Adipose tissue

was not pooled. After 8, 12, and 16 weeks, lipids were extracted from three rats on each diet. Methyl esters were recovered from the extracted lipids and chromatographed.

The deposition of hydroxystearic acid in abdominal fat and other body lipids was reported. In all cases, it was accompanied by hydroxypalmitic acid, hydroxymyristic acid, and hydroxylauric acid (hydroxy-stearic acid metabolites). The percent composition of these HCO-derived hydroxy fatty acids in rat lipids was as follows: 12-hydroxystearic acid (≈81%), 10-hydroxypalmitic acid (≈17%), 8-hydroxymyristic acid (≈1.6%), and 6-hydroxylauric acid (≈0.4%). After 4 weeks on the 1% HCO diet, HCO-derived fatty acids accounted for 0.90% (by weight) of the abdominal fat fatty acids. This proportion decreased to ≈0.35% over the 8- to 16-week feeding period. Compared to the abdominal fatty acids, the acids obtained from the carcass lipids contained a smaller proportion of HCO-derived hydroxyacids (≈0.28% over the 8- to 16-week feeding period). The period encompassing 4 weeks of feeding on the 10% HCO diet yielded the greatest content of HCO-derived hydroxy acids in the lipids (i.e., 4.4% hydroxy acids in abdominal fat). At 16 weeks, this proportion had decreased to <2% (about same as in the carcass lipids).

A rapid decrease in the amount of HCO-derived hydroxy fatty acids in the tissues was noted when the HCO diet was changed to the control diet (Binder et al. 1970).

Ricinoleic Acid and Methyl Ricinoleate

Uchiyama et al. (1963) studied the accumulation of hydroxy acids in depot fat after rats were fed with Ricinoleic Acid in two experiments. In the first experiment, adult male rats (number, strain, and weights not stated) were fed Ricinoleic Acid (5% emulsion, 20 ml) for 7 days. In the second experiment, the animals were fed for 27 days. Lipid extraction from the fat tissue was followed by hydrolysis to yield a fatty acid mixture. A gas-liquid chromatogram indicated appreciable amounts of the following hydroxy fatty acids with shorter chain lengths than Ricinoleic Acid: 10-hydroxyhexadecenoic acid (experiment 1: 0.60% of total fatty acids; experiment 2: 0.33% of total fatty acids), 8-hydroxytetradecenoic acid (experiment 1: 0.03% of total fatty acids; experiment 2: 0.08% of total fatty acids), and 6-hydroxydodecenoic acid (experiment 2: 0.03% of total fatty acids). Ricinoleic Acid comprised 0.51% of total fatty acids in experiment 1 and 3.85% of total fatty acids in experiment 2.

In a study by Okui et al. (1964), the metabolism of hydroxy fatty acids was evaluated using male albino rats (weight = 120 ± 10 g). The rats received 1.5 g Ricinoleic Acid or an emulsion containing 5% (*w*/*v*) Ricinoleic Acid by stomach tube three times per day for a desired period. Feces were collected every 24 h until the animals were killed. The animals were killed 20 h after the last dose, and subcutaneous adipose tissue was removed for analyses. Oral dosing with Ricinoleic Acid resulted in a fecal excretion rate (for Ricinoleic Acid) ranging from 1% to 4%. Following oral administration for up to 30 days, the accumulation of hydroxy acids by 5% of fatty acids in fat tissue was noted. Analyses of adipose tissue indicated an occurrence of shorter chain hydroxy acids other than Ricinoleic Acid.

Ricinoleic Acid was also injected intraperitoneally to determine whether another route of administration would lead to the formation of shorter chain hydroxy acids. After Ricinoleic Acid was injected intraperitoneally daily for 7 days, Ricinoleic Acid accumulated in the adipose tissue; no shorter chain hydroxy acids were reported (Okui et al. 1964).

In a study by Rao et al. (1969), Ricinoleic Acid or Methyl Ricinoleate was administered via gastric intubation to male rats (minimum weight of 400 g) with a cannulated thoracic duct. Lymph was collected for 48 h, and the lipids were then extracted and separated into various lipid classes. Results indicated that Ricinoleic Acid was present in the triglyceride, diglyceride, monoglyceride, and free fatty acid fractions. Peak absorption of Ricinoleic Acid occurrred within 30 min post administration. Ricinoleic Acid was not present in the phospholipid or cholesterol ester fractions of the lymph lipids.

Percutaneous Absorption

Ricinoleic Acid

Butcher (1952) evaluated the skin penetration of Ricinoleic Acid in vivo using rats that were 20 to 30 days old. In order to increase the fluorescence of Ricinoleic Acid, either one part of methyl anthranilate or methylcholanthrene was added to 99 parts Ricinoleic Acid. The test substance was either gently rubbed on to skin that had been clipped free of hair. Biopsies were taken at various intervals post application. The preparations were observed using a Spencer microscope with a quartz condenser. Ricinoleic Acid was retained mainly in the outer strata of the epidermis. There was little evidence of deeper penetration in biopsies that were taken at 2 h post application.

In a study by Baynes and Riviere (2004), the percutaneous absorption of a radiolabeled [^{3}H]Ricinoleic Acid (specific activity = 20.0 mCi/mmol) mixture was evaluated using porcine skin membranes or silastic (polydimethylsioloxane) membranes in the Bronaugh flow-through diffusion cell system. [^{3}H]Ricinoleic Acid (5%) mixtures were prepared in water containing either 5% mineral oil or 5% PEG 200. Other [^{3}H]Ricinoleic Acid mixtures were formulated with the following three commonly used cutting fluid additives: triazine, linear alkylbenzene sulfonate, and triethanolamine. At 8 h after topical exposure, Ricinoleic Acid absorption (based on amount recovered in receptor fluid) ranged from 1% to 13% in silastic membranes and 0.1% to 0.3% in porcine skin membranes. For most mixtures, peak absorption of Ricinoleic Acid occurred within 3 h. The greatest Ricinoleic Acid peak concentrations were associated with the control mixtures containing PEG in both membranes.

At the conclusion of the 8-h perfusion experiments, as much as 5% of the dose of Ricinoleic Acid was detected in the dosed skin, and as much as 16% of the dose was detected in the stratum

corneum with mineral oil formulations. With polyethylene glycol (PEG) formulations, the amount of Ricinoleic Acid remaining in the skin tissues was considerably less. The cutting fluid additives significantly decreased Ricinoleic Acid partitioning from the formulation into the stratum corneum in PEG-based mixtures. Additionally, the individual additives or combinations of these additives significantly reduced Ricinoleic Acid permeability in silastic membranes and porcine skin (Baynes and Riviere 2004).

Skin Penetration Enhancement

Ricinoleic Acid

In a study by Song et al. (2001), the effects of *cis*-9-octadecenoic acid (oleic acid) and a group of chemically related *cis*- (Ricinoleic Acid) and *trans*- (ricinelaidic acid) 12-monohydroxylated derivatives and their ethyl and methyl esters on the skin penetration of model hydrophobic (hydrocortisone) and hydrophilic (5-fluorouracil) drugs were evaluated in vitro using hairless mouse skin. Test solutions were prepared by placing either test compound (5-fluorouracil, 5.4 mg; hydrocortisone, 15 mg) with or without an unsaturated fatty acid (50 mg each) or fatty acid ester (50 mg each) in a screw-capped glass vial, and adding propylene glycol (final volume = 1 ml). The mixture was sonicated to effect complete dissolution. Permeation studies were conducted using Vlia-Chien diffusion cells and full thickness abdominal skin from female hairless HRS/J mice (6 weeks old). Ricinoleic Acid enhanced the in vitro transdermal permeation of 5-fluorouracil.

The transdermal penetration rate of hydroquinone from propylene glycol was very slow. However, in the presence of oleic acid, the penetration rate accelerated and was enhanced approximately 1800-fold. In the presence of Ricinoleic Acid, the enhancement of hydroquinone skin penetration was less than 1.5-fold. Regarding the penetration of 5-flurouracil, fluxes were much higher in the presence of oleic acid (333-fold increase; $p < .001$) than in the presence of Ricinoleic Acid (<5-fold increase) (Song et al. 2001).

Transepidermal Water Loss

Castor Oil

Lieb et al. (1988) evaluated transepidermal water loss (TEWL) using a modification of a flow-through diffusion cell that was originally designed by Bronaugh and Stewart (1985). The membrane was described as full-thickness, cartilage-stripped skin obtained from the ventral ear of the male Syrian golden hamster. Castor oil (10 μl) was placed on the skin (0.32-cm^2 area), and a TEWL rate–versus-time study was conducted. Tritiated water (HTO) permeated through the membrane into the diffusion cell's receptor compartment. Flux (TEWL, μg/cm^2/h) was determined (using a scintillation counter) by measuring the HTO that adsorbed to anhydrous calcium chloride in the receptor cell. Castor oil caused a marked decrease in the TEWL rate. For untreated skin, the mean TEWL rate was approximately 450 μg/cm^2/h at 1 h. Mean values for the TEWL rate were approximately 400 μg/cm^2/h at 1 h and 250 μg/cm^2/h at 24 h. Additionally, castor oil was the only substance that exhibited a burst effect, i.e., initially, the membrane became fully hydrated and swollen and was more permeable, providing an "increased push" effect to pass water through the membrane toward the anhydrous desiccant.

Effect on Smooth Muscle

Castor Oil and Ricinoleic Acid

Mathias et al. (1978) evaluated the effect of Castor Oil and Ricinoleic Acid on smooth muscle of the rabbit small intestine. Anesthetized male New Zealand white rabbits (weights between 1.5 and 3.0 kg) were used in ileal loop studies. Castor oil (dose = 0.85 ml/kg) was administered into the orad end of the ileal loop, and myoelectric recording techniques were used. Ricinoleic Acid was administered by intraluminal infusion (2 μg/kg/min [6 mM] into the orad end). The term migrating action potential complex (MAPC) was used to describe the myoelectric activity that has been observed in certain abnormal states. MAPC has been defined as action potential discharge activity occurring for longer than 2.5 s, on at least two consecutive electrode sites at 2.5-cm intervals, and having a propagation velocity of $\cong$1.0 cm/s. The myoelectric activity of castor oil and Ricinoleic Acid was similar to the MAPC that was observed in the cholera enterotoxin-infected loops. Castor oil induced an alteration in myoelectric activity.

In experiments that were designed to study the motor response in segments of the duodenum, mid-jejunum, terminal ileum, and sigmoid colon (four experiments, respectively), Ricinoleic Acid was diluted with 0.9% sodium chloride solution to a volume that would deliver 1.14 ml/h. No MAPC activity was observed in control experiments in which 0.9% sodium chloride solution was perfused into the duodenum at a rate of 1.14 ml/h. When compared to control values, there was no statistically significant difference in the slow wave frequency or slow wave propagation velocity in loops exposed to castor oil or Ricinoleic Acid (Mathias et al. 1978).

Lodge (1994) evaluated the potential for Ricinoleic Acid to induce vasoconstriction using tissues from male New Zealand white rabbits. After removal of the thoracic aorta and left and right external jugular veins, the vessels were cleaned and cut into rings. Following removal of the endothelium, the rings were suspended between two wire holders in tissue baths. Ricinoleic Acid was diluted with ethanol to produce final bath concentrations ranging from 0.1 to 30 μg/ml (molar concentration range of 0.335 to 100.50 μM). Ricinoleic Acid induced vasoconstriction ($EC_{50} = 0.24 \pm 0.04$ μg/ml) that was concentration-dependent and sensitive to the inhibitory effect of ifetroban, but not indomethacin. Ricinoleic acid also evoked concentration-dependent force development (constriction) in the aorta ($EC_{50} = 4.7 \pm 0.7$ μg/ml), and this response was antagonized by ifetroban.

Sodium Ricinoleate, Castor Oil, and Ricinoleic Acid

Stewart and Bass (1976a) evaluated the effects Sodium Ricinoleate, castor oil, and Ricinoleic Acid on the digestive contractility of the canine small bowel using four male, mixed breed dogs (weights between 10 and 15 g). After feeding, each animal received a single bolus infusion of Sodium Ricinoleate (500 mg in 30 ml of saline) into the duodenum. Saline (30-ml volume) served as the control. A duodenal cannula was implanted in each animal, and circular muscle activity was recorded for 1 h. Each animal was dosed with Sodium Ricinoleate in two experiments, and with isotonic saline (30 ml) in two control experiments. In additional experiments, alterations in digestive contractile patterns were monitored after administration (gastric tube) of castor oil or Ricinoleic Acid (volume = 10 ml) one h after feeding. Each treatment was repeated twice in each of two animals.

Intraduodenal administration of Sodium Ricinoleate produced a biphasic response in the proximal and mid-jejunum consisting of brief initial stimulation, followed by inhibition of digestive contractility. Compared to the control experiments, these stimulatory and inhibitory effects on intestinal contractility were described as significant ($p < .05$) changes in the average force per contraction. The changes in mid-jejunal digestive contractility were similar to those observed in the proximal jejunum.

The oral administration of Ricinoleic Acid (10 ml) induced alterations in digestive patterns that were qualitatively similar to those induced by the intraduodenal administration of Sodium Ricinoleate. Brief initial stimulation, followed by an apparent depression of intestinal contractility, was observed after oral dosing with Castor Oil (10 ml) (Stewart and Bass 1976a).

Sodium Ricinoleate and Methyl Ricinoleate

In a study by Stewart et al. (1975), Sodium Ricinoleate depressed the smooth muscle twitch response of the electrically driven guinea-pig ileum preparation at concentrations ranging from 1.25×10^{-5} to 4×10^{-4} M. Methyl Ricinoleate failed to depress the smooth muscle twitch response over this range of test concentrations. Similar results were reported for spontaneously contracting rabbit jejunum.

Antinociceptive Activity

Ricinoleic Acid and Potassium Ricinoleate

Vieira et al. (2000) evaluated the antinociceptive activity of Ricinoleic Acid (in peanut oil), dissolved in a vehicle containing 10% ethanol, 10% Tween 80, and 80% saline, using groups of 5 male albino Dunkin-Hartley guinea pigs (weights = 250 to 350 g) and groups of 8 to 10 male Swiss mice (weights = 20 to 25 g). A series of experiments was performed. In the first experiment, a single topical application of Ricinoleic Acid (900 μg/mouse) was made to the ventral surface of the right paw of each mouse. Test substance application was followed by intraplantar injection with carrageenan (to induce edema) 30 min later. Ricinoleic acid significantly reduced the reaction time to a heat stimulus, compared to treatment with the vehicle. When intraplantar injection with carageenan was preceded by repeated (8 days) topical applications of Ricinoleic Acid (900 μg/mouse), again, a marked prolongation of paw withdrawal latency to heat, compared to the vehicle control group, was noted.

Another experiment involved the repeated local application (8 days) of Ricinoleic Acid (900 μg/mouse) or the repeated (4 days) intradermal injection of Potassium Ricinoleate (30 μg/mouse) on the ventral surface of the right paw. Freund's adjuvant had been injected into the hindpaw on the first day. The paw withdrawal latency to a painful stimulus (heat) after topical application was increased over at least 2 weeks. The intradermal injection of Potassium Ricinoleate induced a significant antinociceptive effect that lasted for at least 3 weeks (Vieira et al. 2000).

Effect on Enzyme Activity

Ricinoleic Acid

In a study by Gaginella et al. (1978), isolated villus cells from the small intestine of the hamster were used to determine whether Ricinoleic Acid stimulates intestinal adenylate cyclase. In the adenylate cyclase assay, activity of the enzyme was determined using a method that is based upon the conversion of [$\alpha-^{32}$P]ATP to [^{32}P]cyclic AMP. The cell homogenates (30 to 50 μg of protein per tube) were incubated for 20 min. Ricinoleic Acid concentrations of 10^{-9} to 5×10^{-3} M did not cause dose-dependent stimulation of adenylate cyclase. Significant ($p < .05$), but slight, stimulation of adenylate cyclase was noted at a concentration of 10^{-5} M, and higher concentrations inhibited basal activity. Prostaglandin E_1, which is chemically similar to Ricinoleic Acid, was a potent stimulant of adenylate cyclase activity, causing dose-related stimulation ($p < .001$) of adenylate cyclase at concentrations of 10^{-9} to 10^{-4} M.

Simon and Kather (1980) studied the modulation of adenylate cyclase and cAMP-phosphodiesterase, key enzymes of cAMP metabolism, by Ricinoleic Acid in human colonic mucosa. The experiments were performed using histologically normal colonic mucosa obtained from eight patients (five males, three females) who were undergoing hemicolectomy for carcinoma or diverticulosis. Adenylate cyclase activity was determined according to the method of Salomon et al. (1974), and cyclic AMP phosphodiesterase activity was determined according to the method of Pöch (1971). Ricinoleic Acid was tested at concentrations ranging from 1×10^{-8} to 5×10^{-4} mol/l. Basal adenylate cyclase activity in homogenates of human colonic mucosa averaged 250 pmol cAMP/mg protein/15 min. Mean basal cAMP phosphodiesterase activity was 150 ± 15 pmoles per mg protein per minute.

Over the range of concentrations tested, dose-related stimulation of the large bowel adenylate cyclase was not observed. Basal activity of adenylate cyclase was inhibited at concentrations above 1×10^{-5} mol/l. Ricinoleic Acid did not influence soluble cAMP phosphodiesterase activity over the range of concentrations tested. Ricinoleic Acid was an ineffective stimulus of human colonic adenylate cyclase, and also was not a competitive

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inhibitor of soluble cAMP phosphodiesterase activity (Simon and Kather 1980).

In a study by Vanderhoek et al. (1980), the effect of Ricinoleic Acid on the oxygenation of [1-^{14}C]arachidonic acid by platelet cyclooxygenase and lipoxygenase enzymes was monitored using an oxygen electrode and by analysis of the radioactive products formed. The enzymes were obtained from human platelet concentrates (3 to 4 days old). Ricinoleic Acid did not appear to have an effect on either enzyme. The concentration of Ricinoleic Acid that was required for half-maximal inhibition of lipoxygenase or cyclooxygenase activity was >300 μM.

Beubler and Schrirgi-Degen (1992) studied the stimulation of enterocyte protein kinase C by laxatives in vitro using intestinal epithelial cell (from female Sprague-Dawley rats) preparations. A protein kinase C assay system was used to determine the activity of protein kinase C. This assay system is based on protein kinase C–catalyzed transfer of the γ-phosphate group of adenosine-5′-triphosphate to a peptide that is specific for protein kinase C. Ricinoleic Acid (dissolved in DMSO) stimulated protein kinase C activity in a concentration-dependent manner within the concentration range of 2 to 200 μg/ml.

Effect on Uridine Uptake

At a concentration of 50 μM, Ricinoleic Acid suppressed the uptake of uridine into human diploid fibroblasts in culture (Polgar and Taylor 1977).

Effect on Lipid Metabolism

Castor Oil

Ihara-Watanabe et al. (1999) evaluated the effect of the following diets on lipid metabolism using groups of five male Wistar rats (3 weeks old): 10% castor oil, 10% high-oleic safflower oil, and 10% coconut oil. The diets were prepared in the absence or presence of dietary cholesterol, and were fed ad libitum for 20 days. On day 20, blood samples were obtained and liver and perirenal adipose tissues were excised. Serum and hepatic lipids were analyzed for total cholesterol, high-density lipoprotein, triacylglycerols, and phospholipids.

Body weight gain and food intake were lowest for rats fed the castor oil diet enriched with cholesterol, but not for rats fed cholesterol-free diets. Body weight gain to consumption ratios were similar among all of the groups. Compared to rats fed the high-oleic safflower oil diet (enriched with cholesterol), rats fed the castor oil diet enriched with cholesterol had decreased liver weights (g/100 g of body weight). Data on liver weights were not presented in the study.

Values for total cholesterol and phospholipids in the serum were significantly decreased in rats fed castor oil, compared to rats fed high-oleic safflower oil in the absence or presence of cholesterol. For cholesterol-enriched diets, the lowest value for serum high-density lipoproteins was reported for the castor oil dietary group. No significant differences in serum triacylglycerol occurred between either of the dietary groups (with or without cholesterol in the diet).

Compared to the high-oleic safflower oil dietary group (with or without cholesterol), significantly decreased ($p < .05$) hepatic triacylglycerol concentrations were reported for the castor oil dietary group. For cholesterol-enriched diets, the castor oil and coconut oil dietary groups had significantly increased ($p < .05$) hepatic cholesterol when compared to the high-oleic safflower oil dietary group. It was concluded that castor oil had a hypocholesterolemic effect in rats in this study (Ihara-Watanabe et al. 1999).

Effect on Leukocyte Infiltration and Prostaglandin Synthesis

Castor Oil

Ohia et al. (1992) used castor oil as a vehicle control in a study evaluating the effects of steroids and immunosuppressive drugs on endotoxin-induced uveitis in rabbits. The vehicle control group consisted of four male New Zealand rabbits (weights = 1.5 to 2.0 kg). The animals were injected intramuscularly with castor oil (dose = 2 mg/kg). At 1 h post injection, both eyes of each rabbit were cleansed and anesthetized. This procedure was followed by the intravitreal injection of *Escherichia coli* endotoxin (100 ng). The animals were killed 24 h after injection of the endotoxin. Aqueous humor was obtained and leukocytes were counted. The eyes were then enucleated for microscopic examination. Compared to saline-treated controls, castor oil significantly reduced the infiltration of leukocytes and the prostaglandin E_2 (inflammatory mediator) content of the aqueous humor and iris-ciliary body. The authors concluded that Castor Oil had an anti-inflammatory effect in this study.

Effect on Cytokine-Induced Endothelial Cell Activation

Sodium Ricinoleate

De Caterina and Bernini (1998) evaluated the relationship between structural differences in fatty acids and the inhibition of endothelial activation, taking into consideration that dietary long-chain fatty acids may influence processes that involve endothelial activation (e.g., inflammation and atherosclerosis). To test for a potential stimulatory effect of fatty acids on adhesion molecule expression, sodium salts of saturated, monounsaturated (Sodium Ricinoleate included), and n-6 and n-3 polyunsaturated fatty acids were each incubated alone (test concentration = 25 μM) with human saphenous vein endothelial cells (HSVECs) for 72 h. The 72-h incubation period was followed by 16 h of stimulation with the cytokine interleukin (IL)-1α in the continuous presence of fatty acid salt. At the end of the incubation period, vascular cell adhesion molecule-1 (VCAM-1) expression was assessed using a cell surface enzyme immunoassay (EIA).

Sodium Ricinoleate significantly inhibited (considered modest; $p < .05$) cytokine-induced endothelial adhesion molecule

expression. DHA inhibited VCAM-1 expression ($p < .01$) most potently (De Caterina and Bernini 1998).

De Caterina and Bernini (1998) also conducted an experiment to determine whether the fatty acid sodium salts may induce endothelial activation in the absence of cytokines. The salts were incubated with endothelial cell monolayers for 24 h. Incubation periods prior to detection of adhesion molecule surface expression varied from 0 to 72 h. Neither Sodium Ricinoleate (25 μM) nor any other fatty acid sodium salt induced adhesion molecule expression, as assessed by EIA.

Ricinoleic Acid

In a study by De Caterina et al. (1995), the effect of Ricinoleic Acid on VCAM-1 expression was evaluated using rabbit coronary artery endothelium in vitro. VCAM-1 (marker for endothelial cell activation) is a surface protein that is not expressed by endothelial cells in vitro, but is inducible by exposure to inflammatory stimuli such as bacterial endotoxin, IL-1, or tumor necrosis factor α (TNFα). Ricinoleic Acid significantly reduced IL-4–induced VACM-1 expression (50% inhibitory concentration between 10 and 100 μM). Neither cell number nor viability was increased in this concentration range. Ricinoleic Acid did not inhibit TNFα-induced VACM-1 expression to any significant extent.

Effect on Prostaglandin Synthesis

Castor Oil

Gao et al. (1999) evaluated the effect of castor oil in the diet on the synthesis of prostaglandin E_2 (PGE_2) and the induction of labor using two groups of eight pregnant Wistar rats (at gestation day 18; test and control groups, respectively). Two milliliters of castor oil–containing diet were administered by gavage daily for a total of four feedings. The diet (labor-inducing diet) consisted of castor oil (30 ml) + one chicken egg, blended and heated to a thick consistency. At 4 h after the fourth feeding, the pregnant females were killed. Compared to the control group, a significant increase in concentrations of PGE_2 in tissues of the intestinal mucosa, placenta, amnion, and amniotic cells was noted in test animals. The authors stated that the increased synthesis of PGE_2 "is a key of" the initiation of labor that is induced by a castor oil diet.

Cytotoxicity

Sodium Ricinoleate

Gaginella et al. (1977b) evaluated the cytotoxicity of Ricinoleic Acid using epithelial cells that were isolated from the small intestines of male Syrian hamsters. Cytotoxicity was assessed by exclusion of trypan blue, the release of intracellular (prelabeled) ^{51}Cr, and inhibition of the cellular uptake of 3-O-methylglucose. The results produced by all three methods indicated that Sodium Ricinoleate produced a dose-dependent cytotoxicity.

For the trypan blue exclusion method, Sodium Ricinoleate caused dose-related increases in cytotoxicity at concentrations of 0.1 to 5.0 mM. Death of all cells was noted at a concentration of 2.0 mM. Results for control incubation in the ^{51}Cr release assay indicated that 26.8 $\pm$ 1.7% of ^{51}Cr, initially within or bound to the cells, was released into the medium. Sodium Ricinoleate induced concentration-dependent (0.1 to 5 mM Sodium Ricinoleate) increases in ^{51}Cr release, from 4.2% to 54.8% above the control value. In the 3-O-methylglucose uptake assay, Sodium Ricinoleate inhibited the uptake of 3-O-methylglucose over a concentration range of 0.1 to 2.0 mM (Gaginella et al. 1977b).

In a study by De Caterina and Bernini (1998), the cytotoxicity of Sodium Ricinoleate and other fatty acid sodium salts in human saphenous vein endothelial cell cultures was evaluated. Cell count, trypan blue exclusion, and [^{3}H]leucine incorporation into total cell-associated and released proteins were monitored. For the latter of the three, trichloroacetic acid precipitation of total cell extracts and cell supernates was performed. At concentrations $\leq$25 μM, Sodium Ricinoleate and other fatty acid sodium salts did not induce significant toxicity (based on cell count and trypan blue exclusion) for periods up to 72 h prior to cytokine stimulation.

Antimicrobial Activity

Castor Oil

Morris et al. (1979) evaluated the antimicrobial activity of castor oil on *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* using the Petri plate–paper disc procedure. Paper discs were soaked with 20 μl of a 10% Castor Oil solution, and the discs were immediately applied to solidified, seeded agar (1 disc per plate). The plates were incubated for 10 to 24 h. Discs containing 95% ethanol (20 μl) served as negative controls. Castor Oil did not have antimicrobial activity on any of the strains tested.

Sodium Ricinoleate

Whiteside-Carlson et al. (1955) studied the effect of Sodium Ricinoleate on cell division using a laboratory strain of *E. coli*. Sodium Ricinoleate was tested over a concentration range of 1 to 5 mg/ml of medium. The cultivation of *E. coli* on nutrient agar that was saturated with Sodium Ricinoleate caused the development of filamentous forms during the first h of logarithmic growth. By the end of the log phase, organisms of normal morphology were observed. When agar containing Sodium Ricinoleate was adjusted to pH values of 5 to 8, filament formation was more marked and persisted for longer periods at the more alkaline pH value. The utilization of liquid proteose-peptone medium (with periodic readjustment of the pH to a range of 7.6 to 7.8) resulted in maintenance of the cells in filamentous form throughout the entire growth cycle. The tendency toward filament formation was reduced by lowering the incubation temperature to below 37°C. The results of this study indicate

that Sodium Ricinoleate interfered with cell division in *E. coli*, causing the organisms to develop as filaments.

Mordenti et al. (1982) studied the activity of Sodium Ricinoleate against *Streptococcus mutans* strain 6715-13 (plaque) in vitro. The minimum inhibitory concentration of Sodium Ricinoleate against *S. mutans* was 1% (or 3.12×10^{-2} M). During testing for the minimum inhibitory concentration, the following four distinct concentration-dependent cell growth and acid production phenomena were identified: (1) no cell growth, pH > 6.8; (2) cell growth, medium pH > 6.8; (3) cell growth, medium pH of 5.2 to 6.8; and (4) cell growth, medium pH < 5.2. It was concluded that Sodium Ricinoleate had bactericidal activity in this assay. In subsequent experiments, wire-adherent plaque specimens were treated with various concentrations of Sodium Ricinoleate. The intact plaque samples survived in each of these tests. The authors stated that the ability for Sodium Ricinoleate to kill bacteria in suspension, but not in intact plaque, clearly demonstrates the absence of a correlation between antibacterial activity against cells in suspension and antiplaque activity.

Other Biological Effects

Castor Oil

Capasso et al. (1986) evaluated the effect of castor oil on the formation of histamine, 5-hydroxytryptamine (5-HT), and prostaglandin-like material (PG-LM) in the rat intestine using male, fasted Wistar-Nossan rats (number and weights not stated). Castor oil (dose = 2 ml/rat) was administered by gavage. Following the onset of diarrhea, the animals were killed, and sections of colon removed. Untreated rats served as controls. Castor oil induced an approximately fourfold increase in PG-LM ($p < .01$) and a threefold increase in histamine and 5-HT ($p < .01$). A decrease in the Castor oil–induced colonic formation of PG-LM was noted following pretreatment of the animals with indomethacin (inhibitor of prostaglandin biosynthesis) or hydrocortisone. It was concluded that these data support the idea that the laxative effect of castor oil is the result of increased intestinal production of PG-LM, histamine, and 5-HT.

A study was conducted by Pinto et al. (1989) to determine whether oral administration of castor oil leads to changes in the levels of platelet-activating factor (PAF) formed by intestinal tissue, and whether these changes are related to intestinal damage. Fasted, male Wistar-Nossan rats (number not stated; weights = 130 to 140 g) were used. Castor oil (dose = 2 ml/rat) was administered orally, and the animals were killed.

At 3 h post dosing, the formation of PAF by segments of rat intestine was significantly increased (compared to control rats treated with olive oil) in the following intestinal segments: duodenum ($p < .001$), jejunum ($p < .01$), ileum ($p < .2$), and colon ($p < .1$). At macroscopic examination, extensive regions of hyperemia were noted in the entire intestinal mucosa. The duodenum and jejunum regions were the most severely affected. No increase in PAF was noted in control rats dosed with olive oil.

Compared to control rats dosed with olive oil, castor oil also increased the intraluminal release of acid phosphatase (AP) in the duodenum and jejunum ($p < .01$), and a similar trend was reported for the ileum and colon ($p < 0.2$ to .1). A correlation between increased release of AP and intestinal hyperemia was established. The authors noted that the results of this study suggest that PAF is involved in the mechanism underlying castor oil–induced intestinal damage (Pinto et al. 1989).

In a study by Blair et al. (2000), the affinity of castor oil and numerous other chemicals for the estrogen receptor (from uteri of ovariectomized Sprague-Dawley rats) was evaluated using a validated estrogen receptor competitive binding assay. In this assay, the ability for a chemical to compete with [^{3}H]estradiol ([^{3}H]E_2) for the estrogen receptor was determined, based on IC_{50} (concentration resulting in 50% inhibition of [^{3}H]estradiol binding) values. All assays were replicated a minimum of two times. The mean IC_{50} for Castor oil was $>1.0 \times 10^{-4}$ M. Mean IC_{50} values for 4-heptyloxyphenol and phenophthalein (both classified as moderate estrogen receptor binders) were $6.75 \times 10^{-5} \pm 0.75 \times 10^{-5}$ and $6.73 \times 10^{-6} \pm 1.79 \times 10^{-6}$, respectively. The binding affinity of castor oil for the estrogen receptor was not classified.

Ricinoleic Acid

In a study by Grainger et al. (1982), the effect of Ricinoleic Acid on lymph flow in outerperfused segments of cat ileum was evaluated. The cats were anesthetized and a segment of ileum with intact innervation and lymphatic drainage was isolated and perfused by the intact mesenteric artery. A cannula was inserted into a large lymphatic vessel emerging from the mesenteric pedicle, and lymph flow was determined by observing lymph movement in a calibrated pipette that was connected to the lymphatic cannula. The mean control (± *SE*) value for intestinal lymph flow in the experiments was 0.048 ± 0.005 ml/min × 100 g. Net fluid secretion was stimulated by intraluminal instillation of 5 mM Ricinoleic Acid. The peak increase in intestinal lymph flow produced by Ricinoleic Acid in all experiments was 6.3 ± 1.2 ($n = 5$) times the control. The maximal fluid excretion rate observed with Ricinoleic Acid was 0.43 ± 0.23 ml/min × 100 g.

Yagaloff et al. (1995) evaluated the inhibitory activity of a series of fatty acids and fatty acid derivatives on [^{3}H]leukotriene B_4 binding (LTB_4) to pig neutrophil membranes using the LTB_4 receptor binding assay. The most potent chemicals were 15-hydroxy-DGLA (20:3; $K_i = 1$ μM), eicosadienoic acid (20:2; $K_i = 3$ μM), and Ricinelaidic Acid (18:1; $K_i = 2$ μM). Ricinoleic Acid (18:1) had a K_i of 9 μM.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Castor Oil

In a study by Capasso et al. (1994), castor oil (2 ml) was administered orally to ten male Wistar rats (weights = 160 to

180 g). The animals were killed and two segments from standardized regions of the duodenum and jejunum were visibly evaluated for macroscopic damage. Mucosal injury was graded according to the following scale: 0 (normal), 1 (hyperemia), 2 (hyperemia with evidence of hemorrhage into the lumen), and 3 (severe hemorrhage into the lumen).

Copious diarrhea was reported for all animals on days 3, 5, and 7 post dosing. Macroscopic damage, characterized mainly by vasocongestion, was observed throughout the duodenum and jejunum. The injury observed ranged from mild (at 1 h) to severe (at 5 h), and was less severe at 7 h. Injury was not observed at 0.5 or 9 h after dosing. Castor oil–induced mucosal damage was associated with statistically significant intraluminal release of acid phosphatase.

In additional experiments (groups of 10 rats), mucosal damage induced by castor oil was exacerbated in the presence of a nitric oxide synthase inhibitor (N^{ω}-nitro-l-arginine methyl ester), suggesting that nitric oxide provides protection against castor oil-induced mucosal damage (Capasso et al. 1994).

In a study involving male Crl:CD BR rats, the findings suggested that castor oil–induced diarrhea is the result of activation of NK_1 and NK_2 receptors by endogenous tachykinins (Croci et al. 1997).

In a study by Johnson et al. (1993), castor oil was administered orally to 12 ponies (17 months to 20 years old; weights = 160 to 250 kg). The ponies were randomly assigned to two treatment groups and one control group (four ponies per group). Each animal received a single 2.5 ml/kg body weight dose of castor oil via nasogastric tube. Diarrhea occurred within 24 h of dosing. The animals were killed and necropsied at 24, 48, and 72 h post dosing. Intestinal tissues were removed and subjected to gross and microscopic examination.

In ponies killed at 24 or 48 h, gross lesions were most severe in the cecum and ventral colon. At 24 h, the mucosa of the distal jejunum, ileum, cecum, and ventral colon was diffusely red. Most of the ponies dosed with castor oil had generalized hyperemia of the intestinal mucosa at 24, 48, and 72 h post dosing, and mesenteric, cecal, and colonic lymph nodes were edematous. Mucosal and submucosal edema of the ileum, cecum, and ventral colon was noted in all ponies dosed with castor oil. At 72 h post dosing, focal acute ulceration and intense mucosal hyperemia of the glandular stomach was observed in three of four ponies dosed with castor oil.

Microscopic changes in the superficial enterocytes of the cecum and ventral colon that were characterized as follows: loss of microvilli; distortion of the cytoplasmic terminal web; expansion of the cytoplasmic matrix, with formation of precipitates; and widening of intracellular spaces between junctional complexes. Castor oil induced acute superficial enterocolitis in ponies. Dosing was associated with transient diarrhea, neutrophilic inflammation, and mucosal erosion in the cecum and ventral colon (Johnson et al. 1993).

Hydrogenated Castor Oil

The acute oral toxicity of a 25% solution of Hydrogenated castor oil in olive oil was evaluated in a study involving ten male Wistar rats (average body weight = 155 g). The test solution (dose = 10 g/kg) was administered via a gastric probe. Toxic signs were not observed in any of the animals, indicating that the test substance was well tolerated. The LD_{50} was >10 g/kg (Allegri et al. 1981).

Ricinoleic Acid

In a study by Okui et al. (1964), male albino rats (number not stated; weight = 120 ± 10 g) were injected intraperitoneally (i.p.) with 100 mg Ricinoleic Acid. All of the animals were dead within 24 h. The i.p. injection of a 5% Ricinoleic Acid emulsion (1 ml) was tolerable, but caused an increase in the following: amount of ascites, conglutination of peritoneal organs, and swelling of the liver. However, histological changes were not observed in liver specimens.

Cetyl Ricinoleate

In an acute oral toxicity test performed by Laboratoire de Recherche et d'Experimentation (1994), Cetyl Ricinoleate was evaluated using five female NMRI EOPS mice (weights = 19 to 22 g). Oral dosing (single dose 2000 mg/kg) was followed by a 6-day observation period. None of the animals died, and clinical and behavioral evaluations were normal. Weight gain was considered satisfactory. The authors stated that Cetyl Ricinoleate was non-toxic in this study.

Ethyl Ricinoleate

The acute oral toxicity of Ethyl Ricinoleate was evaluated using 10 rats (weights and strain not stated). The acute oral LD_{50} exceeded 5.0 g/kg; one animal receiving this dose died. The following clinical signs were observed during the study: isolated instances of diarrhea, chromorhinorrhea, ptosis, and chromodacryorrhea. At necropsy, gross observations were normal for eight animals. Necropsy of the remaining two animals revealed the following changes in either one or both animals: red and/or yellow areas in the intestines, red areas in the stomach, mottled liver, mottled spleen, mottled kidneys, dark lungs, red exudate in the anogenital area, and a large amount of blood in the bladder (Research Institute for Fragrance Materials [RIFM] 2000).

Acute Dermal Toxicity

Ethyl Ricinoleate

The acute dermal toxicity of Ethyl Ricinoleate was evaluated using six rabbits (weights and strain not stated). The acute dermal LD_{50} exceeded 5.0 g/kg; one animal receiving this dose died. The following clinical signs were observed during the study: isolated instances of lethargy, diarrhea, ptosis, and yellow nasal discharge, and moderate erythema (six rabbits), slight edema (one rabbit), and moderate edema (five rabbits). At necropsy,

gross observations were normal for three animals. Necropsy of the remaining animals revealed the following changes: red areas in the intestines, mottled liver, white nodules in the liver, dark areas in the lungs, mottled kidneys, pale kidneys, dark spleen, and dark areas in the stomach (RIFM 2000).

Acute Intravenous Toxicity

Castor Oil

In a study by Lorenz et al. (1982), castor oil was administered intravenously (single bolus dose = 0.1 ml/kg) to each of eight anesthetized adult mongrel dogs (four males, four females; mean weight = 20.5 kg). Blood for histamine assays was obtained at 2, 5, 10, 15, and 20 min post dosing. The incidence of the following signs was determined: erythema, hives (papules and wheals), edema, defecation, tachypnea, hypotension, and death (circulatory arrest). None of the animals died, and erythema (one animal; score not stated) was the only clinical sign that was reported. An increase in blood histamine occurred in one of the eight animals. At 2 min post dosing, the increase was 0.6 ng/ml of whole blood (maximum response) in this animal. The authors concluded that castor oil was ineffective in terms of its ability to cause histamine release.

Short-Term Oral Toxicity

Castor Oil

Masri et al. (1962) conducted an experiment in which ten male weanling rats (4 weeks old; mean weight = 42.2 ± 0.6 g) were fed (ad libitum) 10% castor oil for approximately 5 weeks. A similar control group (mean weight = 42.2 ± 0.5 g) received corn oil in the diet. The animals were observed for growth and catharsis throughout the duration of the study. Castor oil in the diet did not induce catharsis in any of the 10 rats, and growth of these animals was comparable to that observed in the control group. At the end of the experiment, mean weights for test and control rats were 155.6 ± 4.6 and 160.5 ± 4.1 g, respectively. Grossly, there were no abnormalities. Additionally, no abnormalities of the perirenal fat were noted.

Short-Term Subcutaneous Toxicity

Castor Oil

In a study by Migally (1979), the morphology of the adrenal cortex was examined after injection of a commonly used vehicle consisting of castor oil and benzyl benzoate. Twenty-five adult C57 BL/6J mice (weights not stated) were divided into the following groups: group I (five intact control mice); group II (five sham-injected mice); group III (five mice each injected with 0.1 ml castor oil); group IV (five mice each injected with 0.1 ml benzyl benzoate; and group V (five mice each injected with 0.1 ml castor oil and benzyl benzoate [4:1]). The mice were injected subcutaneously daily for four weeks and then killed. Necropsy was then performed and tissues prepared for light and electron microscopic examination.

Using electron microscopy, parenchymal cells containing electron-dense lipid inclusions were observed in the zona fasciculata of adrenal glands from mice injected with castor oil. By light microscopy, there was no difference between adrenal glands from control mice and mice injected with the vehicle consisting of castor oil and benzyl benzoate; however, by electron microscopy, the following variations were observed: profound disruption of parenchymal mitochondria in the zona fasciculata and a noticeable increase in size for some of the mitochondria. The vesicular orientation of the inner mitochondrial membrane was lost (i.e., random orientation), and diminution of the mitochondrial matrix was also observed.

Unlike the controls, the macrophages of exposed animals had large vacuoles filled with globular material. In the zona reticularis and inner zona fasciculata, parenchymal mitochondria with circular orientation of the inner membrane (normally few) were noticeably increased in number. The authors noted the appearance of similar mitochondria following adrenocorticotrophic hormone (ACTH) stimulation, and that the alteration of ACTH release has been shown to result from stress. The author concluded that subcutaneous injection of the castor oil–benzyl benzoate vehicle caused morphological alterations that are suggestive of stress-induced changes (Migally 1979).

Subchronic Oral Toxicity

Castor Oil

In a study by the National Toxicology Program (NTP) (1992), the subchronic oral toxicity of castor oil was evaluated using groups of 10 male and 10 female F344/N rats (mean body weights = 126 to 132 g [males]; 107 to 110 g [females]) and groups of 10 male and 10 female B6C3F_1 mice (mean body weights = 22.6 to 23.0 [males]; 17.2 to 17.7 [females]). In the core study, five groups of test animals (mice or rats) received diets containing 0.62%, 1.25%, 2.5%, 5.0%, or 10% castor oil continuously for 13 weeks. Two control groups of 20 rats and 20 mice received diets that did not contain castor oil.

Ten additional rats/sex were included at each dose level for evaluation of hematological and clinical chemistry parameters. On days 5 and 21, these animals were anesthetized with CO_2 and blood samples were obtained. These animals were killed following blood collection on day 21. Blood samples for hematology and clinical chemistry were also collected from core-study rats at the end of the study. Also, at the end of the 13-week study, all core-study animals were killed and complete necropsies were performed, including complete microscopic examination on tissues, on all test and control animals.

No effect on survival or significant differences in average food consumption were noted in any of the five groups of male and female rats fed castor oil. There were no significant differences in mean body weights between test and control groups.

The following hematological effects were reported for male rats: a slight decrease in mean corpuscular hemoglobin

concentration (MCHC) (10% castor oil diet), a statistically significant decrease ($p < .05$) in mean corpuscular volume (MCV) (10% castor oil diet), a decrease in mean corpuscular hemoglobin (MCH) (5% and 10% castor oil diets), and an increase in platelets (1.25%, 5%, and 10% castor oil diets). The only hematological abnormality reported for female rats was a statistically significant ($p < .05$) decrease in reticulocyte counts (0.62% or 10% castor oil diets). The authors did not consider the hematological effects to be biologically significant. A dose-related increase (treatment-related) in the activity of serum alkaline phosphatase was noted in male and female rats at days 5 and 21, and at the end of the study.

Increased heart-to-body weight ratios were reported for male rats that received 0.62%, 2.5%, and 10.0% castor oil diets; however, no increase in absolute heart weight was noted. The observed differences in organ-to-body weight ratios were not considered treatment related. Microscopically, no morphologic changes were associated with the slight differences in organ weights between the dietary groups.

Compared to controls, liver weights were increased in male and female mice receiving diets containing 5% or 10% castor oil. Increased kidney weights were reported for female mice that received 5% or 10% castor oil in the diet. Microscopically, there was no evidence of morphologic changes that could be been associated with the slight differences in organ weights between the groups tested. Additionally, there was no evidence of treatment-related lesions in any of the tissues or organs that were examined (all dietary groups).

The authors concluded that diets containing up to 10% castor oil to $B6C3F_1$ mice and F344/N rats was not associated with toxicity to any specific organ, organ system, or tissue in this study (NTP 1992).

Hydrogenated Castor Oil

In a preliminary feeding trial (preparatory to the 16-week feeding study reported below) by Binder et al. (1970), the subchronic oral toxicity of 5%, 10%, and 20% Hydrogenated Castor Oil [HCO] (effective concentrations of 4.33%, 8.65%, and 17.3%, respectively) in the diet was evaluated using groups of three weanling female rats (Slonaker substrain of Wistar strain). The sample of HCO that was incorporated into the diet contained 86.5% 12-hydroxystearic acid, 10.3% nonoxygenated acids, and 3.2% 12-ketostearic acid. The three groups were fed for 90 days, and the control group received diet only. At necropsy, organ weights were recorded and numerous tissues were prepared for microscopic examination. Prior to necropsy, blood samples were obtained for hematological evaluation.

A reduced growth rate in rats fed 8.65% and 17.3% Hydrogenated Castor Oil, respectively, was the only abnormality that was noted. The authors stated that it is likely that Hydrogenated Castor Oil was poorly digested because of its high melting point. Therefore, the poor body weight gains may have been due to the lower caloric density of the diets containing Hydrogenated Castor Oil at concentrations $\geq$8.65%.

To confirm the authors' explanation of the results, the experimental trial was repeated with Hydrogenated Castor Oil at concentrations of 1%, 5%, and 10% in corn oil (effective concentrations of 0.865%, 4.33%, and 8.65%, respectively). The amount of corn oil added to the individual diets was 9%, 15%, and 10%. Corn oil (20%) was present in the control diet. Necropsy was performed at the end of the 90-day feeding period. The growth rate for rats fed 8.65% Hydrogenated Castor Oil in the diet was equivalent to that of the other dietary groups. Based on organ weight determinations and the results of hematological and microscopic evaluations, no adverse effects were observed (Binder et al. 1970).

In the 16-week feeding study (Binder et al. 1970), groups of 15 male albino rats (Slonaker substrain of Wistar strain, weights = 43 to 83 g) received diets containing the following oils: group 1 (fed 0.865% HCO + 19% corn oil for 16 weeks), group 2 (0.865% HCO + 19% corn oil for 8 weeks, then 20% corn oil for 8 weeks), group 3 (8.65% HCO + 10% corn oil for 16 weeks), and group 4 (8.65% HCO + 10% corn oil for 8 weeks, then 20% corn oil for 8 weeks).

The effective dietary concentrations of Hydrogenated Castor Oil in the 0.865% and 8.65% diets were 0.865% and 8.65%, respectively. The control group received 20% corn oil in the diet for 16 weeks.

At 4, 8, 12, and 16 weeks, the number of animals on the HCO diets that were alive was 33, 30, 12, and 6 rats, respectively. The corresponding number of rats remaining on the control diet was 15, 15, 12, and 6.

Weight differences due to the different diets at 4 and 8 weeks were not statistically significant at the 95% level. However, at 12 weeks, rats on the 8.65% HCO diet weighed significantly less than rats on the control diet or 0.865% HCO diet. At 16 weeks, the weight gain of rats on the control diet was significantly greater than that of rats on the 8.65% HCO diet for 16 weeks or on the 8.65% HCO diet for 8 weeks + control diet for the remaining 8 weeks. The weight gain of rats on the 0.865% HCO diet was not significantly different from that of rats on the control diet. Except for the reduced growth rate in rats receiving the 8.65% HCO diet, no adverse effects were observed (Binder et al. 1970).

Ocular Irritation/Toxicity

Castor Oil

Carpenter and Smyth (1946) evaluated the ocular irritation potential of castor oil using albino rabbits. The eyelids were retracted, and undiluted castor oil (0.5 ml) was applied to the center of the cornea. At approximately 1 min post instillation, the eyelids were released. Reactions were scored 18 to 24 h later. To determine the score for ocular injury, the individual numerical scores for each eye were added together and then divided by the number of eyes (usually 5). An ocular injury score of 5.0 represents severe injury, and corresponds to necrosis (covering approximately three-fourths of the corneal surface) that is visible only after staining or a more severe necrosis covering a smaller

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area. An injury grade of 1 (maximum score possible = 20) was reported for castor oil.

In a study by Guillot et al. (1979), the effects of various oils (used in cosmetics) on the rabbit eye were assessed according to the official French methods. Following the instillation of undiluted castor oil (no ocular rinsing), no corneal involvement was found. However, slight congestion of the iris and conjunctiva was observed.

Castor oil served as one of the vehicle controls in a study by Behrens-Baumann et al. (1986) investigating the effect of topical cyclosporin A on the abraded and intact rabbit cornea. Two castor oil vehicle control groups of outbred male rabbits were used. In both groups (10 eyes/group), 10 drops of castor oil were instilled daily for 3 weeks, and all eyes were examined using a slit-lamp. At the end of the 3-week period, the animals were killed and their corneas were excised and prepared for scanning and transmission electron microscopy. For eyes (no corneal abrasion) treated with Castor oil and examined by scanning electron microscopy, there were increased numbers of medium dark and dark epithelial cells (compared to the normal epithelium). The cell borders were intact and the number of holes was reduced. By transmission electron microscopy, corneal endothelial cells were intact. By scanning electron microscopy, an intact cell pattern, with more cell microstructures than normal, for the corneal endothelium was reported. Ultrathin sections appeared normal. The authors concluded that castor oil did not damage the rabbit corneal epithelium or endothelium (Behrens-Baumann et al. 1986).

Skin Irritation

Castor Oil

Butcher (1951) evaluated the effect of castor oil and other substances on rat epidermis using, primarily, 22-day-old albino or Long-Evans rats or rats of either strain in which the hair follicles were in the resting stage; older animals were also used. A total of 216 rats were used in the experiments. Using dry cotton, castor oil was gently swabbed onto a large area of the dorsum (clipped free of hair) daily for 5 days to 2 weeks. At the end of the application period, small areas of skin were obtained from the backs of treated and control (one rat/litter) rats and examined microscopically. Castor oil was described as having a mild effect on the epidermis. The alteration was mainly confined to the stratum granulosum, where the cells were more numerous and the granules were more evident, compared to the litter-mate controls.

In a study by Meyer et al. (1976), castor oil (undiluted, 4 drops) was rubbed onto either side of the shaved left flank of each of six albino guinea pigs (weights = 300 to 400 g) and six young pigs (weights = 10 to 12 kg) within 30 s on 10 successive days. The opposite side served as the control field, and was massaged only. The animals were killed on day 11. A tissue section (1 × 1 cm) was excised from the center of the test fields and prepared for microscopic examination. Five to eight sections of 7 μm thickness per test area were used for evaluation. A micrometer eyepiece was inserted into the microscope, and epidermal width measurements (25 per individual field; 400× magnification) were made. Castor oil induced slight reddening at the application site.

Microscopically (pigs and guinea pigs), hyperplasia, with an increase in the cell and nuclear density of the basal cell layers, was observed. Additionally, widening of the granular layer and thick keratohyalin granules were observed. Average epidermal widths (25 measurements) were as follows at the end of the 10-day application period: guinea pigs (control, 27.9 μm; test, 94.3 μm) and pigs (control, 26.5 μm; test, 32.3 m) (Meyer et al. 1976).

Rantuccio et al. (1981) evaluated the effect of undiluted castor oil on the skin of five female albino rabbits (6 months old; mean weight = 2500 g). The test substance (0.5 ml) was gently massaged into depilated skin of the right flank of each rabbit daily for 30 days. Following each daily application, the test site was covered with a simple protective dressing. Two small skin punch biopsies were obtained from the right and left (control) flank on days 10, 20, and 30. Macroscopic skin changes included slight erythema and slight edema. Microscopic examination of punch biopsies obtained at day 10 revealed "clear-cut" acanthosis with vacuolization and disorganization of the basal layer. These changes were associated with some infiltration of the dermis by mononuclear cells and fibrocytes. After days 20 and 30, the epithelial changes became progressively more evident. However, the appearance of the infiltrate remained unchanged.

In a study by Guillot et al. (1979), the effect of various oils that are used in cosmetics on rabbit skin was assessed according to the official French methods. An open skin irritation test and repeated application test (8 weeks) were performed. The authors stated that the two samples of undiluted castor oil, as well as 10% aqueous castor oil, were well tolerated.

In a study by Motoyoshi et al. (1979), the skin irritation potential of castor oil (undiluted) was evaluated using six albino angora rabbits (average weight = 2.6 kg). The test substance (0.1 g of liquid or semisolid) was applied for 24 h to two test areas (clipped free of hair) on the dorsal surface of each animal. A plastic collar was wrapped around the neck of each animal and remained throughout the application period, after which reactions were scored according to the following scale: − (no reddening) to +++ (severe reddening, beet redness). At 30 min, after reactions were scored, the test areas were clipped free of hair and castor oil was reapplied according to the same procedure. A third application of Castor Oil occurred 48 h later, and reactions were scored. Reactions were scored again at 72 h. Castor oil was severely irritating to the skin of rabbits (score = 3).

The skin irritation potential of Castor oil was also evaluated using guinea pigs, rats, and miniature swine in this study.

Undiluted castor oil (0.1 g) was applied daily to dorsal skin (clipped free of hair) in the mid-lumbar region of six male Hartley guinea pigs (weights = 350 to 500 g) and six male Wistar rats (weights = 250 to 350 g). The period of testing, the frequency of application, and the method of evaluation of skin reactions were

the same as those in the preceding test involving albino angora rabbits. Castor oil was mildly irritating to the skin of guinea pigs and rats.

The skin irritation potential of undiluted castor oil was evaluated using six miniature swine of the Pitman-Moore strain (1 month old). The test substance (0.05 g) was introduced under a 15-mm-diameter patch that was secured with adhesive tape. The entire trunk was wrapped with rubberized cloth during the 48-h exposure period. Reactions were scored after patch removal. The grading scale was the same as that used in the experiment involving albino angora rabbits that is summarized above. Castor oil was not irritating to the skin of miniature swine (Motoyoshi et al. 1979).

Ricinoleic Acid

In a study by Vieira et al. (2000), 8 to 10 male Swiss mice received a single topical application of Ricinoleic Acid (in peanut oil, 10 mg/mouse) on the ventral surface of the paw. Neither erythema nor edema of the paw was observed.

Vieira et al. (2001) presented results on the skin irritation potential of Ricinoleic Acid, using groups of six male albino Dunkin-Hartley guinea pigs, in a study evaluating pro- and anti-inflammatory effects of Ricinoleic Acid (concentration not stated). Ricinoleic Acid (0.1 ml, in peanut oil) was administered topically to the entire eyelid surface. The thickness of the eyelid was measured in mm using ophthalmic microcallipers. Topical treatment with Ricinoleic Acid (10, 30, or 100 mg/guinea pig) caused eyelid reddening and edema. A moderate, dose-dependent eyelid edema was reported as follows: 0.12 ± 0.05 mm (10 mg Ricinoleic Acid), 0.18 ± 0.02 mg (30 mg), and 0.23 ± 0.1 mm (100 mg). Maximal edema was achieved at 2 h post-application. The application of Ricinoleic acid vehicle did not cause any appreciable edema.

Cetyl Ricinoleate

In a skin irritation study conducted by the Laboratoire de Recherche et d'Experimentation (1994), Cetyl Ricinoleate (test concentration not stated) was evaluated using three male New Zealand albino rabbits. Erythema and edema were observed in three and two rabbits, respectively, up to 72 h post application. At 72 h, one rabbit had an erythema score of 2 and the remaining two had an erythema score of 1. Edema (score = 1) was observed in two rabbits at 72 h. All reactions were totally reversible at 7 days post application. Cetyl Ricinoleate was a nonirritant in this study.

Zinc Ricinoleate

In a study by International Bio-Research, Inc. (1977a), the skin irritation potential of 10% Griillocin HY 77 (now TEGODEO HY 77) in soybean oil was evaluated using six New Zealand albino rabbits (weight range = 2.4 to 2.6 kg). TEGODEO HY 77 (trade name mixture for Zinc Ricinoleate) has the following composition: Zinc Ricinoleate (more than 50%), triethanolamine (10% to 25%), dipropylene glycol (1% to 5%), and lactic acid (1% to 5%). The diluted test substance (concentration after dilution not stated) was applied to clipped skin on two areas of the back of each animal; one of the areas was abraded. The test sites were covered with occlusive patches (secured with adhesive tape) and the entire trunk was wrapped in a rubber sleeve. The patches remained in place for 24 h and reactions were scored at 24 and 72 h post application as follows according the Draize scale: 0 (no erythema) to 4 (severe erythema [beet redness] to slight eschar formation [injuries in depth] and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond area of exposure).

At 24 h post application, well-defined erythema was observed at the abraded test sites of all six rabbits and slight erythema was observed at the intact sites of four rabbits. Well-defined erythema was observed at the intact sites of two rabbits during the 24-h reading. At 72 h post application, five rabbits had mild erythema at the abraded site and two rabbits had the same reaction at the intact site. Using the data for abraded and intact test sites, a total primary irritation index of 1.1 was calculated (International Bio-Research, Inc. 1977a).

Effect on Intestinal Membranes

Ricinoleic Acid

In a study by Morehouse et al. (1986), a single 0.1 ml dose of Ricinoleic Acid (100 mg/ml) was administered intragastrically to fasted, specific pathogen-free mice (strain CD-1, number not stated). This dosage of Ricinoleic Acid was determined, on a weight basis, to be approximately the dosage that is used therapeutically in humans. Groups of mice were killed at various intervals, and light microscopy and transmission and scanning electron microscopy were used to identify structural alterations. At 2 h post dosing, the duodenal villi were markedly shortened when compared to control duodenal villi. This erosion of the villi throughout the duodenum caused massive exfoliation of columnar and goblet cells, filling the lumen with cellular debris and mucus. Disruption of the mucosal barrier resulted in continuity between the intestinal lumen and lamina priopria of the villi, with the loss of formed blood elements and lamina propria constituents into the intestinal lumen. The mucosal damage was much more localized at 4 h post dosing, and the erosion of the villi had been largely repaired. Repair was complete at 6 h post dosing.

Sodium Ricinoleate

Gaginella et al. (1977a) studied the morphology of the colon after perfusion of the organ with Sodium Ricinoleate solution, using 25 male New Zealand white rabbits. A Foley catheter was inserted and the colon was perfused with control solution (1.25 ml per minute) for 20 min. The colon was then flushed and perfused with the test solutions. Ten rabbits were perfused with 10 mM Sodium Ricinoleate and the remaining three groups of five were perfused with 2.5, 5.0, and 7.5 mM, respectively. The animals were killed and full thickness samples of colon

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were obtained and prepared for light or scanning electron microscopy. In additional experiments, tissue was obtained from animals that were not perfused and those perfused with control buffer (contained PEG 400) for 60 or 160 min.

Using scanning electron microscopy, mucous membranes of colons perfused with control buffer for 60 min and unperfused colons appeared normal. After 1 h of perfusion with 10 mM Sodium Ricinoleate, patchy loss of epithelial cells was apparent. The loss of epithelial cells was confirmed using light microscopy. A dose response-relationship for mucosal damage was noted. The most severe damage resulted from perfusion with 10 mM Sodium Ricinoleate. Lesser degrees of change and lesser areas of mucosal surface affected were associated with lower concentrations. Small amounts of DNA (due to loss of DNA into the lumen) accumulated in the control buffer, and perfusion with 2.5 mM Sodium Ricinoleate did not cause a significant increase in these amounts. However, DNA accumulation increased significantly after perfusion with 5.0, 7.5, and 10 mM Sodium Ricinolete, and a plateau was reached with 7.5 mM solutions.

The control perfusate that was used contained low (PEG 400) and high-molecular-weight (PEG 4000) polyethylene glycols. The absorption of PEG 400 increased progressively with increases in the concentration of Sodium Ricinoleate (above 2.5 mM) perfused. Sodium Ricinoleate (2.5 mM) did not increase absorption of the individual polymers that comprise PEG 400 (molecular weight 242 to 594). The absorption of lower molecular weight polymers (242 to 462) increased significantly ($p < .005$) in the presence of 5, 7.5, and 10 mM Sodium Ricinoleate. For higher molecular weight polymers (506 to 594), increased absorption in the presence of 5 mM Sodium Ricinoleate was not observed. However, significantly increased absorption ($p < .05$) of the higher molecular weight polymers was observed during perfusion with 7.5 and 10 mM Sodium Ricinoleate (Gaginella et al. 1977a).

Comedogenicity

Castor Oil

Fulton et al. (1976) evaluated the comedogenicity of cosmetics and cosmetic ingredients. Castor oil was applied to the base of the internal right ear of each of three white albino rabbits on Monday through Friday for 2 weeks. The left ear served as the control. Comedogenicity was clinically evaluated on the following Monday using the scale: 0 (no increase in visible hyperkeratosis) to 5 (severe lesions, such as those seen following the application of coal tar). Six-millimeter punch biopsies (right ear) were obtained for microscopic examination, and comedogenicity was evaluated according to the same scale. A score of 1 (increase in visible hyperkeratosis extending to the possible presence of comedones) was reported for castor oil, which was considered nonsignificant because repeated testing in different rabbits often failed to produce identical effects.

In a study by Morris and Kwan (1983), the comedogenicity of castor oil was evaluated using three New Zealand rabbits. Castor oil was applied to the external ear five times weekly (one application per day). The actual amount applied ranged from 5 to 10 mg/cm^2. The animals were killed after the 14th application and several full-thickness sections of the test site and contralateral untreated ear were prepared for microscopic examination. Comedogenic activity was based on the degree of follicular hyperkeratosis and other morphologic changes in the majority of pilosebaceous units, when compared to control sections. Comedogenicity was graded according to the following scale: 0 (negative: pilosebaceous unit normal in appearance when compared to control [untreated] ear section) to 5 (severe: widely dilated follicles, filled with packed keratin; follicular epithelial hyperplasia causing partial or total involution of sebaceous glands and ducts; possible inflammatory changes). Comedogenicity scores for castor oil were 0 to 1, corresponding to a slight increase in keratin content within the follicle, with essentially no change in follicular epithelium.

Fulton (1989) evaluated the comedogenicity of castor oil (mixed in propylene glycol at 9:1 dilution; test concentration = 10%) using three New Zealand albino rabbits. The test substance (1 ml) was applied onto the entire inner surface of one ear 5 days per week for 2 weeks. Untreated ears served as controls. Follicular keratosis was evaluated both macroscopically (visually) and microscopically, using a micrometer to measure the width of the follicular keratosis. Follicular keratosis was evaluated according to the following scale: 0 or 1 (no significant increase in follicular keratosis) to 4 or 5 (an extensive increase in follicular keratosis). The following scale was used to evaluate skin irritation that resulted from repeated application of the test substance: 0 (no irritation) to 5 (epidermal necrosis and slough). A follicular keratosis score of 1 and an irritation score of 0 was reported for castor oil.

Skin Sensitization

Zinc Ricinoleate

International Bio-Research, Inc (1977b) conducted a skin sensitization study on Grillocin HY 77 (now TEGODEO HY 77) using 30 white guinea pigs (average weight = 300 g). TEGODEO HY 77 (trade name mixture for Zinc Ricinoleate) has the following composition: Zinc Ricinoleate (more than 50%), triethanolamine (10% to 25%), dipropylene glycol (1% to 5%), and lactic acid (1% to 5%) (Degussa 2001). Test and control groups consisted of 20 and 10 guinea pigs, respectively. A closed patch containing the trade mixture (0.5 ml, undiluted) was placed on the left shoulder, clipped free of hair, of each animal and remained in place for 6 h. Treatments were repeated once weekly for 3 weeks.

At two weeks after the last exposure, test and control guinea pigs were challenged (same procedure, right side) with duplicate closed patches. At 24 h post removal of the patches, the test site on each animal was treated with a depilatory. Sites were then rinsed and reactions were graded 2, 24, and 48 h later according to the method of Draize. Clinical observations were

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normal throughout the study. Erythema and eschar formation were graded according to the following scale: 0 (no erythema) to 4 (severe erythema [beet redness] to slight eschar formation [injuries in depth]). The following scale for edema formation was used: 0 (no edema) to 4 (severe edema [raised more than 1 mm and extending beyond area of exposure]). A score of 0 (erythema and edema) was reported for each test and control animal during each of the three grading periods. Grillocyn HY 77 did not produce a positive reaction in any of the test animals (International Bio-Research, Inc. 1977b).

Allergenicity

Hydrogenated Castor Oil

Lehrer et al. (1980) investigated the presence of castor bean allergens in Castor Wax (Hydrogenated Castor Oil) using both in vitro and in vivo analyses. The experiments in this study involving human subjects are summarized under the subsection Allergenicity in the Clinical Assessment of Safety section of this report. The following solvents were used to prepare aqueous extracts of Castor Wax: phosphate buffered saline (PBS), urea-NaCl, Triton X-100, or sodium lauryl sulfate (SLS). The aqueous extracts prepared were analyzed for total organic matter and protein (expressed as percent of total organic matter or dry weight). Results from assays for protein in the aqueous extracts of Castor Wax were as follows: 100% protein (urea-NaCl extract), 17.0% (SLS extract), 12.9% (PBS extract), and 0.34% (Triton X-100 extract) protein.

In a qualitative precipitation analysis, Castor Wax aqueous extracts were analyzed for castor bean antigens using an immunodiffusion procedure involving rabbit antiserum (50 μl of antigen or antiserum in each well). The antiserum was produced in rabbits that had been immunized with extracts of castor bean in Freund's complete adjuvant. Of the aqueous extracts tested, only the SLS Castor Wax extract reacted with the rabbit antisera. No reactivity with the antiserum was observed when the SLS solution alone was tested. Because the reaction was unusually strong, suggesting a false-positive reaction, the extract was tested with normal rabbit serum. However, the same precipitin line was observed. It was concluded that the reaction of the SLS Castor Wax extract with rabbit serum proteins was probably a nonspecific reaction.

The aqueous extracts of Castor Wax were also analyzed for allergens by determining their reactivity (48-h passive cutaneous anaphylaxis [PCA] reaction) with mouse anticastor reaginic (immunoglobulin E [IgE]) antibody. CFW female mice were sensitized with reaginic antibody that was produced in BDF mice that had been immunized with heated castor bean extracts and *Bordetella pertussis* adjuvant. The mice were challenged 48 h later by intravenous injection of extracts of Castor Wax in 0.5% Evans blue solution and killed at 30 min post injection. Nonsensitized mice challenged with Castor Wax extracts served as controls. The reactions in control mice were always classified as negative. The antiserum did not react with PBS, urea-NaCl, or Triton X-100 extracts of Castor Wax, but a positive response (positive PCA titer of 40, mean of three determinations) resulted from the reaction of the antiserum with the SLS extract of Castor Wax.

The radioallergosorbent test (RAST) inhibition assay was used for further analysis of allergens in the extracts of Castor Wax. This assay was capable of detecting up to 7.5 μg castor allergen. Patient serum (100 μl) and Castor Wax extract (100 μl) were incubated with antigen-coated discs. Incubation was followed by the addition of radioiodinated anti-IgE and another incubation period. Normal serum incubated with antigen coated discs and test serum incubated with discs coated with a non–cross-reacting antigen served as controls. Assay results were expressed as percent inhibition of the patients' RAS test. Neither the PBS nor Triton X-100 extract of Castor Wax had an inhibitory effect on the RAS test, whereas the urea-NaCl extract induced a small degree (13.4%) of inhibition. However, the SLS Castor Wax extract induced significant inhibition (40.1%) of the RAS reaction.

Based on the nonspecific reaction of the SLS Castor Wax extract with rabbit serum proteins in the first experiment of this study, the authors examined the possibility that this extract may inhibit the RAST nonspecifically using a heterologous RAST inhibition assay. An SLS or Triton X-100 extract of Castor Wax was incubated with reaginic antisera from a patient who was sensitive to peanuts, and then assayed in the peanut RAST. The SLS extract of Castor Wax inhibited the peanut RAST by 37%, suggesting that the results for the RAST inhibition assay in the preceding paragraph may be due entirely or, in part, to a nonspecific inhibition of the RAST reaction, rather than indicating that the SLS extract of Castor Wax contains specific castor allergens.

The results of these experiments (both in vitro and in vivo) indicate that allergens are present at low concentrations in Castor Wax, because the SLS Castor Wax extract induced positive PCA reactions in mice and a positive direct RAS test for reaginic castor allergens (Lehrer et al. 1980).

NEUROTOXICITY

Sodium Ricinoleate

Fox et al. (1983) applied Sodium Ricinoleate (0.01% to 1.0%) to the serosal surface of the rat (anesthetized male Sprague-Dawley rats, weights = 200 to 225 g) jejunum every 5 min for 0.5 h. At 30 days post application, treated and untreated jejunal segments were removed and examined microscopically. At a concentration of 0.1%, Sodium Ricinoleate significantly reduced ($p < .02$) the number of ganglion cells in the myenteric plexus. The highest test concentration (1% Sodium Ricinoleate) significantly reduced the number of cells in the myenteric plexus ($p < .01$) and the submucosal plexus ($p < .02$). The lowest test concentration (0.01%) did not significantly reduce the number of ganglion cells in the myenteric or submucosal plexus.

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Renal Toxicity

Castor Oil

Langer et al. (1968) evaluated effects of castor oil on the rat kidney, following intraluminal injection, using five male white albino rats (weights = 180 to 220 g). The kidney was exposed and proximal tubuli were punctured (using Leitz stereomicroscope) and filled with castor oil. At 15 to 60 min, the proximal tubular segments (filled with oil) were fixed in situ. The kidney was excised and prepared for both light and electron microscopic examination. The injection of castor oil resulted in dilatation of the proximal convoluted tubular lumen and compression of the brush border of proximal tubular cells, although a cessation of the normal pinocytosis was induced in the presence of tubular fluid. A toxic effect of castor oil on the tubular epithelium was not observed.

In a study by Racusen et al. (1986) evaluating the nephrotoxicity of cyclosporine, castor oil served as the vehicle control. Two control groups of eight adult male Munich-Wistar rats (weights = 220 to 270 g) were used. Group 1 vehicle controls (vehicle-ischemia group) underwent bilateral renal artery clamping, and were then dosed intraperitoneally (i.p.) daily (4-day period) with a volume of castor oil vehicle that was equivalent to the i.p. dose of cyclosporine (dose = 60 mg/kg). Group 2 vehicle controls (vehicle-sham group) underwent sham surgery. The incisions were closed prior to daily i.p. dosing with castor oil. On postoperative day 3, feed was withdrawn and urine was collected over a period of 12 h for clearance studies. On postoperative day 4, the animals were killed and tissues prepared for light and electron microscopy (confined to cortical proximal convoluted tubules).

In separate studies, renal blood flow and the glomerular filtration rate were determined. Two groups of eight saline control groups (saline-ischemia and saline-sham groups, respectively) were treated according to the same procedure.

Tubular vacuolization was a prominent feature in vehicle-ischemia control rats, and was observed to a minor degree in the vehicle-sham control rats. The clear vacuoles observed using light microscopy probably corresponded to two ultrastructural changes, dilated endoplasmic reticulum and lipid droplets. With the exception of the saline-sham group, dilated endoplasmic reticulum was observed in all control animals. However, lipid droplets were not observed in any of the control animals. The presence of eosinophilic cytoplasmic inclusions was reported for two of eight vehicle-ischemia rats and four of eight vehicle-sham rats, but not for saline-control rats. Tubular necrosis (confined entirely to outer medullary pars recta) was observed in half of the vehicle-ischemia rats and in all saline-ischemia rats, but was not observed in saline-sham or vehicle-sham control groups. Tubular regeneration was noted in vehicle-ischemia and saline-ischemia control rats.

The renal clearance study involved two control groups that were dosed with castor oil (five rats) or mineral oil (six rats). Two 20-min inulin clearance determinations were made, and the vehicle was then administered i.p. (at dose volume comparable to 60 mg/kg cyclosporine dose; administered to test group of seven) in a region of the upper right abdomen. Dosing was followed by five 20-min clearance periods. Compared to the mineral oil control group (six rats), a significant decrease (25% decrease; $p < .05$) in renal blood flow was noted in rats (group of five) dosed i.p. with castor oil. Renal vascular resistance was also significantly higher ($p < .05$). No significant changes in inulin clearance were reported. A significant decrease in blood pressure was noted in all groups; however, blood pressure remained within the physiologic and autoregulatory range (Racusen et al. 1986).

GENOTOXICITY

Castor Oil

Zeiger et al. (1988) evaluated the mutagenicity of castor oil (United States Pharmacopeia purity grade; in dimethylsulfoxide [DMSO]) in the preincubation assay using *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537. The assay was conducted, with and without metabolic activation, according to a modification of the procedure by Haworth et al. (1983). Castor oil was tested at doses up to 10,000 μg/plate and classified as nonmutagenic (all strains, with and without metabolic activation) over the range of doses tested in this assay.

Hachiya (1987) evaluated the mutagenicity of castor oil using *S. typhimurium* strains TA97, TA98, TA100, TA102, TA1537 and strain WP2/pKM102 of *Escherichia coli*. In each strain, castor oil was tested at doses ranging from 100 to 5000 μg/plate with and without metabolic activation. Results were negative for all strains tested, both with and without metabolic activation. Cytotoxicity (at doses of 100 to 5000 μg/plate) was noted only in strain WP2/pKM102, with and without metabolic activation.

NTP (1992) reported a study in which groups of male and female B6C3F$_1$ mice received diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10% castor oil (in DMSO) for 13 weeks. Blood samples were obtained at the end of the 13-week study. There was no evidence of induction of micronuclei in peripheral erythrocytes.

NTP (1992) also evaluated the induction of sister chromatid changes by castor oil (in DMSO) in Chinese hamster ovary cells. The cells were incubated with castor oil at concentrations up to 5000 μg/ml with and without metabolic activation. Mitomycin-C and cyclophosphamide served as positive controls without and with metabolic activation, respectively. DMSO served as the solvent control. Castor oil did not induce sister chromatid exchanges either with or without metabolic activation.

Sodium Ricinoleate

In a study by Haworth et al. (1983), the mutagenicity of Sodium Ricinoleate was evaluated according to the preincubation procedure of the Salmonella assay (Ames et al. 1975) as described by Yahagi et al. (1975). Sodium Ricinoleate (in distilled water) was tested at concentrations up to 33 μg/plate

at one testing laboratory, and up to 333.3 μg/plate at another laboratory. The following *S. typhimurium* strains were used with and without metabolic activation: TA98, TA100, TA1535, and TA1537. Distilled water served as the vehicle control. The positive controls were as follows: 2-aminoanthracene, 4-nitro-*o*-phenylenediamine, sodium azide, and 9-aminoacridine. Results for Sodium Ricinoleate were negative with and without metabolic activation.

DNA Binding of Reaction Product

Methyl Ricinoleate

Frankel et al. (1987) evaluated the fluorescence formed by the interaction of DNA with lipid oxidation products. The keto ester, methyl ketoricinoleate, was prepared from Methyl Ricinoleate by allylic oxidation with a CrO_3-pyridine complex in methylene chloride. Results from this assay indicated that methyl ketoricinoleate (relative concentration = 1 mM/3 ml) produced very little fluorescence (mean = 29 ± 2 units) with DNA in the presence of ferric chloride–ascorbic acid. The mean value for methyl linolenate hydroperoxides (used as reference) was 362 ± 9 units. Mean values were given as the fluorescence intensity of DNA after 72 h (excitation: 315 nm; emission: 420 nm).

CARCINOGENICITY

Ricinoleic Acid

In a study by Boyland et al. (1966), 2% Ricinoleic Acid, in gum tragacanth, was injected intravaginally into each of 20 BALB/c female mice (5 to 6 weeks old). Injections were made twice per week, and each animal received a total of 100 injections. According to the same dosing schedule, each of 20 positive control and 30 vehicle control mice received 62 injections of 0.3% dimethylbenz(*a*)anthracene and 100 injections of gum tragacanth, respectively. An additional 30 mice served as the untreated control group.

None of the 20 mice injected with Ricinoleic Acid had neoplasms or hyperplastic lesions of the corpus uteri, cervix uteri, vagina, or perineal skin. However, benign lung adenomas were observed in ten of the 13 mice dosed with Ricinoleic Acid and in 6 of the 24 vehicle control mice that were killed after the 14th month of dosing. Benign lung adenomas were also observed in 9 of the 20 untreated control mice that were killed after the 14th month. The difference in benign adenoma incidence between Ricinoleic Acid–treated and untreated control mice was not statistically significant ($p > .1$). Additionally, compared to controls, there was no tendency for Ricinoleic Acid–treated mice with adenomas to have a higher average number of tumor nodules per mouse. Malignant tumors of the vagina and perineal skin were observed in 15 of the 20 (75%) positive control mice. The authors stated that the results of this study do not provide any definite evidence of the carcinogenicity of Ricinoleic Acid (Boyland et al. 1966).

Tumor Promotion Activity

Castor Oil, Ricinoleic Acid, and Glyceryl Ricinoleate

Shubik (1950) evaluated the tumor promotion activity of castor oil, Ricinoleic Acid, Glyceryl Ricinoleate and the following other chemicals using groups of mice (strain and weights not stated): 20% turpentine in liquid paraffin, 0.3% acridine in liquid paraffin, 0.5% fluorene in liquid paraffin, 1% phenanthrene in liquid paraffin, silver nitrate (10% aqueous), and oleic acid. Castor oil, Ricinoleic Acid, Glyceryl Ricinoleate, and oleic acid were not diluted prior to testing.

Initially, the nine substances were tested using groups of three mice (one group per substance). The test substances were applied to a small area of skin in the interscapular region (clipped free of hair). Four applications per mouse, spaced over a period of 2 weeks, were made. At the end of the application period, the animals were killed and tissues were obtained for microscopic examination. The following substances induced slight epidermal hyperplasia: castor oil, Ricinoleic Acid, Glyceryl Ricinoleate, oleic acid, fluorene, and phenanthrene. Turpentine induced minimal histologic change, and acridine induced marked epidermal hyperplasia. Silver nitrate induced hyperplasia most marked in the hair follicles.

In the tumor promotion experiment (groups of 10 mice; strain and weights not stated), each mouse received a single application of 9,10-dimethyl-1,2-benzanthracene in liquid paraffin. The nine test substances (one per group) were then applied semiweekly for 20 weeks. For all groups of mice tested, no tumors were recorded. Castor oil, Ricinoleic Acid, and Glyceryl Ricinoleate, as well as the other test substances that were evaluated, were not tumor promoters in this study (Shubik 1950).

Ricinoleic Acid

Bull et al. (1988) investigated the effect of Ricinoleic Acid (unoxidized) on DNA synthesis and the induction of ornithine decarboxylase activity. The authors noted that unsaturated fatty acids are readily oxidized to a variety of biologically active derivatives, and have suggested that autoxidation products of polyunsaturated fatty acids may also play a role in the enhancement of tumorigenesis. They noted that this suggestion is based on published results (Bull et al. 1984) indicating that hydroperoxy and hydroxy derivatives of arachidonic acid and linoleic acids, the primary autoxidation products of major dietary unsaturated fatty acids, induce ornithine decarboxylase (ODC) and stimulate DNA synthesis (two components of mitogenesis) in colonic mucosa in vivo.

Male Sprague-Dawley rats (weights = 100 to 125 g) fed the following semisynthetic diet (weight percentages indicated) were starved for 24 h prior to intrarectal (i.r.) instillation of Ricinoleic Acid (vehicle: 5% ethanol in 50 mM $NaHCO_3$, pH 8.0): casein (20%), DL-methionine (0.2%), salt mix (3.6%), vitamin mix (2%), beef fat (5%), dextrose (45.2%), cellulose (5%), and cornstarch (19%). Two experiments were performed using Ricinoleic Acid test concentrations of 5 and 10 mM. Test groups

consisted of three to five rats per dose level. The vehicle control group (three rats per experiment) was dosed with 5% ethanol in 50 mM $NaHCO_3$, and positive control animals received 6 mM deoxycholate. Data were presented as an average of the two experiments. The measurement of DNA synthesis in the colon was based on the incorporation of [^{3}H]dThd 12 h after i.r. instillation of Ricinoleic Acid. ODC activity was determined in colonic mucosa that was harvested 3 h after i.r. instillation of Ricinoleic Acid.

Ricinoleic Acid was inactive as a stimulator of DNA synthesis and inducer of ODC activity in the rat colon. Concentrations up to 10 mM resulted in insignificant increases in [^{3}H]dThd incorporation and did not increase the level of ODC activity above control values (Bull et al. 1988).

Anticancer Activity

Extract of Castor Oil

Xie et al. (1992) evaluated the anticancer/antitumor activity of an extract of castor oil using male Kunming mice (weights = 18 to 22 g) and mice bearing S_{180} ARS ascitic fluid tumor cells. Castor oil was saponified and acidified to obtain a coarse, fatty acid mixture that was recrystallized and refined to produce the active anticancer component. Using Tween-80 (Polysorbate 80), an emulsion containing this component was produced. A polyphase liposome from castor oil extract was also produced. The inhibitory action of the anticancer component on S_{180} tumor cells was evaluated. Ascites was obtained from mice that had been inoculated with S_{180} tumor cells (with well-grown ascites) that had been washed with physiological brine in order to collect the cancer cells. The physiological brine was diluted and injected (2 ml) subcutaneously into the right front axilla of each mouse. On the day after injection of the tumor cells, the mice were randomly divided into groups.

The three dilution control groups (8 to 10 mice per group) were injected with 200, 300, or 400 mg/kg of a physiological brine solution containing an equal load of Tween-80. The four polyphase liposome control groups (eight mice per group) were injected with blank liposomes (doses of 300, 300, 400, and 400 mg/kg, respectively). For dilution control and polyphase liposome control groups, injections were made into the abdominal cavity daily for 7 days, after which the mice were killed. Subcutaneous tumors were removed and weighed in order to calculate the tumor suppression rate (%).

Tumor suppression rates for dilution controls were as follows: 30.6% (200 mg/kg dose group), 37% (300 mg/kg dose group), and 53.1% (400 mg/kg dose group). The following tumor suppression rates were reported for the polyphase liposome control groups: 40.2% (300 mg/kg dose group), 36.4% (the other 300 mg/kg dose group), 55.7% (400 mg/kg dose group), and 58% (the other 400 mg/kg dose group).

In another experiment, the inhibitory action of the anticancer component extracted from castor oil on ARS ascites cancer was evaluated according to a similar procedure. Ascites was obtained from mice inoculated with ARS cancer cells (with well-grown ascites) that had been washed with physiological brine in order to collect the cancer cells. The physiological brine was diluted and injected (0.2 ml) into the abdominal cavity of each mouse. On the day after injection of the cancer cells, each of nine mice was injected with a polyphase liposome that was produced from castor oil extract (dose = 200 mg/kg) daily for 7 days. At the end of the treatment period, the animals were monitored (for survival) for an additional 35 days.

Study results indicate that the castor oil extract had a strong suppressive effect on S_{180}body tumors in mice. Its suppressive effect on ARS ascites cancer was also very strong, with 64% of the ascites tumors in mice being completely cured. Compared to controls, the life extension rate was more than 136% ($p < .0012$) (Xie et al. 1992).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Castor Oil

NTP (1992) (see earlier Subchronic Oral Toxicity section) fed groups of rats and mice diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10% castor oil, respectively, continuously for 13 weeks. A slight decrease in epididymal weight (6% to 7%) was observed in mid- and high-dose groups of male rats; however, this finding was not dose related. No effects on any other male reproductive end point (testes weight and epididymal sperm motility, density, or testicular spermatid head count) or female reproductive endpoint (estrous cycle length, or time spent in each phase of the cycle) were noted. Microscopically, there were no treatment-related lesions in any organ or tissue. These results indicate that there was little or no evidence of any reproductive toxicity in rats that was associated with castor oil in the diet. For male and female mice, castor oil in the diet had no adverse effects on any male or female reproductive parameter.

Litvinova and Fedorchenko (1994) evaluated the influence of single doses of different plant oils on the estrous cycle and fertility using female Wistar rats (number and weights not stated). Castor oil (0.2 ml, single dose) was injected intramuscularly on the first day after estrus. Study of the estrous cycle was based on the following: the cytologic picture that was obtained from vaginal smears, the phase structure (proestrus, estrus, metaestrus, and diestrus) of the cycle, and the frequency of estrus over a 15-day observation period prior to injection of castor oil (control) and a similar length of time after injection (test). Fertility was studied using intact animals (control) and animals that were treated with castor oil. On day 2, after castor oil injection (i.e., during diestrus), the females were mated with male rats. Control females were also mated with male rats on day 2. The first day of pregnancy was defined by the presence of spermatozoa in vaginal smears. Pregnant females were killed on day 20. The estrous cycle phases were recorded 3 to 4 times during the 15-day observation period.

The injection of castor oil resulted in a reduction in the frequency of estrus by a factor of 1.4 and lengthening of the

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interestrous phase by 39.6%. The authors concluded that the latter finding may be indicative of prolongation of luteolytic processes and an inhibition of folliculogenesis.

In female fertility experiments, mating occurred over a period of 3.22 ± 0.12 days. The index of fertility was calculated from the ratio of the number of mated females to the total number of females in the test. The fertility index for intact animals (control) was 100%, and pregnancy occurred in 100% of the cases. A decrease in the pregnancy index was reported for female rats injected intramuscularly with castor oil; however, no reliable difference between test and control values was detected.

Compared to controls, castor oil also caused a reduction in the number of corpora lutea in the ovaries, and this observation was said to have been a consequence of the suppression of folliculogenesis and ovulation. Additionally, the number of implantation sites in uteri from female rats injected with castor oil was decreased when compared to control rats. A decrease in the number of live fetuses in uteri and an increase in pre- and postimplantation deaths was also observed in rats injected with castor oil. The authors concluded that castor oil, injected intramuscularly, suppressed ovarian folliculogenesis and also had antiimplantation and abortive effects (Litvinova and Fedorchenko 1994).

Castor oil served as the vehicle control in a study evaluating the effect of long-term treatment with ICI 182,780 (an antiestrogen) on the rat testis (Oliveira et al. 2001). Two groups of four male, 30-day-old Sprague-Dawley rats served as vehicle controls. In one control group, castor oil (0.2 ml) was injected subcutaneously once per week, and the animals were killed 100 days after the first injection. The second group was dosed according to the same procedure; animals were killed 150 days after the first injection. The experiment was extended to 150 days (group 2 rats), based on results for group 1 ICI-treated and control animals on day 100.

Specifically, Group 1 ICI-treated rat testes were significantly heavier (35% heavier, $p < .05$) than those of the control group, and a significant increase in diameter and luminal areas of the semineferous tubules was observed. Additionally, in group 1 ICI-treated and control rats, spermatogenesis appeared normal and there was no evidence of degeneration or sloughing of germ cells.

On day 150, a 33% decrease (compared to day 100 results for ICI-treated rats; $p = .065$) in mean testicular weight was noted in ICI-treated rats. Seventy-five percent of the testes weighed less than the mean control value of 1.71 g. Atrophy of the semineferous tubules was observed in all but one of the testes of ICI-treated rats. Additionally, the rete testis and efferent ductule lumens in all ICI-treated rats were greatly dilated, compared to those of controls.

During the treatment period, mating studies were performed to compare the fertility of ICI-treated and control rats on days 45, 73, 100, 125, and 150. Males were housed individually with two adult females for a 15-day period. Through 100 days of treatment, there was no difference in male reproductive performance between ICI-treated and control rats. However, after day 100, 100% fertility was maintained in control males, but, by day 150, fertility had decreased to 25% in ICI-treated males (Oliveira et al. 2001).

Extract of Ricinus communis Seeds

The following study is included because castor oil may be extracted from the bean of the tropical plant, *Ricinus communis* by a method that involves the use of a solvent.

Okwuasaba et al. (1991) evaluated anticonceptive and estrogenic effects of a methanol extract of *Ricinus communis* var.*minor* seeds (ether-soluble fraction) using the following animals (groups of 10): adult albino Wistar rats (weights = 160 to 210 g), young albino Wistar rats (weights = 40 to 60 g), immature Swiss albino female mice (21 to 23 days old; weights = 10 to 13 g), and adult female New Zealand white rabbits (2.5 to 3.0 kg).

In the antifertility experiment, adult female rats and rabbits with regular estrus cycles were used. The females were mated overnight (3:1 female/male ratio), and the day of mating was considered day 0. Castor bean extract was injected subcutaneously (s.c. dose of 0.6 or 1.2 g/kg) into female rats once daily for two days, and mating occurred on the third day. Female rabbits were injected intramuscularly with Castor bean extract (dose = 200 mg/kg). Control animals were injected s.c. with corn oil for two consecutive days. A laparotomy was performed to confirm that implantation had occurred.

Castor bean extract (0.6 or 1.2 g/kg dose) prevented nidation in rats, and none of the treated rats delivered pups at term. The results for rabbits (200 mg/kg dose) paralleled those for rats. Nidation was prevented, and the extract protected the rabbits against pregnancy for over three gestation periods (i.e., 110 to 120 days). The normal gestation period for rabbits is 28 to 30 days. Effects induced by Castor bean extract were reversible in rats and rabbits. No fetal abnormalities were observed.

In the study to determine estrogenic activity, the following endpoints were used to estimate the estrogenicity of the Castor bean extract: uterine weight ratio, degree of vaginal cornification, and quantal vaginal opening. In one experiment, groups of 10 Swiss albino female mice (21 to 23 days old; weights = 10 to 13 g) were injected s.c. with 1.0 or 4.0 mg/kg Castor bean extract (in corn oil, 0.2 ml) daily for 4 days. In a similar experiment, bilateral ovariectomy was performed on young, immature rats (groups of five), and the wound was sutured. After a 15-day recovery period, the groups of rats were injected s.c. with 0.6 or 1.2 g/kg Castor bean extract (in corn oil, 0.2 ml) daily for 4 days. In both experiments, suitable controls (injected s.c. with corn oil only) were maintained. Additionally, estradiol-17β (reference hormone; dose = 10 μg/kg) was administered to rats (group of 10) and mice (group of 10). Mice and rats were necropsied 24 h after the last injection. Body and uterine wet weights were recorded.

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Results for bilaterally ovariectomized rats indicated that doses of 0.6 and 1.2 g/kg induced increases in relative uterine weight of 116.7 ± 6.5 ($p < .01$) and 211.6 ± 8.2 mg/100 g body weight ($p < .001$), respectively, compared to a control value of 83.3 mg/100 g body weight. Compared to rats, Castor bean extract (1.0 and 4.0 mg/kg) induced a qualitatively similar effect in immature mice. In rats and mice, the effect on relative uterine weight appeared to have been dose-dependent. Estradiol-17β also increased uterine weight in rats and mice. The relative uterine weights (mg/100 g body weight) for rats and mice dosed with estradiol-17β were reported as follows: 309.2 ± 11.4 (rats) and 517.5 ± 12.3 (mice).

Cornification of the vaginal epithelium and quantal opening of the vagina were noted in immature mice and bilaterally ovariectomized rats (both dose groups for each). A dose-related decrease in the number of leukocytes and increases in cornified and epithelial cell counts were also reported for both species. No significant changes in body weight were observed.

The authors concluded that the ether-soluble portion of the methanol extract of *Ricinus communis* var. *minor* seeds possesses anti-implantation, anticonceptive, and estrogenic activity in rats and mice when administered subcutaneously (Okwuasaba et al. 1991).

CLINICAL ASSESSMENT OF SAFETY

Metabolism and Excretion

Castor Oil

Watson et al. (1963) studied the absorption and excretion of castor oil in five subjects (ages and weights not stated). The composition of the castor oil was as follows: palmitic acid (1%), palmitoleic acid (0.1%), stearic acid (1%), oleic acid (3.2%), linoleic acid (4.7%), and Ricinoleic Acid (90%). The castor oil (of medicinal purity) contained a trace amount of oil labelled with ^{131}I, and the doses administered ranged from 4 to 60 g (approximately 6 μCi of radioactivity per dose). Castor oil was administered to the five hypertensive patients on the day before a scheduled intravenous pyelogram; thereafter, only a light meal of coffee and toast was allowed. Stool collections were made during the first 24 h after dosing and during the subsequent 72 h. Urine was collected in 24-h samples. Small doses of oil were administered to the three normal volunteers, and free diet was allowed. Stools were collected at 2 and 3 days after dosing.

Fecal recovery of ^{131}I (%) ranged from 11.4% (for 10 g dose of castor oil) to 86.0% (for 44.4 g dose of castor oil). The authors concluded that castor oil can be absorbed by human subjects, that absorption is inversely related to the administered dose, and, at small doses (4 g), that absorption is virtually complete (Watson et al. 1963).

Hagenfeldt et al. (1986) administered castor oil (10 to 15 ml) orally to three healthy subjects. Urine was collected between 2 and 8 h post dosing. The following three epoxydicarboxylic acids were excreted in the urine: 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid. These three Ricinoleic Acid metabolites were also detected in the urine of rats as described earlier.

Induction of Labor

Castor Oil

Davis (1984) investigated the use of castor oil to stimulate labor using 196 patients with premature rupture of membranes (PROM), at least 4 h in duration, who were between 37 and 42 weeks of gestation. Patients were identified by reviewing charts of all patients who were admitted at an out-of-hospital birthing center from 1976 through 1981. Of the 196 patients, 107 (mean age = 28.6 years) were dosed orally with castor oil (2 oz) and 89 (mean age = 27.6 years) were not. Castor oil was administered only to PROM patients who had a latency period of at least 4 h. All patients were observed for labor onset for 24 h after the onset of PROM. If labor did not occur at this time, the patients were transferred to a hospital for oxytocin stimulation. The longest interval between rupture of the membranes and delivery was 48 h.

Of the 107 patients dosed with castor oil, 80 (75%) had labor onset. Spontaneous labor occurred in 52 (58%) of the 89 control patients. This difference between patients dosed with castor oil and controls was statistically significant ($p < .05$). The interval between castor oil administration and the onset of labor ranged from 1 to 13 h (mean = 4 h).

Labor outcomes were also evaluated for type of delivery, incidence of oxytocin stimulation, and infant well-being. The need for cesarean sections was nearly three times greater in the control group (15.7% incidence) than in patients dosed with castor oil (5.6% incidence). This difference was found to be statistically significant ($p < .01$). Additionally, the group dosed with castor oil did not require oxytocin stimulation as frequently (36% incidence) when compared to the control group (43% incidence), and the difference was not statistically significant.

Infant outcomes in the two groups were studied by observing Apgar scores at 1 and 5 min, and looking for any evidence of meconium staining. Two infants with Apgar scores of <7 were reported for both groups. At the time of membrane rupture, the presence of meconium was very low in both groups. Meconium staining was not observed after dosing with castor oil. It is also important to note that there were no maternal deaths and no significant maternal morbidity. The authors concluded that castor oil can be used safely and effectively to stimulate labor (Davis 1984).

In a study by Mitri et al. (1987), the amniotic fluid was examined at the time of rupture of membranes in 478 of the 498 women in labor. The amniotic fluid was meconium-stained in 174 subjects (mean age = 28.5 ± 0.65 years) and clear in the remaining 304 subjects (mean age = 25.9 ± 0.37 years). Cesarean section, low Apgar score, and the recent ingestion of castor oil were significantly more common in subjects with meconium-stained amniotic fluid. The authors concluded that

the passage of fetal meconium was predictive of poor labor outcome in terms of Apgar scores and the need for cesarean section. It was recommended that women who take castor oil in late pregnancy should be identified as a high-risk group for the passage of fetal meconium.

In a case report by Steingrub et al. (1988), a 33-year-old pregnant female (at week 40 of gestation) ingested castor oil to induce labor. Within 60 min of ingestion, cardiopulmonary arrest occurred and was reportedly due to amniotic fluid embolism.

Garry et al. (2000) evaluated the use of castor oil to induce labor in 52 pregnant women (mean age = 24.8 ± 6.7 years) at Saint Mary's Hospital in Brooklyn, New York. The untreated control group consisted of 48 pregnant women (mean age = 24.4 ± 4.9 years). The two groups of women did not differ in maternal age, parity, or gestational age. Castor oil was administered as a 60-ml dose in orange or apple juice, and its use was deemed successful only if active labor began within 24 h. Labor was defined as one or more contractions every 5 min, with cervical dilatation of 4 cm or more. Active labor was induced in 30 (57.7%) of the 52 women dosed with castor oil, compared to 2 of the 48 women in the control group ($p < .001$). The cesarean section rate for women dosed with castor oil was 19.2% (10 of 52 women), compared to 8.3% (4 of 48 controls) in the untreated control group. No relationship between dosing with castor oil, birth weight, and mode of delivery ($p = .66$) was found. Additionally, no adverse outcomes for the mother or fetus were identified. The authors concluded that women dosed with castor oil had an increased likelihood of initiation of labor within 24 h, compared to women who were not dosed with castor oil.

Ocular Irritation

Castor Oil

In a study by Secchi et al. (1990), a double-masked clinical trial was performed using a group of nine patients (ages not stated) with vernal keratoconjunctivitis. One eye was treated with 2% cyclosporine in castor oil four times daily for 15 days. The other eye was treated with castor oil solution only according to the same procedure. Mild and transient discomfort and minor epithelial changes were observed in both eyes.

In another clinical study (Gluud et al. 1981), vital staining was used to investigate the eyes of 100 patients (ages not stated) following the instillation of castor oil and the eyes of 50 patients following the instillation of 0.9% saline. One drop (0.01 ml) of sterile fluorescein–rose bengal (RB) dye mixture was instilled into the lower conjunctival sac and the ocular mucosa was examined using a slit lamp. White light was used to examine RB-stained spots and cobalt blue light was used to examine fluorescein-stained spots. The ocular mucosa was divided into five regions, and the number of stained spots in each region was counted/estimated and graded. The authors concluded that castor oil affected the cornea and conjunctiva, i.e, degeneration and death of epithelial cells (stained with RB) and continuity breaks in the epithelium (stained with fluorescein).

Skin Irritation/Dermal Toxicity

Castor Oil

Motoyoshi et al. (1979) evaluated the skin irritation potential of undiluted castor oil using 50 adult male volunteers (ages not stated). Individuals with known allergic reactions were excluded. Patches containing 0.05 g of the test material were applied to skin of the back and remained for 48 h. At the end of the application period, test sites were swabbed with dry gauze to remove any residual test material and reactions were scored 30 minutes later according to the following scale: − (negative reading) to + + ++ (bullous reaction). Castor oil was mildly irritating to the skin of human subjects.

In a study by Meyer et al. (1976), undiluted castor oil was applied to test fields delineated on the right thigh of each of three male subjects (22 to 31 years old). The control field was located on the opposite side. According to the test procedure, castor oil was rubbed onto the skin gently (<30 s) on 10 sucessive days. The control field was massaged only. A tissue section (1 × 1 cm) was excised from the center of each test field and five to eight sections (7 μm in thickness) per test area were subjected to microscopic examination. Macroscopic skin changes were not observed in either of the three subjects.

At microscopic examination, clear hyperchromasia and an increase in the number of cells were observed in the basal cell layer. Slight widening of the granular cell layer was also noted (Meyer et al. 1976).

Hydrogenated Castor Oil

In a study by de Groot (1994), members of the Dutch Contact Dermatitis Group and nonmember dermatologists patch tested 1 to 20 patients (ages not stated) either suffering from or suspected of suffering from contact allergy to cosmetic products. Details regarding the patch test procedure were not included. Patch test results indicated no reactions to 30% Hydrogenated Castor Oil in petrolatum.

Ethyl Ricinoleate

The skin irritation potential of 20% Ethyl Ricinoleate in petrolatum was evaluated using 32 healthy male volunteers (ages not stated) in a 48-h closed patch test. Skin irritation was not observed (RIFM 2000).

Allergenicity

Predictive Tests

Ethyl Ricinoleate

The skin sensitization potential of 20% Ethyl Ricinoleate in petrolatum was evaluated using 32 healthy male volunteers in the maximization test. The test substance was applied (under occlusion) to the same site on the forearms of each subject for five alternate-day 48-h periods. Each test site was pretreated with 5% aqueous sodium lauryl sulfate (under occlusion) for 24 h. At the end of a 10- to 14-day nontreatment period, challenge

patches were applied (under occlusion) to new test sites for 48 h. Challenge applications were preceded by 30-min applications of 2% aqueous sodium lauryl sulfate (under occlusion) on the left side. On the right side, the challenge application was not preceeded by treatment with sodium lauryl sulfate. A fifth site (challenge with petrolatum) served as the control. Reactions classified as either significantly irritating or allergic were not observed (RIFM 2000).

Provocative Tests

Castor Oil

Fujimoto et al. (1997) conducted a study involving 332 patients (25 males, 307 females; ages ≈20 to 70) suspected of having cosmetic contact dermatitis. The subjects were patch-tested with numerous cosmetic products and cosmetic ingredients. Patch tests (Finn chambers) were applied to the back for 48 h, and the test sites were examined at 30 minutes after patch removal, 1 day later, and 4 to 5 days after patch removal. None of the 49 patients patch-tested with castor oil had a positive reaction.

In a study by Hino et al. (2000), 346 patients (31 males, 315 females; ages ≈ 20 to 70 years) suspected of having cosmetic dermatitis were patch tested with various cosmetic products and cosmetic ingredients. Patch tests (Finn chambers) were applied to the back for 48 h. Test sites were examined according to the schedule in the preceding study. Of the 76 patients patch-tested with castor oil, one had a positive reaction. This reaction was observed only during the second reading (i.e., the day after the 30-min reading).

Hydrogenated Castor Oil

Lehrer et al. (1980) evaluated the sensitivity of three human subjects (with occupational hypersensitivity to castor allergens) to castor bean extract and four Castor Wax extracts (solvent = SLS, PBS, urea-NaCl, or Triton X-100). Seven normal laboratory personnel served as controls. The test substances were applied to the skin using both patch and prick tests. Only the castor bean extract and the SLS extract of Castor Wax were evaluated in the prick test, and the four Castor Wax extracts were evaluated in the patch test. In the prick test (to detect IgE-mediated hypersensitivity), a drop of allergen extract was applied to the skin. Following application to the skin, the underlying superficial layer of the skin was pricked with a 25-gauge needle. Reactions were scored 15 min after application of the allergen. A positive prick test reaction was defined as a wheal and flare reaction with edema >5 mm. Castor bean extract was tested at concentrations up to 1000 μg/ml and, SLS Castor Wax extract, at concentrations up to 22,000 μg/ml. Results from the prick test indicated no immediate skin reactivity to castor bean extract or the SLS Castor Wax extract.

In patch tests (to detect cell-mediated hypersensitivity), a semiocclusive patch containing either of the four Castor Wax extracts (concentration not stated) or paraffin (control) was applied to the skin for 24 and 48 h. Reactions were scored at 24 and 48 h post removal.

The three patients were highly sensitive to castor allergen in the prick test (positive skin reaction to 1.0 or 0.1 μg/ml castor bean extract). The patients also had a positive skin reaction to the SLS Castor Wax extract, where the level of sensitivity was 100- to 100,000-fold less than that induced by castor bean extract. None of the seven normal subjects had a delayed reaction to any of the four Castor Wax extracts that were tested. Prick test results (normal subjects) indicated no immediate skin reactivity to castor bean extract or the SLS Castor Wax extract.

Because immediate hypersensitivity to Castor Wax was observed in the three patients who were sensitive to castor bean, additional tests (prick tests) were performed to determine whether Castor Wax solubilized in different organic solvents or an underarm deodorant stick containing Castor Wax would induce irritation and elicit a positive immediate hypersensitivity reaction in these three patients. Positive skin reactions to Castor Wax (in different solvents or in a deodorant stick) were not detected.

The four Castor Wax extracts and paraffin (control) were evaluated in patch tests for cell-mediated hypersensitivity. None of the three patients had a delayed reaction to any of the four Castor Wax extracts (test concentration not stated).

The positive skin reactions (immediate skin reactivity) in sensitized individuals, together with the positive PCA reactions in mice and positive direct RAST for reaginic castor allergens (summarized earlier in this report) that were induced by SLS Castor Wax extract, indicate that allergens are present in Castor Wax at low concentrations.

A direct RAS study was conducted to determine whether the SLS extract of Castor Wax contains specific antigens or nonspecifically inhibits the RAS assay. Discs were coated with castor bean extract or the SLS Castor Wax extract and a direct RAS assay was performed using serum from one patient who was sensitive to castor allergens, a patient who was sensitive to peanuts, or pooled human serum (control). The patient sensitive to castor allergens had a significant RAS test ratio of 18.87 to castor bean allergen and a significant RAS test ratio of 8.04 to SLS Castor Wax extract. The patient sensitive to peanuts did not have a significant RAS test to either castor bean extract or the Castor Wax extract. The results from this direct RAS study indicate that SLS Castor Wax extract does contain Castor bean allergens, although the SLS Castor Wax extract can nonspecifically inhibit the RAS assay (Lehrer et al. 1980).

Ricinoleic Acid

In a retrospective study by Lim and Goh (2000), 202 consecutive patients (182 females, 20 males) with eczematous cheilitis who attended a contact and occupational dermatoses clinic in Singapore between January of 1996 and December of 1999 were patch-tested. Mean ages for female and male patients were 31.1 and 28.8 years, respectively. Patch tests were conducted according to International Contact Dermatitis Research Group (ICDRG) recommendations. Twenty-nine patients (2 males,

27 females) had positive reactions to Ricinoleic Acid. Of the 29 reactions, 22 were considered relevant positives.

Allergenicity/Photoallergenicity

Castor Oil

In a study by Hashimoto et al. (1990), 103 patients (ages not stated) suspected of having cosmetic-related contact dermatitis were patch tested with castor oil (as is). Both patch tests and photopatch tests were conducted according to ICDRG basic standards. The patch test units consisted of a combined use of both Finn chambers and Scanpor tape. One patient had a positive patch test reaction to castor oil. No positive photopatch test reactions were reported.

Case Reports

Case reports involving Castor Oil and Ricinoleic Acid esters are summarized in Table 6.

Occupational Exposure

Göhte et al. (1983) conducted a study involving 28 persons (14 men, 14 women; age range = 17 to 65 years) who were employed by a company involved with importing, preparing, and distributing plant products that are used in spices and as ingredients of health foods. The period of employment varied from two months to 20 years, and 25 of the 28 were smokers. Thirteen of the 28 developed the following work-related symptoms: rhinitis, conjunctivitis, asthma, itch, or urticaria. Blood samples from 25 subjects were subjected to IgE analysis using Phadebas IgE PRIST (paper radioimmunosorbent test). Phadebas RAST (radioallergosorbent test) was performed on 25 persons against antigens from an extract of castor oil bean. Fifteen subjects were prick-tested and 14 were patch-tested with an extract of castor oil bean. Of the three tests, only the RAST test yielded positive results; 1 of 25 subjects had an allergic reaction to an extract of castor oil bean. None of the subjects without work-related symptoms had positive reactions.

SUMMARY

Ricinus Communis (Castor) Seed Oil, Ricinoleic Acid, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate function, in cosmetics, as skin-conditioning agents, emulsion stabilizers, and surfactants. Ricinus Communis (Castor) Seed Oil also functions as a fragrance and Hydrogenated Castor Oil also functions as a viscosity-increasing agent—nonaqueous. In the case of Zinc Ricinoleate, functions include deodorant agent, opacifying agent, and anticaking agent.

Ricinoleic Acid accounts for 87% to 90% of the fatty acyl groups of Ricinus Communis (Castor) Seed Oil and the following other fatty acids comprise the remaining fatty acyl groups: oleic acid (2% to 7%), linoleic acid (3% to 5%), palmitic acid (1% to 2%), stearic acid (1%), dihydrostearic acid (1%), and trace amounts of other fatty acyl groups.

Hydrogenated Castor Oil consists primarily of glyceryltrihydroxystearate. The National Formulary has the following requirements for Hydrogenated Castor Oil: free fatty acids (free fatty acids in 20 g require for neutralization not more than 11.0 ml of 0.1 N sodium hydroxide), heavy metals (0.001%), hydroxyl value (between 154 and 162), iodine value (not more than 5), and saponification value (between 176 and 182).

Ricinus Communis (Castor) Seed Oil is produced by cold pressing of the seeds of *Ricinus communis* and subsequent clarification of the oil by heat. Castor Oil does not contain ricin because ricin does not partition into the oil, due to its water-solubility. Hydrogenated Castor Oil is the end product of controlled hydrogenation of Ricinus Communis (Castor) Seed Oil. One of the simplest methods for obtaining Ricinoleic Acid is the hydrolysis of castor oil.

Ricinus Communis (Castor) Seed Oil and Glyceryl Ricinoleate absorb UV light, with a maximum absorbance at 270 nm.

Reportedly, Ricinus Communis (Castor) Seed Oil and Hydrogenated Castor Oil were used in 769 and 202 cosmetic products, respectively, in 2002. The following use frequencies were reported for Ricinoleic Acid and its salts and esters: Glyceryl Ricinoleate (16), Ricinoleic Acid (6), Sodium Ricinoleate (12), Zinc Ricinoleate (3), and Cetyl Ricinoleate (55).

The highest reported use concentration for Ricinus Communis (Castor) Seed Oil is associated with lipsticks (81%). Other maximum ingredient use concentrations are: Hydrogenated Castor Oil (up to 39%), Glyceryl Ricinoleate (up to 12%), Zinc Ricinoleate (up to 2%), Cetyl Ricinoleate (up to 10%), and Octyldodecyl Ricinoleate (up to 5%).

Potassium Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, and Methyl Ricinoleate are not currently reported to FDA as in use, nor are there industry survey data indicating a current use concentration.

Castor oil is classified by FDA as generally recognized as safe and effective for use as a stimulant laxative. An acceptable daily intake (for man) of 0 to 0.7 mg/kg body weight has been established by FAO/WHO for castor oil.

Castor oil is a triglyceride that is hydrolyzed in the small intestine by pancreatic enzymes, leading to the release of glycerol and Ricinoleic Acid. Ricinoleic Acid was rapidly metabolized in a study of adult rats fed a diet containing 48.4% castor oil for 4 to 6 weeks. These animals did not have significant amounts of Ricinoleic Acid in phospholipids of the small intestine, liver, and skeletal muscle, nor in glycerides of the liver. A close correlation between the dose administered in the diet and the percentage of Ricinoleic Acid in the feces (greater absorption of the smaller dose) was noted in rats. Castor oil was readily absorbed and metabolized in two groups of male rats that were fed 10% castor oil in the diet (cholesterol-enriched and cholesterol-free, respectively) for 20 days. Fecal recovery of Ricinoleic Acid was

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TABLE 6
Case reports with patch test results for Castor Oil and Ricinoleic Acid esters and salts

Subjects	Findings/patch test results	References
22-year-old female (with cheilitis)	Cheilitis worsened after application of various lipsticks and lip creams. Product concentrations of Castor Oil ranged from 10% to 67%. ++ patch test reactions to Castor Oil and each lipstick or lip cream that contained Castor Oil. Also, ++ patch test reactions to Ricinoleic Acid (as is), 30% Ricinoleic Acid in petrolatum, and purified Castor Oil (as is). No reactions to products that did not contain Castor Oil.	Sai 1983
23-year-old female (history of facial eczema) with acute dermatitis of the face	++ reactions to Castor Oil and make-up remover containing Castor Oil.	Brandle et al. 1983
29-year-old female (history of deodorant dermatitis)	Acute edematous dermatitis on the lips and perioral area, which spread to entire face and neck, after using a lipstick product containing Castor Oil. ++ patch test (Finn chambers, International Contact Dermatitis Research Group [ICDRG] recommendations) results for Castor Oil.	Andersen and Nielsen 1984
24-year-old female	Swelling of lips over 10-month period. Negative patch test results for Castor Oil and five brands of lipstick containing Castor Oil.	Yoshikawa et al. 1986
31-year-old female (no history of dermatitis)	Developed itchy rashes in the axillae, which spread over the entire body. Positive patch test reaction (++, at 38 and 96 h) to a deodorant that was used. Repeated open application test results for Castor Oil and a Zinc Ricinoleate mixture (Zinc Ricinoleate (88%), triethanolamine, zinc resinate, isostearic acid, dipropylene glycol, sodium lactate, and abietic acid) were positive.	Dooms-Goosens et al. 1987
45-year-old female (history of intolerance to cosmetics and adhesives)	Presented with an itchy dermatitis on both axillae, and red papules scattered over face and trunk. Patch test results indicated a red erythematous response to a deodorant that was used. Patch test results for Castor Oil were negative at 72 h and +/? at 96 h. Repeated open application test results for Castor Oil were negative after 7 days; ++ patch test results for 20% Glyceryl Ricinoleate (in petrolatum) at 72 and 96 h. Also, ++ reaction to Zinc Ricnoleate mixture (defined in preceding case report) at 96 h. This mixture also produced an erythematous test response in 1 of 10 control subjects.	Dooms-Goosens et al. 1987
40-year-old chemist (history of eczema due to chemical exposure on the job)	Developed eczema on the knee 10 days after joint surgery. Positive patch test results for surgical adhesive containing Castor Oil. Negative patch test results for Castor Oil.	Jost et al. 1989
20-year-old female	Allergic cheilitis (itching, swelling, and redness of the lips) after using a total of 16 lipstick products. Positive patch test results for Castor Oil and each product.	Fisher 1991
17-year-old female (with lip dermatitis)	Positive patch test reactions to Castor Oil and 3 lipsticks.	Fisher 1991

TABLE 6
Case reports with patch test results for Castor Oil and Ricinoleic Acid esters and salts *(Continued)*

Subjects	Findings/patch test results	References
17-year-old female (allergic to metals)	Developed itchy erythematovesicular reaction on right hand after using a liquid wart remover containing flexible collodion (contains 1.67% Castor Oil). + + + patch test reaction to wart remover. ++ patch test reactions to Castor Oil and 20% Castor Oil in petrolatum. Negative patch test reactions to Castor Oil and 20% Castor Oil in petrolatum in 15 control subjects.	Lodi et al. 1992
51-year-old female	Developed two roundish, erythematous vesicular plaques in left gluteal and right anterolateral neck regions (application sites) after 20 days of treatment with an anti-wart solution (flexible collodion, common component of wart removers, contains Castor Oil). ++ patch test reactions to Castor Oil 20% Castor Oil in petrolatum, and the wart remover.	Tabar et al. 1993
65-year-old male (history of rash following wood cutting in orchard)	Rash on face, neck, and hands. Same rash appeared 3 years earlier, following wood cutting. Patch test results for Castor Oil (100%) were negative.	Manzur et al. 1995
30-year-old female (history of mild atopic eczema)	Hand dermatitis after exposure to cream containing Castor Oil and zinc. + + + patch test reaction to Castor Oil. Negative results for 10 control subjects.	Wakelin et al. 1996
29-year-old female (nonatopic)	Sore, cracked lips, followed by vesicular facial edema, after use of the same lipstick product for several years. ++ patch test (Finn chambers, ICDRG criteria) results for Castor Oil.	Tan et al. 1997
24-year-old female (history of hay fever and dry lips)	Pruritic papules, swelling, and pigmentation on and around lips after applying lipstick. Negative patch test results for Castor Oil (as is).	Inoue et al. 1998
20-year-old army recruit	Rashes developed after applying a camouflage stick containing 47.1% Castor Oil. A mildly pruritic vesicular eruption appeared on the neck, chin, face, and hands; swelling of eyelid also observed. Symptoms lasted for 3 or 4 days.	Goon et al. 1999
43-year-old female (history of sinus aspergillosis and facial edema after oral dosing with tixocortol pivalate)	Recurrent facial dermatitis and cheilitis after use of a facial moisturizer containing 8% Castor Oil. +/+ patch test (Finn chambers) reactions to the moisturizer, Castor Oil, 15% Castor Oil in petrolatum, and 10% Castor Oil in petrolatum. + to ++ reactions to several lipstick and lip balm products containing Castor Oil.	Le Coz and Ball 2000
51-year-old female	Pruritic erythema in both axillae after use of a deodorant containing 76% Zinc Ricinoleate. One week later, developed acute contact dermatitis of the lips after using perfumed lipstick containing Glyceryl Ricinoleate. Lipstick was previously tolerated. + patch test reaction to deodorant and lipstick. + patch test reaction to 30% Glyceryl Ricinoleate in petrolatum. Re-patch testing yielded the following results: 76% Zinc Ricinoleate in petrolatum (?+ reaction on day 3) and no reactions to 30%, 15%, or 1% Zinc Ricinoleate in petrolatum 20% Glyceryl Ricinoleate in petrolatum (+ reaction on day 3), 30% Glyceryl Ricinoleate in petrolatum (+ reaction on day 3), and Castor Oil, as is (no reaction).	Magerl et al. 2001

(Continued on next page)

TABLE 6
Case reports with patch test results for Castor Oil and Ricinoleic Acid esters and salts *(Continued)*

Subjects	Findings/patch test results	References
58-year-old female (history of allergy to adhesive tapes)	After knee surgery, acute contact dermatitis around surgical incision rapidly became blistered and spread to right lower limb. Patch test results for Castor Oil (1% and 10% in petrolatum) were negative.	Reichert-Pénétrat et al. 2001
50-year-old female (history of allergy to adhesive tapes)	After hip surgery, acute dermatitis around surgical incision spread to lower right limb. Patch test results for Castor Oil (1% and 10% in petrolatum) were negative.	Reichert-Pénétrat et al. 2001
30-year-old female (with pigmented contact cheilitis)	Presented with scaly erythema with associated diffuse hyperpigmentation and itchy swelling for past one year after using various lipsticks. ++ patch test reactions to Ricinoleic Acid at day 3.	Leow et al. 2003

approximately 0.5% of the total ingested. 3,6-epoxyoctanedioic acid, 3,6-epoxydecanedioic acid, and 3,6-epoxydodecanedioic acid were excreted by rats given castor oil intragastrically. These acids were not detected in the urine prior to dosing with castor oil.

Following the oral administration of Hydrogenated Castor Oil to rats at dietary concentrations of 0.865% and 8.65%, the deposition of hydroxystearic acid in the abdominal fat and other body lipids was reported. In all cases, hydroxystearic acid was accompanied by hydroxypalmitic acid, hydroxymyristic acid, and hydroxylauric acid (hydroxystearic acid metabolites). Ricinoleic Acid or Methyl Ricinoleate administered by gastric intubation to male rats resulted in peak absorption of Ricinoleic Acid within 30 min post dosing in the following fractions: triglyceride, diglyceride, monoglyceride, and free fatty acid.

Castor oil (labeled with ^{131}I) was administered to five hypertensive patients on the day before a scheduled intravenous pyelogram, with results demonstrating that castor oil can be absorbed by human subjects, that absorption is inversely related to the administered dose, and, at small doses (4 g), that absorption is virtually complete.

Following oral administration of castor oil (10 to 15 ml) to three healthy subjects, the following three epoxydicarboxylic acids were excreted in the urine: 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid.

Castor oil caused a marked decrease in the transepidermal water loss rate from full-thickness, cartilage-stripped skin from the ventral ear of the male Syrian golden hamster. In another study, Ricinoleic Acid enhanced the in vitro transdermal permeation of 5-fluorouracil in hairless mouse skin.

Oral dosing with Sodium Ricinoleate, Ricinoleic Acid, or castor oil had both stimulatory and inhibitory effects on smooth muscle (canine small bowel) contraction in vivo. Sodium Ricinoleate, but not Methyl Ricinoleate, depressed the smooth muscle twitch response in a guinea pig ileum preparation at concentrations ranging from 1.25×10^{-5} to 4×10^{-4} M.

Unlike prostaglandin E_1 (chemically similar to Ricinoleic Acid), Ricinoleic Acid did not induce dose-dependent stimulation of adenylate cyclase in villus cell (from hamster small intestine) homogenates. Compared to saline-treated controls, castor oil significantly reduced the infiltration of leukocytes and the prostaglandin E_2 (inflammatory mediator) content of the rat aqueous humor and iris-ciliary body.

Sodium Ricinoleate significantly inhibited (considered modest; $p < .05$) cytokine-induced endothelial adhesion molecule expression when incubated with human saphenous vein endothelial cells. In a similar experiment, Ricinoleic Acid significantly decreased IL-4-induced VACM-1 expression (50% inhibitory concentration between 10 and 100 μM). Neither cell number nor viability was increased in this concentration range. Ricinoleic Acid did not inhibit TNFα-induced vascular cell adhesion molecule-1 expression to any significant extent. Castor oil in the diet induced a significant increase in prostaglandin E_2 concentrations in tissues of the intestinal mucosa, placenta, amnion, and amniotic cells in groups of pregnant Wistar rats.

Castor oil did not have antimicrobial activity in the *Staphylococcus aureus*, *Escherichia coli*, or *Candida albicans* bacterial strains. There was no correlation between Sodium Ricinoleate antibacterial activity against cells in suspension and antiplaque activity.

Following the oral administration of castor oil (2 ml), macroscopic damage, characterized mainly by vasocongestion, was observed throughout the duodenum and jejunum in rats. After male albino rats were dosed intraperitoneally with 100 mg Ricinoleic Acid, all animals were dead within 24 h. The acute oral LD_{50} for Ethyl Ricinoleate exceeded 5.0 g/kg in rats. A single oral dose (2.5 ml/kg) of castor oil caused generalized hyperemia of the intestinal mucosa up to 72 h post dosing in most of 12 ponies. An acute oral LD_{50} of >10 g/kg was reported for Hydrogenated Castor Oil in a study involving rats. The acute dermal LD_{50} for Ethyl Ricinoleate exceeded 5.0 g/kg in rabbits. One of the rabbits died. The skin reactions observed included

moderate erythema in six rabbits, moderate edema in five rabbits, and slight edema in one rabbit.

In an acute intravenous toxicity study in which eight mongrel dogs were dosed with castor oil (single bolus dose = 0.1 ml/kg), none of the animals died. Erythema was the only clinical sign that was reported. An increase in blood histamine occurred in one animal.

The short-term subcutaneous administration of a vehicle consisting of castor oil and benzyl benzoate to groups of five C_{57}Bl/6J mice caused morphological alterations suggestive of stress-induced changes. Using electron microscopy, the changes observed in the adrenal cortex included disruption of parenchymal mitochondria in the zona fasciculata, increase in the size of some of the mitochondria, loss of the vesicular orientation of the inner mitochondrial membrane, and diminution of the mitochondrial matrix. Mitochondrial changes were also observed in the zona reticularis and zona fasiculata.

Intragastric administration of Ricinoleic Acid (single 0.1 ml dose) to CD-1 specific pathogen–free mice resulted in the erosion of duodenal villi. In another study, perfusion of the rabbit colon with Sodium Ricinoleate solution (5.0, 7.5, and 10 mM) led to mucosal damage (i.e., the loss of epithelial cells). A dose-response relationship for mucosal damage was noted.

In an NTP subchronic oral toxicity study, the administration of diets containing up to 10% castor oil to groups of male and female F344/N rats continuously for 13 weeks was not associated with any toxicities.

The subchronic oral toxicity of Hydrogenated Castor Oil (dietary concentrations up to 17.3%) was evaluated in female rats in a preliminary feeding trial. A reduced growth rate in rats fed 8.65% and 17.3% Hydrogenated Castor Oil, respectively, was the only abnormality that was observed. Based on organ weight determinations and the results of hematological and microscopic examinations, no adverse effects were observed.

In a 16-week study, groups of 15 male albino rats were fed diets containing 0.865% or 8.65% Hydrogenated Castor Oil. Except for the reduced growth rate in rats fed 8.65% Hydrogenated Castor Oil, no adverse effects were observed.

The instillation of undiluted castor oil (0.5 ml) into the rabbit eye resulted in an ocular injury score of 1 (maximum score possible = 20). In contrast, undiluted castor oil induced slight congestion of the iris and conjunctiva in the rabbit eye in another study, but the instillation of castor oil (10 drops daily for 3 weeks) into the eyes of ten rabbits in a third study produced no damage to the corneal epithelium or endothelium.

Castor oil swabbed onto the dorsum of each of 216 albino or Long-Evans rats daily for five days to 2 weeks produced a mild effect on the epidermis. Undiluted castor oil was applied for 24 h to two areas on the dorsal surface of six albino angora rabbits. Severe skin irritation was observed. Undiluted castor oil applied to the dorsal skin of six male Hartley guinea pigs, six male Wistar rats, and six miniature swine produced mild skin irritation in guinea pigs and rats, but not in miniature swine. Repeated applications of undiluted castor oil to the flanks of five female albino rabbits daily for 30 days induced slight erythema and edema. Both open skin irritation and repeated application (8 weeks) tests for undiluted castor oil and 10% aqueous castor oil were well tolerated by rabbits in another study. Slight reddening of the application site (flank) was observed in a study in which six albino guinea pigs and six young pigs received applications of undiluted castor oil on 10 successive days.

In a predictive prick test in which seven normal subjects were tested with an SLS extract of Castor Wax (concentrations up to 22,000 μg/ml), no immediate skin reactivity was observed. None of the seven subjects patch tested with the SLS Castor Wax extract or the remaining three extracts of Castor Wax (concentrations not stated) had a delayed skin reaction. In a provocative prick test in the same study, three patients with occupational hypersensitivity to castor allergens were tested with the SLS extract of Castor Wax at concentrations up to 22,000 μg/ml. All three patients had a positive reaction to the SLS Castor Wax extract. None of the three patients patch-tested had a delayed reaction to the SLS Castor Wax extract or the remaining three extracts of Castor Wax (concentrations not stated).

The positive skin reactions (immediate skin reactivity) in sensitized individuals, together with the positive PCA reactions in mice and positive direct RAST for reaginic castor allergens that were induced by SLS Castor Wax extract, indicate that allergens are present in Castor Wax at low concentrations.

Neither erythema nor edema was observed following a single topical application of Ricinoleic Acid (in peanut oil) to the paws of 8 to 10 male Swiss mice. The application of Ricinoleic Acid (in peanut oil) to the entire eyelid surface of each of six male albino Dunkin-Hartley guinea pigs induced eyelid reddening and edema at doses of 10, 30, or 100 mg. Cetyl Ricinoleate was classified as a non-irritant following application to the skin of three male New Zealand albino rabbits. Diluted TEGODEO HY 77 (trade name mixture that generally contains >50% Zinc Ricinoleate) was applied, under occlusive patches and after patch removal. Well-defined erythema was observed at 48 and 72 h at the abraded sites of all six rabbits and at the intact sites of four rabbits. This mixture did not produce skin sensitization in a study involving 30 white guinea pigs.

Castor oil was not comedogenic when applied to the ears of rabbits for 2 weeks, but there was a slight increase in keratin content within the follicle, with essentially no change in the follicular epithelium.

Sodium Ricinoleate caused dose-related increases in cytotoxicity in cultures of epithelial cells that were isolated from the small intestines of male Syrian hamsters. In another study, Sodium Ricinoleate did not induce significant toxicity in human saphenous vein endothelial cell cultures at concentrations $\leq$25 μM. At concentrations of 0.1% and 1.0% Sodium Ricinoleate, applied to serosal surface or rat jejunum, a significant reduction in the number of ganglion cells in the myenteric or submucosal plexus was noted. This was not true for the lowest test concentration (0.01%). Castor oil did not have a toxic effect

on the tubular epithelium following intraluminal injection into the kidneys of five male white albino rats. In a study evaluating the nephrotoxicity of cyclosporine, castor oil served as the vehicle control.

Neither castor oil nor Sodium Ricinoleate was mutagenic to the following *Salmonella typhimurium* strains either with or without metabolic activation: TA98, TA100, TA102, TA1535, and TA1537. Results were also negative for castor oil in *Escherichia coli* strain WP2/pKM102. Groups of male and female mice that received diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10.0% castor oil (in DMSO) for 13 weeks had no evidence of induction of micronuclei in peripheral erythrocytes. Castor oil did not induce sister chromatid exchanges either with or without metabolic activation. Sodium Ricinoleate interfered with cell division in an *Escherichia coli* strain, causing the organisms to develop as filaments. Ricinoleic Acid was inactive as a stimulator of DNA synthesis and inducer of ornithine decarboxylase activity in the rat colon. Concentrations up to 10 mM resulted in insignificant increases in [^{3}H]dThd incorporation and did not increase the level of ornithine decarboxylase activity above control values.

None of the 20 mice injected intravaginally with 2% Ricinoleic Acid (in gum tragacanth) had neoplasms or hyperplastic lesions of the corpus uteri, cervix uteri, vagina, or perineal skin. However, benign lung adenomas were observed in 10 of the 13 mice dosed with Ricinoleic Acid and in 6 of the 24 vehicle control mice that were killed after the 14th month of dosing.

Neither undiluted castor oil, Ricinoleic Acid, nor Glyceryl Ricinoleate was a tumor promoter in a study involving groups of ten mice. However, the three test substances induced slight epidermal hyperplasia in groups of three mice following the application of each to a small area of skin in the interscapular region.

Castor oil extract had a strong suppressive effect on S_{180} body tumors in male Kunming mice. Its suppressive effect on ARS ascites cancer was also very strong, with 64% of the ascites tumors in mice being completely cured. Compared to controls, the life extension rate was more than 136% ($p < .0012$).

Groups of mice and rats fed diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10% Castor Oil continuously for 13 weeks had a slight decrease in epididymal weight (6% to 7%) in mid- and high-dose groups of male rats; however, this finding was not dose-related. No effects on any other male reproductive end point (testes weight and epididymal sperm motility, density, or testicular spermatid head count) or female reproductive endpoint (estrous cycle length, or time spent in each phase of the cycle) were noted.

Female Wistar rats injected intramuscularly with castor oil (0.2 ml, single dose) on the first day after estrus had suppressed ovarian folliculogenesis and anti-implantation and abortive effects. Anticonceptive and estrogenic effects of a methanol extract of *Ricinus communis* var.*minor* seeds (ether-soluble fraction) were studied in adult albino Wistar rats, young albino Wistar rats, immature Swiss albino female mice, and adult female New Zealand white rabbits. Subcutaneous administration of the extract produced anti-implantation, anticonceptive, and estrogenic activity in rats and mice.

Castor oil served as the vehicle control in a study evaluating the effect of long-term treatment with ICI 182,780 (an antiestrogen) on the rat testis. In the control group, four male Sprague-Dawley rats were injected subcutaneously with castor oil (0.2 ml) once per week and then killed 100 days after the first injection. Spermatogenesis appeared normal in each of the four control rats.

Castor oil (2 oz) was used to stimulate labor in 196 patients (between 37 and 42 weeks of gestation) with premature rupture of membranes. The need for cesarean sections was nearly three times greater in the control group (15.7% incidence) than in patients dosed with castor oil (5.6% incidence). No relationship between dosing with Castor Oil (administered as a 60-ml dose in orange or apple juice), birth weight, and mode of delivery was found in a study in which castor oil was used to induce labor in 52 pregnant women. The cesarean section rate for women dosed with castor oil was 19.2% (10 of 52 women), compared to 8.3% (4 of 48 controls) in the untreated control group. No adverse outcomes for the mother or fetus were identified.

Mild and transient discomfort and minor epithelial changes were observed in the eyes of nine patients after treatment (instillation) with a castor oil solution four times daily for 15 days. In another study involving 100 patients, the instillation of castor oil affected the cornea and conjunctiva. Specifically, the degeneration and death of epithelial cells and continuity breaks in the epithelium were observed.

Mild skin irritation was reported in 50 adult males patch tested with undiluted castor oil (0.05 g applied to back). None of the 1 to 20 patients, either suffering from or suspected of suffering from contact allergy to cosmetic products, patch tested with 30% Hydrogenated Castor Oil had irritant reactions. Undiluted castor oil rubbed gently onto the right thigh of each of three male subjects on 10 successive days produced, at microscopic examination of excised skin, clear hyperchromasia and an increase in the number of cells was observed in the basal cell layer. Slight widening of the granular cell layer was also noted. No skin irritation was seen with 20% Ethyl Ricinoleate in petrolatum using 32 healthy male volunteers in a 48-h closed patch test.

No skin sensitization or irritation was seen with 20% Ethyl Ricinoleate in a maximization test using 32 healthy male volunteers. In 49 patients with contact dermatitis patch-tested (48-h Finn chambers) with castor oil, none had a positive reaction. One of the 76 dermatitis patients patch-tested with Castor Oil had a positive reaction, observed only during the second reading (i.e., the day after the 30-min reading). Of 202 consecutive patients with eczematous cheilitis who attended a contact and occupational dermatoses clinic in Singapore, 29 patients had positive reactions to Ricinoleic Acid. Of the 29 positive reactions, 22 were considered relevant positives. In an allergenicity-photoallergenicity study, 103 patients suspected of having cosmetic-related dermatitis were patch tested

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with castor oil. One patient had a positive patch test reaction. None of the patients had a positive photopatch test reaction.

In case reports that included patch test results for castor oil, Ricinoleic Acid, or esters of Ricinoleic Acid, both positive and negative reactions were reported. Of a group of 25 employees at a company involved with the preparation of plant products, 1 employee had an allergic reaction to an extract of the castor oil bean.

DISCUSSION

The CIR Expert Panel considered that the available data on Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Ricinoleic Acid, and salts and esters of Ricinoleic Acid in the current safety assessment are sufficient for evaluating the safety of Glyceryl Ricinoleate and Glyceryl Ricinoleate SE, as well. Because Ricinus Communis (Castor) Seed Oil contains Ricinoleic Acid as the primary fatty acid group, safety test data on the oil is considered broadly applicable to this entire group of cosmetic ingredients. Overall, the available data demonstrate few toxic effects in acute, subchronic, or chronic toxicity tests. Additionally, there were no genotoxic effects of castor oil in in vitro or in vivo tests. It was noted that the available data include a 50-week chronic study in which none of the 20 mice injected with Ricinoleic Acid twice per week had neoplasms or hyperplastic lesions of the corpus uteri, cervix uteri, vagina, or perineal skin. UV absorption spectra on Ricinus Communis (Castor) Seed Oil and Glyceryl Ricinoleate indicate maximum absorbance at 270 nm, suggesting that there would be no photosensitization potential of Glyceryl Ricinoleate or Ricinus Communis (Castor) Seed Oil in human subjects at relevant solar UV exposures.

Reactions classified as either significantly irritating or allergic were not observed in a maximization test on Ethyl Ricinoleate involving 32 healthy male subjects. Although there is a paucity of predictive patch test data on Ricinoleic Acid esters/salts, the Panel agreed that the negative guinea pig sensitization data on a trade name mixture containing more than 50% Zinc Ricinoleate, in conjunction with the human predictive patch test data, may be extended to support the safety of all of the cosmetic ingredients that are included in this safety assessment.

The Panel did consider the 22 positive reactions to Ricinoleic Acid in a retrospective study involving 202 consecutive patients with eczematous cheilitis. Recognizing that this study represents a case series on cheilitis that involves a select patient population, the Panel agreed that the incidence of sensitization reactions reported in the study may be expected in that select patient group, but not in the general population. Based on the Panel's experience and expertise in the area of patient patch testing, the incidence of positive reactions to Ricinoleic Acid is generally very low.

In the absence of inhalation toxicity data on Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Ricinoleic Acid, and salts and esters of Ricinoleic Acid in this safety assessment, the Panel determined that these ingredients can be used safely in aerosolized products because packaging and use ensure that particulates are not respirable (are greater than 10 μm). The Panel reasoned that the particle size of anhydrous hair sprays (60 to 80 μm) and pump hair sprays (>80 μm) is large compared to the median aerodynamic diameter of 4.25 ± 1.5 μm for a respirable particulate mass.

The CIR Expert panel recognizes that certain ingredients in this group are reportedly used in a given product category, but the concentration of use is not available. For other ingredients in this group, information regarding use concentration for specific product categories is provided, but the number of such products is not known. In still other cases, an ingredient is not in current use, but may be used in the future.

Although there are gaps in knowledge about product use, the overall information available on the types of products in which these ingredients are used and at what concentration indicate a pattern of use. Within this overall pattern of use, the Expert Panel considers all ingredients in this group to be safe.

CONCLUSION

The CIR Expert Panel concluded that Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate, Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

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Final Amended Report on the Safety Assessment of Mink Oil[1]

Mink Oil, obtained from the fatty tissues of minks, is a mixture of the natural glycerides of 14 to 20 carbon chain fatty acids There are 100 current reported uses as a hair-conditioning agent, an occlusive skin-conditioning agent, and as a surfactant; up to a maximum concentration of 3% Mink Oil is manufactured by harvesting animal hides and scraping the fat layer from the hide It is rendered and refined using high temperature processes (230°F to 240°F) and saponification to reduce free fatty acids Analyses demonstrate that Mink Oil can be substantially free of impurities, including pesticides Mink Oil does not absorb significant UVA or UVB radiation In a clinical test of skin penetration, 1 h after application, Mink Oil was detected on the skin surface of all five panelists; it was detected within the stratum corneum in 2/5 panelists Mink Oil has an oral LD_{50} of >64 0 cc/kg in albino rats No erythema or edema was noted after refined Mink Oil was applied for 24 h to intact and scarified area of albino rabbits A 50% dilution of a Mink Oil cream did not sensitize guinea pigs in a maximization test Mink Oil was not an ocular irritant to albino rabbits Clinical studies using single occlusive patches found no irritation with up to 2 8% Mink Oil, although transient mild to no irritation was noted in two exaggerated-use studies Mink Oil is used in aerosols and sprays Although there are no inhalation toxicity data available on Mink Oil, the available data on particle sizes of cosmetic aerosols and sprays indicates diameters more than an order of magnitude larger than the diameter of respirable particles Most of the glycerides in Mink Oil are triglycerides (glyceryl triesters), the safety of which has been substantiated in previous safety assessments; e g , dermal absorption is nil to slight; there is little or no acute, subchronic, or chronic oral toxicity; dermal application was not associated with significant irritation or sensitization; ocular exposures were, at most, mildly irritating; most of the genotoxicity test systems are negative; use as vehicles in carcinogenicity testing of other chemicals has produced no adverse reaction; and clinical tests produce no irritation or sensitization reactions—but, they may enhance the of penetration of other chemicals Formulators should be aware of the possible penetration-enhancing properties of Mink Oil Although pesticide residues have been analyzed and found to be below levels of detection, the Panel is concerned that the available data suggesting the absence of pesticide residues in Mink Oil are limited The Panel advised the industry that the total polychlorinated biphenyl (PCB)/pesticide contamination should be limited to not more than 40 ppm, with not more than 10 ppm for any specific residue

INTRODUCTION

This amended safety assessment updates and supersedes an earlier Cosmetic Ingredient Review (CIR) safety assessment of Mink Oil (CIR 1995) New information is included on the manufacturing process, batch analysis data; pesticide residue analysis, updated concentration of use, and ultraviolet (UV) absorption spectra Information provided by the Cosmetic, Toiletry, and Fragrance Association (CTFA) indicated that most glycerides in Mink Oil are triglycerides (CTFA 2001a) The safety of triglycerides in cosmetics was assessed by CIR, with the conclusion that these ingredients are safe as used in cosmetics (CIR 1999) In addition, CIR has published a safety assessment of Oleic, Lauric, Palmitic, Myristic, and Stearic Acids (Elder 1987) Uses of both the triglycerides group and fatty acid group of ingredients in cosmetics at maximum concentrations ranging from 25% to 50% were determined to be safe On the basis of the available data the Panel issued this amended safety assessment

CHEMISTRY

Method of Manufacture

Mink Oil is a mixture of the natural glycerides of 14 to 20 carbon chain fatty acids obtained from the subdermal fatty tissues of the mink (Pepe et al 2002)

EMULAN, Inc (1990) uses Northern Ranch Mink as the source for Mink Oil Animals are raised in cages and kept free from disease and are harvested typically in late fall/early winter.

The fat is scraped from the hides of the mink and frozen until it is rendered and refined The fat is rendered at temperatures ranging from 220°F to 240°F for a minimum of 5 h, after which the saturated fat is separated from the unsaturated fat using filtration A saponification process then further separates the free fatty acids, i e , the saponified free fatty acids form soap at the bottom The oil is further bleached and clarified using diatomaceous earth, again at the high temperature described above Impurities such as any remaining soap or any proteinaceous impurity (e g , collagen) are removed at this stage (EMULAN, Inc 1990; Complete Analysis Laboratories, Inc 1996, CTFA 1999a)

Chemical Composition

According to the *Compendium of Cosmetic Ingredient Composition* (Nikitakis and McEwen 1990), the oil is a mixture of the natural glycerides of 14 to 20 carbon chain fatty acids; approximately 75% of the composition is 16 to 18 carbon chain

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TABLE 1
Fatty acid composition of two Mink Oils (CTFA 1994)

Fatty acid	Carbon chain length/ number of unsaturated C C bonds	Mink Wax Oil (as %)	Mink Crude Oil (as %)
Lauric	12/0	0 1	0 1
Myristic	14/0	4 0	3 5
Myristoleic	14/1	0 7	0 9
Pentadecanoic	15/0	0 2	0 1
Palmitic	16/0	28 0	17 2
Palmitic	16/1	13 3	17 0
Heptadecanoic	17/0	0 5	0 4
Heptadecanoic	17/1	0 6	0 5
Stearic	18/0	4 7	2 5
Oleic	18/1	35 3	40 9
Linoleic	18/2	10 6	15 0
Linolenic	18/3	0 4	0 6
Eicosanoic	20/0	0 1	—
Eicolenoic	20/1	0 7	0 6
Total fatty acid		99 2	99 3
Unsaturated		61 6	75 5
Saturated		37 6	23 8

fatty acid glycerides The detailed fatty acid composition of two forms of Mink Oil (Mink Wax Oil and Mink Crude Oil) provided by one supplier is given in Table 1 (CTFA 1994)

Physical and Chemical Properties

Mink Oil is a pale yellow liquid with a mild characteristic odor It is soluble in chloroform, carbon tetrachloride, ether, benzene, acetone, and isopropanol and is insoluble in water The refractive index at 25°C is between 1 4665 and 1 4675 The freezing point is 5°C maximum; the saponification value is 190 to 220, the iodine value is 80 to 90 (Nikitakis and McEwen 1990) SGS Control Services Inc (1994) reported a specific gravity of 0 91437 and a refractive index at 40°C of 1 4623 Jennings Laboratories, Inc (1999) reported a specific gravity at 25°C of 0 9110 and a refractive index at 25°C of 1 4680 One supplier reported that because of its iodine value, Mink Oil "exhibits very low oxidation and degradation" (CTFA 1994)

UV Absorption

Mink Oil prepared according to the manufacturing process described above has significant absorbance only in the UVC region Absorption maxima in a 0 5% sample occur at 212 nm (2 59700 absorption units), 270 nm (0 55858 absorption units), and a small absorption at 316 nm (0 07776 absorption units) A 0 05% solution had no detectable absorption at 316 nm (CTFA 1999b)

Impurities

One analysis reported 0 0628% moisture, 0 0012% unsaponifiable matter, and 0 0002% insolubles (Jennings Laboratories, Inc 1999)

Analysis of one sample of Mink Oil found no detectable levels of the following tradename polychlorinated biphenyls (PCBs): Aroclor 1016, 1221, 1232, 1242, 1248, 1254, and 1260 The assay had a minimum detection limit of 0 5 μg/L (New Jersey Laboratories/A A Labs Division 1995)

Pesticide analyses of two samples produced the results shown in Table 2 No explanation was provided for the different detection limits for the two sample analyses, although it was reported that they were done at different times (CTFA 2001a)

The United States Pharmacopeia (USP) standards for lanolin, for comparison purposes, limit PCB/pesticide contamination to not more than 40 ppm, with not more than 10 ppm for any specific residue (U S Pharmacopeia 1995)

COSMETIC USE

Mink Oil is used in formulations as a hair conditioning agent, an occlusive skin conditioning agent, and a surfactant (Pepe et al 2002) Based on information received from industry, the Food and Drug Administration (FDA) lists 100 current uses of Mink Oil (FDA 2001) The uses of Mink Oil as a function of product type are given in Table 3 The product types and the total number of each product type reported to FDA (FDA 2001) are given, with the number of formulations of that product type that were reported to contain Mink Oil; e g , of 187 mascara products, only one contains Mink Oil Current concentration of use data provided by industry (CTFA 1999c, 2001b) as a function of product type are also included in Table 3 These data indicate that Mink Oil is reportedly used in a given product category, but the concentration of use is not available In other cases, information regarding use concentration for specific product categories is provided, but the number of such products is not known

Mink Oil is used in products that are or may be found in sprays or aerosols Cosmetic product sprays and aerosols produce large particle sizes For example, aerosol hair sprays have particles of 60 to 80 μ diameter, with <1% below 10 μ, and pump hair sprays have particle diameters of $\geq$80 μ (Bower 1999) These particle sizes are larger than the mean aerodynamic diameter of respirable particles, which is 4 25 $\pm$ 1 5 μ (Jensen and O'Brien 1993)

The European Commission (EC) has not included Mink Oil in the list of substances which cosmetic products must not contain or must not contain except subject to restrictions and conditions laid down (EC 2002) In the current Japanese Ministry of Health, Labor and Welfare (MHLW) regulations, Mink Oil is not included on a negative list (MHLW 2000a), on a list of ingredients for which there are restrictions to use in cosmetics (MHLW 2000b), or on a list of quasi-drugs for which listing is required (MHLW 2000c)

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TABLE 2
Pesticide residues in Mink Oil (CTFA 2001b)

	8/7/96 sample		10/7/96 sample	
Pesticide	Level in Mink Oil (mg/kg)	Min detectable level (mg/kg)	Level in Mink Oil (mg/kg)	Min detectable level (mg/kg)
A-BHC	U*	0 020	U	0 020
B-Bhc	U	0 020	U	0 020
G-BHC (Lindane)	U	0 020	0 11	0 020
D-BHC	U	0 020	U	0 020
Heptachlor	U	0 020	U	0 020
Aldrin	U	0 020	U	0 020
Heptachlor Epoxide	U	0 020	U	0 020
Endosulfan I	U	0 020	U	0 020
A-Chlordane	U	0 020	U	0 020
G-Chlordane	U	0 020	U	0 020
Dieldrin	U	0 020	U	0 020
4,4′-DDE	0 27	0 020	U	0 020
Endrin	U	0 020	U	0 020
Endosulfan II	U	0 020	U	0 040
4,4′-DDD	U	0 020	U	0 040
Endrin Aldehyde	U	0 020	U	0 040
Endosulfan Sulfate	U	0 020	U	0 040
4,4′-DDT	U	0 020	U	0 040
Endrin Ketone	U	0 020	U	0 040
Methoxychlor	U	0 020	U	0 020
Toxaphene	U	0 020	U	1 00

*U = undetectable

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Absorption

Xienta Institute for Skin Research (1988) conducted an attenuated total reflectance–infrared spectroscopy study (ATR-IR) to determine the penetration of a commercial preparation of Mink Oil into human stratum corneum Five healthy Caucasian females were instructed to refrain from applying any topical agents to their forearms 24 h prior to the study A site on one forearm of each panelist was treated with 50 μl of the test substance The same site on the other forearm was not treated and served as control Both sites were scanned prior to product application Scanning consisted of placing the subject's forearm directly onto a germanium plate and conducting an IR spectra for wavelengths between 800 and 4000 cm^{-1} The germanium plate served as an internal reflection crystal One hour after application, the sites were again scanned This was followed by tape stripping and scans after 5, 10, and 15 tape strippings The same scans were conducted on the untreated sites

Based on the IR spectra of the test substance, wavelengths of 1746, 1466, and 1163 cm^{-1} were chosen for analysis Presence of Mink Oil in each of the four scans (surface, 5, 10, 15 layers all done at 1 h post treatment) was defined as a greater absorbance value at the treated site versus the control For each of the four scans, there were 15 absorbance pairs (a pair consisting of an absorbance value for the control and treated sites) Mink Oil was detected at the surface scan of all panelists It was detected within 5 layers in 4/5 panelists, 10 layers in 2/5 panelists, and 15 layers in 2/5 panelists The authors concluded that, after 1 h, Mink Oil remains on the skin surface (Xienta Institute for Skin Research 1988)

Distribution, Metabolism, and Excretion

No studies were available describing the distribution, metabolism, or excretion of Mink Oil

ANIMAL TOXICOLOGY

Acute Oral Toxicity

A commercial preparation of Mink Oil had an oral LD_{50} of >64 0 cc/kg in albino rats (Bio-Toxicology Laboratories, Inc 1974) In another study, a Mink Oil cream had an oral LD_{50} of >5 0 ml/kg in rats (Wells Laboratories, Inc 1990e)

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TABLE 3
Frequency of use of Mink Oil

Product category (number of formulations in category) (FDA 2001)	Number of formulations containing Mink Oil (FDA, 2001)	Concentration of use (CTFA 1999c, 2001) (%)
Baby lotions, oils, powders, and creams	—	1
Other bath preparations (193)	1	0 1
Eye shadow	—	0 1
Eye lotion (23)	1	—
Mascara (187)	1	0 3–1
Other fragrance preparations	—	1
Hair conditioner (630)	14	3
Hair spray—aerosol fixatives (267)	3	—
Hair straighteners (63)	4	—
Permanent waves (211)	1	—
Rinses—noncoloring	—	3
Shampoos—noncoloring (851)	4	—
Tonics, dressings, and other hair-grooming aids (577)	9	—
Other hair preparations (276)	4	—
Blushers—all types	—	0 1
Face powders (301)	1	0 1
Lipstick (942)	12	0 001
Makeup bases	—	0 5
Shaving cream (133)	5	—
Skin cleansing products (733)	7	—
Face and neck creams, lotions, powders and sprays—excluding shaving products (304)	2	0 2–0 5
Body and hand creams, lotions, powders and sprays—excluding shaving products (827)	10	0 1
Moisturizing (881)	8	0 2
Night products (200)	5	—
Paste masks—mud packs (269)	1	—
Other skin care preparations (715)	6	—
Suntan gels, creams, liquids (131)	1	0 3
Other suntan preparations	—	2
2001 total uses/ranges for Mink Oil	100	0 001–3

Dermal Irritation

Patches containing 0 5 ml of a commercial preparation of refined Mink Oil were applied to intact and scarified areas of guinea pig skin The treatment areas had earlier been clipped free of hair Animals were immobilized for a 24-h period; the sites were evaluated at the end of the treatment period and 24 h afterwards Scores were made according to the Draize scale No erythema or edema was noted (Leberco Laboratories 1972a)

Patches containing 0 5 ml of refined Mink Oil (neat) were applied to intact and abraded skin of six rabbits (strain not specified) No irritation was noted at observations made 24 and 72 h after application (Wells Laboratories, Inc 1979b) Similar results were reported by Wells Laboratories, Inc (1990d) when a cream containing Mink Oil was tested on three New Zealand white rabbits using the same protocol

Dermal Sensitization

Over a period of 20 days, eight male guinea pigs received 10 subcutaneous injections of a 0 1% suspension of refined Mink Oil; the injections were administered to the clipped back and sides The test material was suspended in physiological saline and was administered in 0 1 ml doses except for the first injection, which contained 0 05 ml Two weeks after the final induction injection, a test injection of 0 05 ml was

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administered Reaction areas were measured 24 h after each injection Irritation reactions were noted throughout the induction period The reaction on challenge was less than the irritant reaction seen during induction and the authors concluded that the test material was not a sensitizer (Leberco Laboratories 1972b)

CTFA (1983) reported a study in which female Dunkin-Hartley guinea pigs were treated with Mink Oil using the Magnusson-Kligman maximization procedure induction, dose range, booster, and challenge During induction, sites on the upper back were injected intradermally with 50% Freund's complete adjuvant, 5% Mink Oil in propylene glycol, and 5% Mink Oil in 50% Freund's complete adjuvant Control animals were injected with complete adjuvant, propylene glycol, and 1 1 propylene glycol in complete adjuvant During the dose range phase, 10 animals were tested with 24 h occlusive patches containing 25%, 50%, and 100% Mink Oil Sites were evaluated for irritation at 24, 48, and 72 h after patch application Two of the animals reacted to the 25% concentration with a response graded as "barely perceptible", by 72 h the condition cleared These two animals also reacted to the higher concentrations of Mink Oil, the reactions cleared by the 72-h observation Another four had "barely perceptible" or "mild" reactions to the 50% concentration These reactions also cleared by 72 h and three of these four animals did not react to the 100% concentration Three animals reacted for the first time to the 100% concentration with a "barely perceptible" response (two also had desquamation); these conditions cleared by 72 h

During the booster phase (1 week after induction injections) undiluted Mink Oil was topically applied Sodium lauryl sulfate (SLS) at 5% was applied to the induction site 24 h before the booster Control animals were pretreated with SLS before receiving a booster of undiluted petrolatum; positive controls were treated with 25% phenylacetaldehyde without SLS pretreatment During the booster phase, all test and control animals were wrapped occlusively for 48 h Two weeks following the booster, test animals were challenged with a 24-h occlusive patch of 25% and 50% Mink Oil in petrolatum Reactions were scored at 48 and 72 h after patch application There were no reactions to 25% Mink Oil noted in the ten animals at the 48-h reading, one animal had a "barely perceptible" reaction at 72 h Four animals had a "barely perceptible" and one had a "mild" response to 50% Mink Oil at the 48-h reading At the 72-h reading, erythema was noted in 7 of 10 animals, which ranged from "barely perceptible" (4 animals) to "desquamation" (2 animals) and "mild with desquamation" (1 animal) Mink Oil at 50% in petrolatum was considered to produce a weak allergenic response (CTFA 1983)

The Buehler Technique was used by Wells Laboratories (1990a) in a guinea pig sensitization assay During induction nine occlusive patches containing 0 5 ml of a 50% dilution (in corn oil) of a Mink Oil cream was applied to the clipped back and flank of 10 animals The patches remained for 6 h of contact and readings were made at the time of patch removal and at the end of 24 h Positive controls were treated with dinitrochlorobenzene (DNCB) After a 2-week nontreatment period animals were challenged with two identical applications of the test material One patch was applied at the site of induction, and the other on a previously unexposed site Challenge patches were applied for 6 h of contact and observations were made at the time of patch removal and at the end of 24 h A reading of "very slight" erythema was noted in all animals during induction; "slight" erythema and "slight" edema were noted in positive controls During challenge, no irritation was noted in animals of the Mink Oil group, marked erythema and very slight edema was noted in animals of the positive-control group

Ocular Irritation

A commercial preparation of refined Mink Oil (0 1 ml) was instilled into the right conjunctival sac of three albino rabbits The untreated left eye served as control Eyes were evaluated every 24 h for 4 days and then again on the 7th day Scores were made according to the Draize scale No irritation was noted (score 0) (Leberco Laboratories 1972c)

Another ocular irritation test was conducted using three rabbits and the above described protocol (Wells Laboratories 1979a) Undiluted Mink Oil (commercial preparation, dose not reported) did not produce any observable irritation

A Mink Oil cream (0 1 ml) was applied to one eye of each of three New Zealand white rabbits The contralateral eye was not treated and served as control Eyes were unwashed for 24 h and observations made 24, 48, and 72 h after treatment No irritation was noted (Draize score 0 01) (Wells Laboratories, Inc 1990c)

Comedogenicity

A Mink Oil cream was considered to be noncomedogenic following repetitive applications (10 applications in 2 consecutive weeks) to the external ear canal of six albino rabbits Observations noted include "minimal to mild" hyperemia and "very minimal" hyperkeratosis in the treated areas of all animals towards the end of the treatment period (Wells Laboratories, Inc 1990b)

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Twenty panelists received a single 24-h occlusive patch containing a 25% aqueous dilution of a hair rinse containing 3% Mink Oil (effective concentration of Mink Oil tested: 0 75%) No reactions were noted in 16 panelists, reactions of ± (the mildest non-zero score possible) were noted in four panelists The primary irritation index (PII) was 0 10 out of a maximum possible score of 4 0 (CTFA 1989) Identical results were reported in a second patch test study in which a formulation containing 2 8% Mink Oil was tested at full strength in 20 panelists (CTFA 1992a) A third human patch test study reported a PII of

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0 08 after 19 panelists were tested with a (full-strength) formulation containing 2 8% Mink Oil (CTFA 1993)

A 4-day minicumulative patch test of a body spray containing 1% Mink Oil had a PII of 0 50 Of 20 panelists, 5 had no response, 12 had a "barely perceptible" response, 2 had a "mild" response, and 1 had a "moderate" response (CTFA 1991)

In an exaggerated-use study, 19 female panelists applied to the lower arm, a rinse-off hair product containing 2 8% Mink Oil once a day for 5 days with no rinse off A commercially available rinse-off hair product was applied to a different site to serve as a reference Four subjects experienced some transient mild to moderate erythema (CTFA 1992b) In a second study using the same protocol, no clinical responses were observed in 24 females who also tested a rinse-off hair product containing 2 8% Mink Oil (CTFA 1994)

Sun-Protection Factor

Wells Laboratories (1988a, 1988b) tested the sunscreening ability of Mink Oil In six subjects, 20% Mink Oil with 3% Octyl Dimethyl PABA and 77% Isopropanol had a sun-protection factor (SPF) value of 5 36 In five subjects, a preparation containing Mink Oil had an SPF value of 2 2 Further study details and the specific light source used were not reported

SUMMARY

Mink Oil, obtained from the fatty tissues of minks, is a mixture of the natural glycerides of 14 to 20 carbon chain fatty acids In 2001, it was reportedly used in 100 cosmetic formulations as a hair-conditioning agent, an occlusive skin-conditioning agent, and as a surfactant at concentrations no greater than 3%

Mink Oil is manufactured by harvesting animal hides and scraping the fat layer from the hide It is rendered and refined using high temperature processes (230°F to 240°F) and saponification to reduce free fatty acids

Most of the glycerides in Mink Oil are triglycerides, the safety of which has substantially assessed in previous safety assessments; e g , dermal absorption is nil to slight, there is little or no acute, subchronic, or chronic oral toxicity; dermal application was not associated with significant irritation or sensitization, ocular exposures were, at most, mildly irritating; most of the genotoxicity test systems are negative, use as vehicles in carcinogenicity testing of other chemicals has produced no adverse reaction; and clinical tests produce no irritation or sensitization reactions—but, they may enhance the penetration of other chemicals

Analyses demonstrate that Mink Oil can be substantially free of impurities, including pesticides Mink Oil does not absorb significant UVA or UVB radiation

An attenuated total reflectance–infrared spectroscopy study found that 1-h after application, Mink Oil was detected on the skin surface of all five panelists, it was detected within the stratum corneum in 2/5 panelists

Mink Oil has an oral LD_{50} of >64 0 cc/kg in albino rats

No erythema or edema was noted after refined Mink Oil was applied for 24 h to intact and scarified area of albino rabbits

Although reactions were noted during induction, a 50% dilution of a Mink Oil cream did not sensitize guinea pigs using the Buehler technique In a second study, using the Magnusson-Kligman maximization procedure, 50% Mink Oil in petrolatum-induced sensitization reactions

Mink Oil was not an ocular irritant to albino rabbits

Clinical studies using single occlusive patches found no irritation with up to 2 8% Mink Oil (PII scores of 0 08 to 0 10) Transient mild to no irritation was noted in two exaggerated-use studies

DISCUSSION

The CIR Expert Panel had previously issued a final safety assessment of Mink Oil with an insufficient data conclusion The Panel has now considered information on the manufacturing process; batch analysis data, pesticide residue analysis; updated concentration of use; and UV absorption spectra newly provided by industry

The Panel noted that Mink Oil is used in aerosols and sprays Although there are no inhalation toxicity data available on Mink Oil, the available data on particle sizes of cosmetic aerosols and sprays indicate diameters more than an order of magnitude larger than the diameter of respirable particles Inhalation, therefore, is not believed to produce significant exposure of lung tissue

It was noted that most of the glycerides in Mink Oil are triglycerides, and the Panel agreed that the safety test data in the triglycerides safety assessment are relevant to Mink Oil The triglycerides data demonstrate, among other things, that dermal absorption of triglycerides is nil to slight; there is little or no acute, subchronic, or chronic oral toxicity; dermal application is not associated with significant irritation or sensitization; ocular exposures are, at most, mildly irritating; most genotoxicity test system results are negative; use as vehicles in carcinogenicity testing of other chemicals has produced no adverse reaction; and clinical tests produce no irritation or sensitization reactions Because triglycerides may enhance the penetration of other chemicals, it has been recommended that care be exercised in using them in cosmetic products That same caution should be applied to Mink Oil

Although pesticide residues have been analyzed and found to be below levels of detection, the Panel is concerned that the available data suggesting the absence of pesticide residues in Mink Oil are limited The Panel advised the industry that the total PCB/pesticide contamination should be limited to not more than 40 ppm, with not more than 10 ppm for any specific residue As with any animal-derived ingredient, Mink Oil should be free of detectable pathogenic viruses or infectious agents

The CIR Expert panel recognizes that Mink Oil is reportedly used in some product categories, but that the concentration of

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use is not available In other cases, information regarding use concentration for specific product categories is provided, but the number of such products is not known Although there are gaps in knowledge about product use, the overall information available on the types of products in which Mink Oil is used and at what concentration indicate a pattern of use Within this overall pattern of use, the Expert Panel considers Mink Oil to be safe

CONCLUSION

Based on the available information, the CIR Expert Panel concludes that Mink Oil is safe as a cosmetic ingredient in the practices of use and concentration described in this safety assessment

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Final Report of the Cosmetic Ingredient Review Expert Panel

Safety Assessment of Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil

September 23, 2008

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Cosmetic Ingredient Review

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Cosmetic Ingredient Review

Final Report on the Safety Assessment of Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil

ABSTRACT: Several cosmetic ingriedients derive from the desert shrub *Simmondsia chinensis*, including Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed, and Simmondsia Chinensis (Jojoba) Butter. Further processing produces other ingredients including Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, and Jojoba Alcohol. Synthetic Jojoba Oil also is used in cosmetics. In this group Simmondsia Chinensis (Jojoba) Seed Oil, the most widely used ingredient, and safe at concentrations up to 100% in body and hand creams, is expressed from seeds and is composed almost completely (97%) of wax esters of monounsaturated, straight-chain fatty acids and alcohols with high-molecular weights. Amounts and composition of the expressed oil varies with maturity of the seeds and somewhat with plant location and climate. Plant derived material may also contain pesticide residues and/or heavy metals. Most available safety test data examined the expressed oil. For example Simmondsia Chinensis (Jojoba) Seed Oil was reported to readily penetrate nude mouse skin and to increase penetration of other agents such as aminophylline in clinical tests. Simmondsia Chinensis (Jojoba) Seed Oil was not an acute oral toxicant to mice or rats (LD_{50} generally greater than 5.0 g/kg). Short-term subcutaneous administration of Simmondsia Chinensis (Jojoba) Seed Wax to rats at 1 ml/kg was not toxic. Neither the wax nor the oil were toxic when applied dermally to the shaved backs of guinea pigs in short-term tests. A dermal irritation test found aqueous Hydrolyzed Jojoba Esters (20%) to be non-irritating to guinea pigs. Jojoba Alcohol was found to be non-irritating to the skin of albino marmots at 10.0%. Simmondisa Chinensis (Jojoba) Butter was classified as a non-irritant when applied to the intact and abraded skin of New Zealand white rabbits at 0.5 ml for 24 h under an occluded patch. Jojoba Alcohol at concentrations up to 50% was minimally irritating in rabbits. Simmondsia Chinensis (Jojoba) Seed Oil was non- to slightly irritating when instilled into the eyes of white rabbits, but Simmondsia Chinensis (Jojoba) Seed Wax, Jojoba Esters, and Jojoba Alcohol were not. Simmondsia Chinensis (Jojoba) Seed Wax was moderately comedogenic in tests using rabbits, but Jojoba Esters was noncomedogenic, and Jojoba Esters were non- to slightly- comedogenic. Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Jojoba Esters were non-mutagenic in Ames testing. No carcinogenicity and no reproductive or developmental toxicity data were available. In clinical tests, Simmondsia Chinensis (Jojoba) Seed Oil was neither a significant dermal irritant, nor a sensitizer. In repeat insult patch tests Jojoba Alcohol , Jojoba Esters and Hydrolyzed Jojoba Esters were not irritating during induction or sensitizing at challenge. Simmondsia Chinensis (Jojoba) Seed Oil and Jojoba Alcohol were not phototoxic. The available safety test data were combined with the expected uses of these ingredients, which includes use in aerosolized products. Because the particle size of aerosol hair sprays (~38 μm) and pump hair sprays (>80 μm) is large compared to respirable particulate sizes (≤10 μm), the ingredient particle size is cosmetic aerosols is not respirable. Relevant information also included uses with baby and eye products at low concentrations, and at 100% in hand and body creams. There were no structural alerts for the fatty acids, fatty alcohols, or other structures that would be found in these ingredients relative to reproductive/developmental toxicity, and these ingredients are not expected to easily penetrate skin. None of the tested ingredients were genotoxic and there were no structural alerts for carcinogenicity. The cosmetic industry should continue to limit pesticide and heavy metal impurities in the plant-derived ingredients before blending into cosmetic formulations. The CIR Expert Panel recognizes the gaps in use and use concentration data of these ingredients. Generally, the information available on the product types that include these ingredients and at what concentrations indicate a pattern to the Expert Panel when it assessed ingredient safety. Were unused ingredients used in the future, use is expected in comparable product categories and concentrations.

INTRODUCTION

Simmondsia Chinensis (Jojoba) Seed Oil and Simmondsia Chinensis (Jojoba) Seed Wax were previously reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel and were found to be "...safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1992). In the original safety assessment, the name of Simmondsia Chinensis (Jojoba) Seed Oil was Jojoba Oil and the name of Simmondsia Chinensis (Jojoba) Seed Wax was Jojoba Wax. The original safety assessment also considered data relevant to the safety of Jojoba-derived ingredients in addition to the oil and wax. Newly available published and unpublished data on all Jojoba-derived ingredients have been included in this report. Accordingly, this amended safety assessment includes Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

CHEMISTRY

Definition and Structure

Simmondsia Chinensis (Jojoba) Seed Oil (CAS No. 61789-91-1) is defined as the fixed oil expressed or extracted from seeds of the desert shrub, Jojoba, *Simmondsia chinensis*. It is also known as Buxus Chinenesis Oil, Jojoba Oil, and Jojoba Seed Oil. Its chemical classification is ester. It only has plant sources

(Gottschalck and Bailey 2008).

According to Wendel (1980), the following chemical formula is typical of an ester found in Jojoba Oil.

$$CH_3(CH_2)_7CH=CH\text{-}(CH_2)_7CO\text{-}O\text{-}(CH_2)_{11}CH=CH(CH_2)_7CH_3$$

Simmondsia Chinensis (Jojoba) Seed Wax (CAS No. 61789-91-1, same as the oil) is defined as the wax obtained from the seed of the jojoba plant, *S. chinensis*. Its chemical classification is wax, and it comes from plant sources (Gottschalck and Bailey 2008).

Hydrogenated Jojoba Oil (no CAS No.) is defined as the end product of the controlled hydrogenation of Simmondsia Chinensis (Jojoba) Oil. Its chemical classification is wax. It has both plant and synthetic sources (Gottschalck and Bailey 2008). According to the *International Cosmetic Ingredient Dictionary and Handbook*, a synthetic source is assigned to an ingredient that is prepared ("synthesized") by the reaction of a substance with one or more other substances to form a new chemical entity. In cases when it is very clear that a raw material used to synthesize an ingredient is plant or animal derived, that source may be listed (Gottschalck and Bailey 2008).

Hydrolyzed Jojoba Esters (no CAS No.) is defined as the hydrolysate of Jojoba Esters (q.v.) derived by acid, enzyme, or other method of hydrolysis. Its chemical classification is esters. It has only a plant source (Gottschalck and Bailey 2008).

Isomerized Jojoba Oil (no CAS No.) is defined as a mixture of esters produced by the enzymatic intraesterification of Simmondsia Chinensis (Jojoba) Oil (q.v.). Its chemical classification is ester. It has both plant and synthetic sources (Gottschalck and Bailey 2008).

Jojoba Esters (no CAS No.) is defined as a complex mixture of esters produced by the transesterification/ interesterification of Simmondsia Chinensis (Jojoba) Oil (q.v.), Hydrogenated Jojoba Oil (q.v.), or a mixture of the 2. Its chemical classifications are transesters and waxes. It has both plant and synthetic sources (Gottschalck and Bailey 2008).

Simmondsia Chinensis (Jojoba) Butter (no CAS No.) is defined as the material obtained by the isomerization of Simmondsia Chinensis (Jojoba) Oil (q.v.). Its chemical classification is wax (natural and sythethic). It has only plant sources (Gottschalck and Bailey 2008).

Jojoba Alcohol (no CAS No.) is defined as the alcohol fraction obtained by the saponification of Simmondsia Chinensis (Jojoba) Oil (q.v.). Its chemical classification is fatty alcohols. It has only plant sources (Gottschalck and Bailey 2008).

Synthetic Jojoba Oil (no CAS No.) is defined as a synthetic oil intended to be generally indistinguishable from natural jojoba oil with regard to chemical composition and physical characteristics. Its chemical classification is wax and it only has synthetic sources (Gottschalck and Bailey 2008).

Physical and Chemical Properties

Simmondsia Chinensis (Jojoba) Seed Oil

The reaction of Simmondsia Chinensis (Jojoba) Seed Oil with sulfur yields a stable product; the liquidity of the oil is not affected by this reaction. Simmondsia Chinensis (Jojoba) Seed Oil also readily undergoes hydrogenation in the presence of a variety of nickel catalysts. The crystalline, hydrogenated product formed has a melting point of approximately 70°C. The epoxidation of Simmondsia Chinensis (Jojoba) Seed Oil and the amidation of transesterified Simmondsia Chinensis (Jojoba) Seed Oil have also been reported. Simmondsia Chinensis (Jojoba) Seed Oil is not easily oxidized and remains chemically unchanged for years. It also remains essentially unchanged when heated repeatedly to temperatures above 285°C, or after being heated to 370°C for 4 days. The yellow color of Simmondsia Chinensis (Jojoba) Seed Oil disappears permanently when the oil is heated to 300°C over a short period of time (McKeown 1983).

Rheological analysis of Simmondsia Chinensis (Jojoba) Seed Oil gave a viscosity of 37.7 mPa/s (Esquisabel et al 1997).

Chung et al. (2001) reported that Simmondsia Chinensis (Jojoba) Seed Oil formed stable emulsions in water with small particles (225 nm; polydispersity 0.21; viscosity 43.0 cSt/s).

Esquisabel et al. (2002) reported that the emulsion of Simmondsia Chinensis (Jojoba) Seed Oil and water encapsulating Bacillus Calmette-Guérin were stable after freeze-drying and storage at room temperature for a year.

Properties of what Habashy et al. (2005) referred to as "jojoba liquid wax", thought to be Simmondisa Chinenesis (Jojoba) Seed Oil, are listed in Table 1.

Table 1. Physical properties of jojoba liquid wax (Habashy et al. 2005).

Property	Value
Freezing point	9°C
Boiling point	398°C
Smoke point[a]	195°C
Flash point	295°C
Refractive index at 25°C	1.46
Specific gravity at 15°C	0.87
Viscosity (25°C)	50 cP
Iodine value	81
Saponification value	93
Acid value	2
Acetyl value	2
Unsaponifiable matter	51%
Total acids	52%

[a] Determined according to official method, Cc9a-48, of the American Oil Chemists' Society

Simmondsia Chinensis (Jojoba) Seed Wax

Kampf et al. (1986) reported that crude Simmondsia Chinensis (Jojoba) Seed Wax has an initial peroxide value of 17 meq/kg, and reaches almost zero after stripping or bleaching. The induction time was 45 to 50 h for crude wax, 12 h for bleached, and 2 h for stripped. Freshly bleached Simmondsia Chinensis (Jojoba) Seed Wax had a low peroxide value of 0 to 0.5 meq/kg for several months when stored in the dark at room temperature; the value elevated to 70 meq/kg within 6 to 7 weeks when stored in a transparent glass bottle. The authors suggest that crude Simmondsia Chinensis (Jojoba) Seed Wax contains a natural antioxidant that is lost in the bleaching and stripping processes.

Simmondsia Chinensis (Jojoba) Seed Wax is a hard crystalline material with properties that are comparable to carnauba and beeswax, and it is miscible with polyethylene glycol in all proportions. The properties of Simmondsia Chinensis (Jojoba) Seed Wax are as follows: appearance of white to off-white free flowing hard wax flakes, slight fatty odor, saponification number of 90 to 95, iodine value of 1, and melting point of 69°C (Reinhardt and Brown 1990).

Jojoba Esters

The physical consistency of Jojoba Esters ranges from a semisolid paste to a liquid with properties that are almost identical to those of Simmondsia Chinensis (Jojoba) Oil. The properties of 2 Jojoba Esters are as follows: soft white to off-white appearance, typical fatty odor, saponification number of 90, iodine values of 60 and 40, and melting points of 29 and 58°C (Reinhardt and Brown 1990).

Brown et al. (1997) tested the stability of Jojoba Esters 15 (melting point 15°C) and Jojoba Esters 60 (melting point 60°C) using an oxidative stability index (OSI; also referred to oil stability index) using a method developed by the American Oil Chemists' Society (AOCS 1997). Jojoba Esters 15 had a stability of ~35 OSI hours and Jojoba Esters 60 175 OSI hours. For comparison, the stability of sesame oil was ~15 OSI hours, palm oil ~30 OSI hours, macademia oil ~30 OSI hours, hybrid sunflower oil ~35 OSI hours, traditional sunflower oil ~5 OSI hours, and almond oil ~10 OSI hours. Table 2 shows the OSI for the Jojoba Esters when exposed to cosmetic actives.

The melting point of Jojoba Esters-70 is 70°C (Arquette et al. 1998).Jojoba Esters have melting points ranging from 15°C to 70°C. The texture and crystallinity of Jojoba Esters may be modified by rapid cooling, thus altering their properties. Jojoba Esters are resistant to oxidation (International Jojoba Export Council 2004).

Floratech (2005a,b,c) reported on 5 Jojoba Ester products (see COMPOSITION SECTION). The properties are reported in Table 3. The shelf life of all 5 Jojoba Esters in an unopened container at or below 35°C is 1 year.

Table 2. OSI of Jojoba Esters 15 and 60 when exposed to cosmetic actives (Brown et al. 1997).

Cosmetic active (%)	15 h	60 h
None	~35	~175
Tocopherols*	~80	~230
Iron oxides (10%) and tocopherols	~80	~225
Zinc oxides (10%) and tocopherols	~15	~90
Titanium dioxide (10%) and tocopherols	~135	~300
Malic acid (5%) and tocopherols	~110	~20
Salicylic acid (2%) and tocopherols	~25	~50
Salicylic acid (2%), titanium dioxide (10%), and tocopherols	~60	~180
Malic acid (5%), titanium dioxide (10%), and tocopherols	~120	~20
Arbutin (7%) and tocopherols	~50	~90
Kojic acid (1%) and tocopherols	~100	~250
Magnesium ascorbyl phosphate (3%) and tocopherols	~85	~170

* concentration of tocopherols not provided.

Hydrolyzed Jojoba Esters

Hydrolyzed Jojoba Esters mixed with water (20:80 wt.%) are described as a soft white to off-white viscous liquid. The maximum saponification value is 1 mg KOH/g, no trans isomers were detected, the peroxide value was a maximum of 5 meq/kg, and the wax ester content was a maximum of 0.5 area %. The expected shelf life in an unopened container at or below 35°C is 1 year (Floratech 2005d).

Jojoba Alcohol

The properties of Jojoba Alcohol are as follows: specific gravity (25°C) of 0.8499, refractive index (20°C) of 1.4621, acid value of 0.01, saponification number of 0.75, hydroxy value of 178.4, iodine value of 83.1, and freezing point of 12°C (Reinhardt and Brown 1990).

Mixtures

Floratech (2006) analyzed a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters, and tocopherol (approximate weight % 35:35:30:0.1). It was described as a clear pale yellow liquid at or above room temperature (24°C). Below room temperature, partial crystallization may appear as cloud-like formations which may settle to the bottom. This can be used as is or warmed to remove cloudiness. The product may slightly darken over time. The product was said to have a shelf life of 1 year. The other values reported are listed in Table 4.

Table 3. Chemical properties of 5 Jojoba Ester products (Floratech 2005a,b,c).

Property	Jojoba Ester 15	Jojoba Ester 20	Jojoba Ester 30	Jojoba Ester 60	Jojoba Ester 70
Appearance	Clear, colorless liquid	Creamy white paste	Soft white paste	Firm white paste	Crystalline jojoba wax particles, hard, white, odorless
Saponification Value	88-96 mg KOH/g	88-96 mg KOH/g	88-96 mg KOH/g	88-96 mg KOH/g	88-96 mg KOH/g
Trans isomers	none	none	none	none	none
Acid value	1 mg KOH/g	1 mg KOH/g	1 mg KOH/g	1 mg KOH/g	1 mg KOH/g
Dropping point	10-15°C	42-48°C	47-51°C	56-60°C	-
Iodine value	78-85 g/100 g	64-70g/100 g	57-61 g/100 g	40-44 g/100 g	2 g/100 g
Monounsaturated Esters	-	25-35 area %	40-47 area %	46-53 area %	-
Peroxide value	4 meq/kg	4 meq/kg	4 meq/kg	4 meq/kg	2 meq/kg
Absence of microbial contamination	100 CFU/g	100 CFU/g	100 CFU/g	100 CFU/g	100 CFU/g
Refractive index @ 40°C	1.458-1.460 n_D	-	-	-	-
Specific gravity	0.862-0.867	-	-	-	-
Triglyceride content	1 wt.%	-	-	-	-
Melting Point	-	-	-	-	66-70°C

Table 4. Properties of an Isopropyl Jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol mixture (Floratech 2006).

Property	Value
Dropping point	6 - 12°C
Hydroxyl value	40 - 70 mg/KOH/g
Iodine value	75 - 85 g/100 g
Refractive Index (40°C)	1.452 - 1.454 n_D
Saponification value	80 - 90 mg KOH/g
Specific gravity	0.855 - 0.860
Trans isomers	none detected
Viscosity (25°C)	15 - 25 cP
Acid value	5 mg KOH/g
Peroxide value	3 meq/kg
Absence of microbial contamination	100 CFU/g

Composition

Simmondsia Chinensis (Jojoba) Seed Oil is composed almost completely (97%) of wax esters of monounsaturated, straight-chain acids and alcohols with high-molecular weights (C16-C26). These wax esters exist principally (83%) as combinations of C20 and C22 unsaturated fatty acids and alcohols (McKeown 1983). The long aliphatic chains of both the acids and alcohols make Simmondsia Chinensis (Jojoba) Seed Oil a highly lipophilic chemical (Shani 1983).

The unsaturated fatty acids are mixtures of cis-11-eicosenoic acid (C20) and cis-13-docosenoic acid (C22); small quantities of oleic acid (C18) and cis-15-tetracosenoic acid (C24) are also present. The unsaturated alcohols are mixtures of cis-11-eicosenol, cis-13-docosenol, and cis-15-tetracosenol. Total free acids (C16 to C24) and total alcohols (C16 to C26) each account for 1% of the composition of Simmondsia Chinensis (Jojoba) Seed Oil. Small quantities of sterols (< 0.5%) are also present (McKeown 1983).

Miwa (1971) reported that the composition of Simmondsia Chinensis (Jojoba) Seed Oil was consistent between 2 adjacent regions of Arizona even in samples collected 5 years apart. Simmondsia Chinensis (Jojoba) Seed Oil collected in the California desert had a similar composition to the oil collected in Arizona. However, Simmondsia Chinensis (Jojoba) Seed Oil collected near the ocean in San Diego had a shift in composition toward larger molecule sizes. Simmondsia Chinensis (Jojoba) Seed Oil from an unknown source had shorter chain lengths than the Arizona samples. The major component, eicosenoic acid, was consistent at 35% for all samples.

Simmondsia Chinensis (Jojoba) Seed Oil contains ~0.05% tocopherols (Yaron 1987).

Simmondsia Chinensis (Jojoba) Seed Wax

Yermanos (1975) reported on the Simmondsia Chinensis (Jojoba) Seed Wax from seeds collected weekly for the 8 weeks leading up to maturity. The amount of the wax increased from 13.5% to 49.4% of the seed weight over time. The composition of the wax as characterized by the carbon chain length and the level of saturation also changed over time as shown in Table 5.

Table 5. Fatty acids and alcohols in Simmondsia Chinesis (Jojoba) Seed Wax in immature and mature seeds[A] (Yermanos 1975).

Number of carbon atoms and double bonds	Acids % in seeds collected on:			Alcohols % in seeds collected on:		
	6/20	7/25	8/25	6/20	7/25	8/25
16:0	2.6	0.9	0.8	-	-	-
18:1	16.1	7.7	7.0	-	-	-
20:1	26.3	35.3	36.4	28.4	27.7	28.8
22:0	-	-	-	5.2	5.4	5.4
22:1	5.0	6.0	5.8	16.5	16.9	15.8

[A] Data represent means form 3 bulk wax samples, each from 15 single plant seed samples/date of sampling.

The main constituents of Simmondsia Chinensis (Jojoba) Seed Wax were the wax esters: eicosenyl octadecenoate (C20:1-C18:1; 5.5%), docosenyl eicosenoate (C20:1-C20:1; 21.4%), docosenyl eicosenoate (C22:1-C20:1; 37.8%), eicosenyl docosenoate (C20:1-C22:1), and tetracosenyl eiosenoate (C24:1-C20:1) (Tada et al. 2005).

Jojoba Esters are proper waxes, with no triglyceride components. Jojoba Esters are a complex mixture of long chain (C35 to C46) fatty acids and fatty alcohols joined by an ester bond and do not contain any trans-unsaturation (International Jojoba Export Council 2004).

Floratech (2005a,b) reported the ester chain length and saturation of 4 Jojoba Ester products as shown in Table 6. Each was reported as being 99.95% Jojoba Esters and 0.05% tocopherol.

Table 6. Ester chain length composition and saturation of Jojoba Ester 20, 40, 60, and 80 (Floratech 2005a,b).

Number of carbons and double bonds	% of different chain lenths in Jojoba Ester:			
	20	30	60	70
38:0	1	1	1 - 4	5 - 8
38:1	1 - 2	2 - 4	3 - 4	-
38:2	3 - 5	2 - 4	1 - 3	-
40:0	1 - 2	2 - 4	7 - 18	26 - 34
40:1	8 - 13	14 - 18	18 - 20	-
40:2	20 - 28	17 - 21	5 - 15	-
42:0	1 - 4	2 - 4	6 - 15	44 - 56
42:1	22 - 30	17 - 21	4 - 12	-
42:2	1	2	2 - 5	8 - 12
44:0	2 - 6	4 - 7	4 - 7	-
44:1	2 - 6	4 - 7	4 - 7	-
44:2	5 - 9	4 - 7	1 - 4	-

Floratech (2005b) reported the ester chain length composition of Jojoba Ester 15 as shown in Table 7, without specifying saturation.

Table 7. The ester chain length composition of Jojoba Ester 15 (Floratech 2005b).

Ester chain length	% in Jojoba Ester 15
C 36	2
C 38	5-8
C 40	34-40
C 42	35-44
C 44	11-15
C 46	2

Methods of Manufacture

Jojobutter-51 is an isomorphous mixture of Simmondsia Chinensis (Jojoba) Seed Oil, partially Isomerized Jojoba Oil, and Hydrogenated Jojoba Wax (Brown 1984).

Simmondsia Chinensis (Jojoba) Seed Wax is the product of complete reduction of the unsaturated alcohols and acids comprising the wax ester combinations of Simmondsia Chinensis (Jojoba) Seed Oil (Reinhardt and Brown 1990).

Jojoba Alcohols are prepared via the sodium reduction of Simmondsia Chinensis (Jojoba) Seed Oil and Hydrogenated Simmondsia Chinensis (Joboba) Seed Wax. The alcohols are then further refined to render them suitable for use in cosmetics (Reinhardt and Brown 1990).

Simmondsia Chinensis (Jojoba) Seed Oil is combined with Hydrogenated Jojoba Oil and sodium methylate (catalyst) to get mixed Jojoba Esters (Floratech 2005a). Refined Simmondsia Chinensis (Jojoba) Seed Oil is combined with sodium methoxide to get randomized Jojoba Esters. Tocopherol is then added to make the commercial Jojoba Ester 15 (Floratech 2005b).

Simmondsia Chinensis (Jojoba) Seed Oil is combined with nickel (catalyst) to get Hydrogenated Jojoba Oil. This is converted to powder to get Jojoba Esters (Floratech 2005c). Simmondsia Chinensis (Jojoba) Seed Oil is combined with isopropyl alcohol and sodium methoxide (catalyst) to get isopropyl esters, Jojoba Alcohols, and Jojoba Esters (interesterified [randomized] Simmondsia Chinensis (Jojoba) Seed Oil) in approximately equal amounts (Floratech 2006).

Synthetic Jojoba Oil

Kalscheuer et al. (2006) developed a recombinant strain of *Escherichia coli* that produced an oil that was similar to Simmondsia Chinensis (Jojoba) Seed Oil. Cultivation in the presence of oleate produced $C_{23:1}$, $C_{34:1}$, and $C_{36:2}$ wax esters which were chemically similar to jojoba wax esters. The amounts produced were small.

Analytical Methods

Simmondsia Chinensis (Jojoba) Seed Oil has been analyzed via the following methods: thin layer chromatography (TLC), gas chromatography (GC), nuclear magnetic resonance spectroscopy, infrared spectroscopy, differential scanning calorimetry, and equivalent carbon number analyses (Miwa 1973; Hamm 1984).

Garver et al. (1992) used reversed-phase C_{18} high-performance liquid chromatography (HPLC) coupled with efficient and sensitive detection by an on-line flow-through radiochemical detector to analyze the components of crude jojoba seed homogenate.

Van Boven et al. (1997) used GC, mass spectrometry (MS), gas chromatography/mass spectrometry (GC/MS), and TLC to isolate and identify the phytosterols and fatty alcohols in Simmondsia Chinensis (Jojoba) Seed Oil. Tada et al. (2005) used liquid chromotography/mass spectrometry (LC/MS) and GC/MS analysis to find the main constituents of Simmondsia Chinensis (Jojoba) Seed Wax.

Impurities

The Cosmetic, Toiletry, and Fragrance Association (CTFA) specification for Simmondsia Chinensis (Jojoba) Seed Oil defines positive identification of the oil as a close match to the infrared (IR) spectrum, with no indication of foreign materials (CTFA 1989).

The specification for crude Simmondsia Chinensis (Jojoba) Seed Oil includes less than 0.8 ppm elemental lead (Pb) and less than 0.1 ppm arsenic (as As_2O_3) (Taguchi and Kunimoto 1977).

When Simmondsia Chinensis (Jojoba) Seed Oil was refined via a standard alkali refining process (Swern 1982), a trace amount of nitrogen-containing compounds (6.0 ± 2 ppm) was found (Hamm 1984). Data on the presence and nature of terpenoid compounds were not available.

Jojoba Alcohols contain less than 20 ppm lead and less than 2 ppm arsenic (Reinhardt and Brown 1990).

SGS Canada Inc. (2005a, 2006) analyzed samples of two materials: (1) a mixture of isopropyl jojobate, Jojoba Alcohol and Jojoba Esters, and (2) Hydrolyzed Jojoba Esters and water to determine the presence of impurities (data given in Table 8).

Table 8. Impurities found in a mixture of isopropyl jojobate, Jojoba Alcohol and Jojoba Esters and Hydrolyzed Jojoba Esters and water (SGS Canada Inc. 2005a, 2006).

Impurity	Jojoba mixture	Hydrolyzed Jojoba Esters and water	Detection Limit
As	0.1 µg/g	none	0.1 µg/g
Ca	18 µg/g	none	0.2 µg/g
Cd	none	none	2 methods: 0.1 and 0.2 µg/g
Co	none	none	0.3 µg/g
Cr	none	none	1 µg/g
Cu	6 µg/g	none	0.2 µg/g
Fe	none	1.6 µg/g	2 µg/g
Hg	none	none	0.1 µg/g
K	1 µg/g	10376 µg/g	-
Mg	none	2.5 µg/g	3 µg/g
Mn	none	none	0.7 µg/g
Na	none	72.1 µg/g	10 µg/g
Ni	none	none	2 µg/g
P	none	4.3 µg/g	5 µg/g
Pb	0.8 µg/g	none	0.2 µg/g
Sr	none	none	0.2 µg/g
Zn	4 µg/g	none	0.2 µg/g

SGS Canada Inc. (2005b,c,d,e,f 2006) reported the analysis of Jojoba Esters 15, 20, 30, 60, and 70 as shown in Table 9. Detection limits are not given in Table 9, but were comparable to those shown in Table 8.

USE

Cosmetic

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Registration Program (VCRP), Simmondsia Chinensis (Jojoba) Seed Oil was used in a total of 188 cosmetic products, at the time of the original safety assessment, at use concentrations up to 25% (Elder 1989). Currently VCRP data indicated that Simmondsia Chinensis (Jojoba) Seed Oil is used in 1123 products (FDA 2007). A survey of current use concentrations conducted by the CTFA reported use concentrations up to 100% (CTFA 2007). These data are given in Table 10, as a function of product category, along with the total number of products reported in each category. From Table 10, for example, it can be seen that the Seed Oil is used in 109 of a total of 715 conditioners, at a wide concentration range from 0.001 to 67%. In some cases, there were no reported uses to the VCRP, but a current use concentration is provided — for example, the Seed Oil in hair coloring rinses. It should be presumed that there is at least 1 use. In other cases, there is a reported use (Seed Oil in shampoos), but no use concentration is provided.

Simmondsia Chinensis (Jojoba) Seed Wax had no uses listed in 1989 and is currently reported to be used in 8 cosmetic products (FDA 2007) at up to 2% (CTFA 2007).

Hydrogenated Jojoba Oil is reported to be used in 71 cosmetic products, Jojoba Esters in 121 cosmetic products, Hydrolyzed Jojoba Esters in 86 cosmetic products, Simmondsia Chinensis (Jojoba) Butter in 18 cosmetic products, Jojoba Alcohol in 21 cosmetic products, and Synthetic Jojoba Oil in 6 cosmetic products (FDA 2007) at up to 31%, 44%, 2%, 6%, 1%, and 0.1%, respectively (Table 10) (CTFA 2007).

Isomerized Jojoba Oil is not reported as being used, nor were any use concentrations provided.

Apropos of the use of certain of these ingredients in product categories known to be aerosols or sprays, Jensen and O'Brien (1993) reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.

The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, $\mathbf{d_a}$, defined as the diameter of a sphere of unit density possessing the same terminal setting velocity as the particle in question. These authors reported a mean aerodynamic diameter of 4.25 ± 1.5 μm for respirable particles that could result in lung exposure (Jensen and O'Brien, 1993).

Bower (1999), reported diameters of anhydrous hair spray particles of 60 - 80 μm and pump hair sprays with particle diameters of ≥80 μm. Johnsen (2004) reported that the mean particle diameter is around 38 μm in a typical aerosol spray. In practice, he stated that aerosols should have at least 99% of particle diameters in the 10 - 110 μm range.

Table 9. Impurities found in Jojoba Ester 15, 20, 30, 60, and 70 (SGS Canada Inc. 2005b,c,d,e,f, 2006).[a]

Impurity	Jojoba Esters 15	Jojoba Esters 20	Jojoba Esters 30	Jojoba Esters 60	Jojoba Esters 70
As	none	none	none	none	none
Ca	9 µg/g	none	none	none	none
Cd	none	none	none	none	none
Co	none	none	none	none	none
Cr	none	1 µg/g	1 µg/g	1 µg/g	none
Cu	2 µg/g	none	none	none	none
Fe	none	none	none	5 µg/g	none
Hg	none	none	none	none	none
K	2 µg/g	13 µg/g	2 µg/g	none	3 µg/g
Mg	none	none	none	none	4 µg/g
Mn	0.8 µg/g	none	9 µg/g	none	0.8 µg/g
Na	none	none	none	none	none
Ni	none	none	none	none	2 µg/g
P	none	none	none	none	none
Pb	0.4 ppm	none	0.2 ppm	none	0.5 ppm
Sr	none	none	none	none	none
Zn	none	none	1 µg/g	none	none

[a] Detection limits comparable to those given in Table 8.

Table 10. Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
Simmondsia Chinensis (Jojoba) Seed Oil		
Baby products		
Lotions, oils, powders, and creams (67)	7	1
Other (64)	2	-
Bath products		
Oils, tablets, and salts (207)	17	0.002-100
Soaps and detergents (594)	15	0.1-5
Bubble baths (256)	3	0.002-2
Capsules (5)	-	2
Other (276)	8	0.08-2
Eye makeup		
Eyebrow pencils (124)	3	0.08-0.1
Eyeliners (639)	20	0.1-4
Eye shadow (1061)	7	0.7-7
Eye lotions (32)	11	0.1-0.5
Eye makeup remover (114)	2	0.1-5
Mascara (308)	2	0.1-1
Other (229)	9	0.1
Fragrance products		
Colognes and toilet waters (948)	-	5
Perfumes (326)	1	5
Powders (324)	1	5
Sachets (28)	-	5
Other (187)	9	5
Noncoloring hair care products		
Conditioners (715)	109	0.001-67
Sprays/aerosol fixatives (294)	12	0.001-1
Straighteners (61)	9	0.01-20
Permanent waves (169)	1	0.01-0.9
Rinses (46)	2	0.01
Shampoos (1022)	51	0.001-2
Tonics, dressings, etc. (623)	30	0.01-4
Wave sets (59)	-	1-2
Other (464)	30	0.1-2[a]
Hair coloring products		
Dyes and colors (1600)	84	0.2
Rinses (15)	-	0.2
Shampoos (1022)	1	-
Color sprays (4)	-	0.3
Bleaches (103)	2	0.05

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
Simmondsia Chinensis (Jojoba) Seed Oil (continued)		
Makeup		
Blushers (459)	12	0.4-53
Face powders (447)	10	0.1-53
Foundations (530)	29	0.5-53
Leg and body paints (10)	1	0.1
Lipsticks (1681)	110	1-46
Makeup bases (273)	2	5-53
Rouges (115)	-	12
Makeup fixatives (37)	1	53
Other (304)	24	5-53[b]
Nail care products		
Basecoats and undercoats (43)	2	0.0001-0.2
Cuticle softeners (20)	4	0.1-10
Creams and lotions (13)	-	0.1-25
Extenders (1)	-	0.2
Nail polishes and enamels (398)	20	0.000005-0.001
Nail polish and enamel removers (39)	-	0.0001-0.2
Other (58)	5	0.0001-13[c]
Personal hygiene products		
Underarm deodorants (281)	-	0.002-5
Douches (8)	-	5
Feminine deodorants (7)	-	5
Other (390)	4	0.05-9[d]
Shaving products		
Aftershave lotions (260)	3	0.002-3
Preshave lotions (20)	2	1
Shaving cream (135)	3	0.002-2
Shaving soap (2)	-	0.01
Other (64)	4	0.002
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	29	0.001-53
Depilatories (49)	3	0.001-53
Face and neck creams, lotions, powder and sprays (546)	67	0.5-53[e]
Body and hand creams, lotions, powder and sprays (992)	106	0.00003-100[f]
Foot powders and sprays (43)	-	53
Moisturizers (1200)	114	0.5-100[g]
Night creams, lotions, powder and sprays (229)	33	0.8-53[h]
Paste masks/mud packs (312)	7	0.5-53
Skin fresheners (212)	3	53
Other (915)	51	1-53[i]

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
Simmondsia Chinensis (Jojoba) Seed Oil (continued)		
Suntan products		
Suntan gels, creams, liquids and sprays (138)	3	0.1
Indoor tanning preparations (74)	20	0.0003-2
Other (41)	3	0.1
Total uses/ranges for Simmondsia Chinensis (Jojoba) Seed Oil	**1123**	**0.000005-100**
Simmondsia Chinensis (Jojoba) Seed Wax[j]		
Bath products		
Soaps and detergents (594)	1	0.1
Eye makeup		
Mascara (308)	1	-
Noncoloring hair care products		
Conditioners (715)	-	0.05
Shampoos (1022)	2	0.05
Other (464)	1	-
Shaving products		
Shaving cream (135)	-	2
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	-	1
Face and neck creams, lotions, powder and sprays (546)	1	-
Body and hand creams, lotions, powder and sprays (992)	1	-
Paste masks/mud packs (312)	1	-
Total uses/ranges for Simmondsia Chinensis (Jojoba) Seed Wax	**8**	**0.05-2**
Hydrogenated Jojoba Oil[k]		
Bath products		
Soaps and detergents (594)	5	0.01-0.5
Other (276)	1	0.1-2
Eye makeup		
Eyeliners (639)	1	-
Eye shadow (1061)	1	2
Eye lotions (32)	1	1
Mascara (308)	30	7
Noncoloring hair care products		
Conditioners (715)	1	-
Sprays/aerosol fixatives (294)	-	0.001
Tonics, dressings, etc. (623)	1	-

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
Hydrogenated Jojoba Oil (continued)		
Hair coloring products		
Dyes and colors (1600)		
Hair tints (56)	-	0.1
Rinses (15)	-	0.1
Color sprays (4)	-	0.1
Lighteners with color (14)	-	0.1
Bleaches (103)	-	0.1
Other (73)	-	0.1
Makeup		
Blushers (459)	3	0.1-2
Face powders (447)	-	0.1
Foundations (530)	3	0.1-10
Lipsticks (1681)	1	31
Makeup bases (273)	-	0.1
Makeup fixatives (37)	-	0.1
Other (304)	-	0.1-2
Nail care products		
Creams and lotions (13)	-	0.8
Oral hygiene products		
Other (10)	3	-
Personal hygiene products		
Underarm deodorants (281)	-	0.01
Douches (8)	-	
Feminine hygiene deodorants (7)	-	0.01
Other (390)	-	0.01
Shaving products		
Shaving soap (2)	1	-
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	9	1-5
Depilatories (49)	-	0.1
Face and neck creams, lotions, powder and sprays (546)	2	0.1[l]
Body and hand creams, lotions, powder and sprays (992)	1	0.01-8[m]
Foot powders and sprays (43)	-	0.1
Moisturizers (1200)	-	0.1[n]
Night creams, lotions, powder and sprays (229)	-	0.1[o]
Paste masks/mud packs (312)	-	0.01-0.4
Skin fresheners (212)	-	0.1

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
Hydrogenated Jojoba Oil (continued)		
Suntan products		
Other (41)	1	-
Other (915)	6	0.1
Total uses/ranges for Hydrogenated Jojoba Oil	**71**	**0.001-31**
Jojoba Esters		
Bath products		
Soaps and detergents (594)	7	0.2-2
Other (276)	1	-
Eye makeup		
Eyebrow pencils (124)	1	5
Eyeliners (639)	3	5-14
Eye shadow (1061)	3	0.5-5
Eye lotions (32)	4	0.5-5
Eye makeup remover (114)	-	5
Mascara (308)	6	3-5
Other (229)	2	5
Fragrance products		
Colognes and toilet waters (948)	-	0.05
Perfumes (326)	-	0.002
Other (187)	1	0.8
Makeup		
Blushers (459)	1	7
Face powders (447)	1	3-7
Foundations (530)	14	1-7
Leg and body paints (10)	-	5
Lipsticks (1681)	8	5-44
Makeup bases (273)	2	7
Rouges (115)	-	5-7
Makeup fixatives (37)	1	7
Other (304)	2	5-11[b]
Nail care products		
Basecoats and undercoats (43)	-	18
Cuticle softeners (20)	-	18
Creams and lotions (13)	-	18
Extenders (1)	-	18
Nail polishes and enamels (398)	-	0.5-18
Nail polish and enamel removers (39)	-	18
Other (58)	-	18
Personal hygiene products		
Other (390)	1	2-4[q]

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
Jojoba Esters (continued)		
Shaving products		
Aftershave lotions (260)	1	0.002
Other (64)	-	0.000005
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	26	0.3-10
Depilatories (49)	-	7
Face and neck creams, lotions, powder and sprays (546)	9	0.2-7[r]
Body and hand creams, lotions, powder and sprays (992)	7	0.3-7[r]
Foot powders and sprays (43)	-	7
Moisturizers (1200)	14	7[r]
Night creams, lotions, powder and sprays (229)	4	7[r]
Paste masks/mud packs (312)	1	1-7
Skin fresheners (212)	-	7
Other (915)	1	7
Total uses/ranges for Jojoba Esters	**121**	**0.000005-44**
Hydrolyzed Jojoba Esters		
Fragrance products		
Colognes and toilet waters (948)	53	2
Perfumes (326)	23	0.07
Other (187)	-	0.0002
Noncoloring hair coare products		
Tonics, dressings, etc. (623)	1	-
Shaving products		
Aftershave lotions (260)	7	0.07
Other (64)	-	0.0002
Skin care products		
Face and neck creams, lotions, powder and sprays (546)	1	-
Moisturizers (1200)	1	-
Total uses/ranges for Hydrolyzed Jojoba Esters	**86**	**0.0002-2**
Simmondsia Chinensis (Jojoba) Butter		
Bath products		
Soaps and detergents (594)	2	0.8
Eye makeup		
Mascara (308)	1	6
Makeup		
Lipsticks (1681)	1	3

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
Simmondsia Chinensis (Jojoba) Butter (continued)		
Noncoloring hair care products		
Conditioners (715)	1	-
Personal hygiene products		
Other (390)	1	-
Skin care products		
Face and neck creams, lotions, powder and sprays (546)	-	
Body and hand creams, lotions, powder and sprays (992)	6	0.1
Moisturizers (1200)	4	-
Night creams, lotions, powder and sprays (229)	1	-
Other (915)	1	-
Total uses/ranges for Simmondsia Chinensis (Jojoba) Butter	**18**	**0.1-6**
Jojoba Alcohol[s]		
Eye makeup		
Eye shadow (1061)	1	1
Eye Lotion (32)	2	-
Noncoloring hair care products		
Conditioners (715)	-	0.5
Sprays/aerosol fixatives (294)	-	0.5
Straighteners (61)	-	0.1
Permanent waves (169)	-	0.1
Rinses (46)	-	0.1
Shampoos (1022)	-	0.1
Tonics, dressings, etc. (623)	-	0.5
Wave sets (59)	-	0.5
Other (464)	-	0.5
Makeup		
Foundations (530)	2	1
Shaving products		
Shaving cream (135)	-	0.1
Shaving soap (2)	-	0.1
Skin care products		
Face and neck creams, lotions, powder and sprays (546)	1	-
Body and hand creams, lotions, powder and sprays (992)	11	-
Moisturizers (1200)	4	-
Total uses/ranges for Jojoba Alcohol	**21**	**0.1-1**

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
Synthetic Jojoba Oil		
Eye makeup		
Eyeliners (639)	1	-
Noncoloring hair care products		
Conditioners (715)	5	-
Skin care products		
Depilatories (49)		0.1
Total uses/ranges for *Synthetic Jojoba Oil*	6	0.1

[a] 0.1% in a liquid hair lotion, 2% in a hair mask; [b] 5% in a concealer; [c] 0.0001% in a solution used to dilute nail enamel, 10% in a hand and foot exfoliator; [d] 0.05%, 1%, and 9% in body scrubs; [e] 53% in face and neck sprays; [f] 0.00003 - 53 in body and hand sprays; [g] 53% in moisturizing sprays; [h] 5% in night sprays; [i] 1% in an oil stick; [j] listed as Jojoba Wax by the FDA; [k] listed as both Hydrogenated Jojoba Oil and Wax; [l] 0.1% in face and neck sprays; [m] 0.1% in body and hand sprays; [n] 0.1% in moisturizing sprays; [o] 0.1% in night sprays; [p] 2% in a shower gel; [q] 7% in face and neck creams, body and hand sprays, moisturizing sprays, and night sprays; [r] listed as both Jojoba Alcohol and Jojoba (Simondsia Chinensis)

Non-cosmetic

Yaron (1987) reported that jojoba seeds are used by Native American Indians as food and medicine. It is reported that jojoba seeds are good for the stomach, facilitate parturition when mixed with chocolate, and treat sores that erupt on the face. The seeds are also reported to treat sores, scratches, and cuts rapidly; treat suppression of the urine; promote hair growth; and considered a remedy for cancer.

Dweck (1997) reported that the jojoba plant has been used by Native Americans for wound healing and as a skin salve. The expressed juices of the seeds are used to treat eye soreness.

Simmondsia Chinensis (Jojoba) Seed Oil

Non-cosmetic uses of Simmondsia Chinensis (Jojoba) Seed Oil include: high-temperature lubricant for high-speed machinery, sulfurization for extreme-pressure lubricants, treatment of leather, benzene or gasoline-soluble factice for rubber, varnishes, linoleum, or chewing gum, and hydrogenation into hard wax for use as polishing wax, in carbon paper, or as candles that give a brilliant flame with no smoke (Miwa 1973). Jojoba Oil is also used in the pharmaceutical industry as an antifoaming agent in the fermentation of tetracycline and penicillin (Buckley 1981) and as a substitute for sperm whale oil (Scott and Scott 1982).

Simmondsia Chinensis (Jojoba) Seed Oil may be used in the microencapsulation of live cells and enzymes as a drug delivery system (Esquisabel et al. 1997).

Simmondsia Chinensis (Jojoba) Seed Oil is used in pesticides to control white flies. Jojoba products are used for controlling powdery mildew on grapes and on ornamental plants at a concentration ≤1% (Environmental Protection Agency [EPA] 2006).

Simmondsia Chinensis (Jojoba) Seed Wax is used to extract metal ions from aqueous solutions so that the ions may be reused (Binman et al. 1998).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism and Excretion

Simmondsia Chinensis (Jojoba) Seed Oil was detected in the feces of dd Y-S mice (5 weeks old) 1 week after the mice were force-fed doses of 0.5, 0.75, 1.13, and 1.69 mg/10 g. Four groups of 20 mice were evaluated (Taguchi and Kunimoto 1977).

Yaron (1987) reported that nude mouse skin was used to study Simmondsia Chinensis (Jojoba) Seed Oil penetration. After 22 h, there was 6.7-fold more penetration than at 1 h. The cell solution contained ~4 meq Simmondsia Chinensis (Jojoba) Seed Oil/area tested. Based on histological examination of the skin, the main route of penetration was the hair follicle.

Verschuren and Nugteren (1989) tested the effects of Simmondsia Chinensis (Jojoba) Seed Oil on intestinal transit time in 7-week-old, male SPR Wistar rats (Cpb/WU). After 1 week of acclimation on a commercial diet, the diet of the control group (n = 19) was changed to the commercial diet mixed with lard/sunflower seed oil (4:1) with a fat content of 18% (equivalent to 40% energy). The diet of the experimental group was changed to the commercial diet with the lard/sunflower seed oil (9%) and Simmondsia Chinensis (Jojoba) Seed Oil (9%). The rats were fed ad libitum for 10 d, then were trained to eat all of their food in 2 half-hour shifts (7:00 AM to 7:30 AM and 7:00 PM to 7:30 PM). The rats were allowed to eat ad libitum during meal times for 10

d; in the last 3 d, the exact food consumption was recorded. The meals were then adjusted over the next 8 d so that the rats ate exactly the same amount at each meal time.

After a total of 4 weeks, the morning meal was marked by incorporation of [^{3}H]retinol (1 µCi/animal) and the marker carmine (37.5 mg/kg). After 5 h the feces were sampled every 30 min up to 20 h, then hourly up to 33 h, then at 36, 41, 48, 60, 72, 84, and 96 h.

The feces were examined for carmine and the level of radioactivity was determined by liquid scintillation counting. After the subsequent meal, the rats were killed in groups of 4 at 0, 1.5, 3, 6, and 12 hr and the stomach contents sampled, freeze-dried, and weighed.

The treatment group had a lower growth rate (299 ± 4.1 g vs 239 ± 5.3 g). Food consumption over the period of fixed meal times was lower for the Simmondsia Chinensis (Jojoba) Seed Oil-fed rats than for the controls (6.3 ± 0.46 g vs. 5.2 ± 0.78 g). The absolute amounts of radioactivity measured over 96 h were not different between the groups, even with the difference in food consumption. The Simmondsia Chinensis (Jojoba) Seed Oil fed rats excreted more retinol than the control group ($p < .01$), possibly due to reduced retinol absorption. There was no difference in transit time of the radioactivity.

Comparison of the weights of feed consumed and the amount of feed in the rats' stomachs showed that the emptying of the animals' stomachs was not affected by Simmondsia Chinensis (Jojoba) Seed Oil ingestion. No ill effects from the consumption of Simmondsia Chinensis (Jojoba) Seed Oil were reported by the authors.

In a second experiment, the authors fed 10 male rats the treatment diet from the first experiment. After 3 weeks, the rats were anesthetized (2 rats/d) and the ductus thoracicus was cannulated for 1 h. The animals were then killed and the small intestine ligatured and removed. The intestinal mucosa and contents were sampled separately. Lymph was collected. The intestinal mucosa and contents and lymph were analyzed for lipid content as were fecal samples over the previous week by TLC.

The free fatty acids concentration in the intestinal contents was < 5%, with larger amounts in the feces (30%). The authors stated that these findings suggested that hydrolysis of Simmondsia Chinensis (Jojoba) Seed Oil must have continued in the gut beyond the small intestine, possibly by bacteria. Table 11 gives the analysis of the fatty acids and fatty alcohols chain length and saturation found as a function of location (Verschuren and Nugteren 1989).

Simmondsia Chinensis (Jojoba) Seed Wax

Yaron et al. (1980) determined the absorption and distribution of Simmondsia Chinensis (Jojoba) Seed Wax (described as the semisolid fraction of Simmondsia Chinensis (Jojoba) Seed Oil) using 24 male albino mice (5 weeks old; 25-30 g). The animals were divided equally into 4 groups and [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax (90 ± 10 mg; specific activity 1.14 µCi/g) was injected subcutaneously into the right leg of each animal. Randomly labeled Simmondsia Chinensis (Jojoba) Seed Wax was obtained by exposure of fruiting branches of the shrub (*S. chinensis*) to $^{14}CO_2$ fluxes. The 4 groups of animals were killed 1, 8, 15, and 23 days after injection, and radioactivity in the testis, skin, carcass, and lipid and aqueous fractions of the brain and liver was counted. The results indicated that only a small fraction of the injected [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax was absorbed. At day 1 post-injection, most of the [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax was detected in the carcass and in lipid fractions of the brain and liver. In the brain lipid fraction, the amount decreased from 108 ± 46 µg (day 1) to 9 ± 4 µg (day 23), and, in the liver lipid fraction, from 57 ± 16 µg (day 1) to 15 ± 7 µg (day 23). The amount of [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax in the carcass (100 ± 4 g) was detected on day 1, but not on day 23.

Table 11. Analysis of the fatty acid content (%,) of the semi-synthetic diets containing 9% Simmondsia Chinensis (Jojoba) Seed Oil fed to rats and of the lipids extracted from the various components of the digestive system (Verschuren and Nugteren 1989).

Fatty acid/fatty alcohol chain length/saturation	As given in the diet		As measured in the rat			
	Lard/sunflower seed oil	Jojoba Oil	Lymph	Intestinal mucosa	Intestinal content	Feces
14:0	-	-	0.9	0.7	0.5	0.4
16:0	23.0	-	15.4	14.0	6.0	5.2
16:1 (1)	-	-	2.0	1.5	0.4	0.3
18:0	11.5	-	8.3	12.4	7.0	6.7
18:1 (2)	29.0	10/1[a]	26.3	20.2	15.8	10.2
18:2 (2)	19.0	-	11.2	9.8	5.4	1.5
20:1 (2)	-	71/44[a]	20.6	20.0	39.4	41.9
20:4 (2)	-	-	1.4	3.6	1.9	9.9
22:1 (2)	-	14/45[a]	4.4	4.7	11.9	16.2

[a] Mean of 2 determinations

In a second experiment, 10 albino mice (5 males, 5 females) were injected subcutaneously with [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax (same dose and specific activity) and killed at intervals after injection. Most of the ^{14}C (>99%) was detected in the carcass. At 8 and 23 days post-injection, the radioactivity TLC profile of carcass lipids indicated that 75% to 83% of the ^{14}C remained in the lipid form in which it had been injected. The remaining ^{14}C was incorporated mainly into neutral lipids, such as triglycerides and fatty acids.

The absorption and distribution of radioactivity from [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax were further evaluated using 21 male albino mice (5 weeks old; 25-30 g). In this study, the specific activity of [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax was greater than that used in the preceding 2 experiments. The animals were divided equally into 3 groups, and [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax was injected subcutaneously into the neck at doses of 9, 23, and 120 mg. Animals were killed 8 days after injection. Following the injection of each dose, radioactivity was detected in the liver, brain, testes, lungs, heart, spleen, kidneys, and carcass lipids, but not in the skin or epididymal fat. The greatest counts of radioactivity were frequently detected in the liver, brain, lungs, and carcass lipids. The smallest amount of radioactivity (all organs included) was detected in the animals injected with 9 mg of [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax. There were no significant differences between counts of radioactivity in animals injected with 23 mg and those given 120 mg of [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax (Yaron et al 1980).

Heise et al. (1982) used weanling rats to study the digestibility of Simmondsia Chinensis (Jojoba) Seed Wax. The rats were fed: 1) a standard diet 12% of which was Simmondsia Chinensis (Jojoba) Seed Wax; 2) standard diet with an equivalent amount in calories to the Simmondsia Chinensis (Jojoba) Seed Wax of corn oil; 3) standard diet with an equivalent amount in calories of medium-chain triglycerides; 4) standard diet with equivalent amount in calories of 1:1 mixture of Simmondsia Chinensis (Jojoba) Seed Wax and corn oil; or 5) standard diet with an equivalent amount in calories of 1:1 mixture of Simmondsia Chinensis (Jojoba) Seed Wax and triglycerides. Digestibility was determined during weeks 2 and 4 with the 30-d growth assay.

Weight gain on the Simmondsia Chinensis (Jojoba) Seed Wax diet was half that of the control groups. The mixed diets had minimal weight reduction compared to controls. Digestibility of Simmondsia Chinensis (Jojoba) Seed Wax was 41%. The fecal matter contained 51% fat in the 12% Simmondsia Chinensis (Jojoba) Seed Wax group; this was the only group in which the carcass fat was not increased above baseline level. The efficiency of energy conversion into tissue was half that of the mixed groups and one-third that of the control diets. Biological nitrogen was decreased; the authors suggest that there was an increased use of dietary protein as energy (Heise et al. 1982).

Yaron et al. (1982b) orally administered ^{14}C-Simmondsia Chinensis (Jojoba) Seed Wax (25% in peanut oil;10.9 µCi/g; 0.1 ml) to male albino mice (5 weeks old; n = 20). After 24 h, 10 of the mice were killed and the absoption and distribution of the radioactivity analyzed. The liver and epididymal fat were analyzed in detail using TLC. The remaining 10 mice were killed and analyzed on day 8 after treatment. The experiment was then repeated. Intestinal absorption and distribution of Simmondsia Chinensis (Jojoba) Seed Wax is shown in Table 12. Radiolabel was distirbuted among phospholipids, etc. in the liver and epididymal fat as given in Table 13.

Table 12. Distribution of ^{14}C in the body of mice 1 and 8 days after oral administration of ^{14}C-labeled Simmondsia Chinensis (Jojoba) Seed Wax (Yaron et al. 1982b).

	^{14}C sp act in the tissue (dpm/g wet tissue ± SE)			
	1st Run		**2nd Run**	
Tissue	**Day 1**	**Day 8**	**Day 1**	**Day 8**
Liver lipids	805 ± 88	136 ± 13	1570 ± 390	776 ± 280
Heart	2140 ± 880	980 ± 78	2080 ± 328	904 ± 248
Lungs	Not determined	Not determined	2300 ± 308	1170 ± 296
Spleen	2020 ± 560	685 ± 82	2300 ± 404	1180 ± 330
es	1266 ± 360	974 ± 196	1180 ± 224	772 ± 150
Kidneys	2964 ± 674	984 ± 32	3720 ± 544	1404 ± 310
Muscle	1414± 290	1346 ± 578	1210 ± 194	882 ± 136
Epididymal fat	3770 ± 430	1740 ± 770	7760 ± 2160	4460 ± 1335

Table 13. Radioactivity TLC profile of liver and epididymal fat lipids one day after ingestion of ^{14}C-labeled Simmondsia Chinensis (Jojoba) Seed Wax (Yaron et al. 1982b).

	Incorporation of ^{14}C into lipid fraction (%)		
R_f	Liver	Epididymal fat	Lipid standards
0.03	27.0 ± 3.1	0	Phospholipids and glycolipids
0.08	5.5 ± 0.5	5.7 ± 3.2	Cholesterol
0.19	5.5 ± 3.2	0	Fatty acids
0.31 - 0.35	51.3 ± 6.8	92.0 ± .02	Triglycerides
0.80	11.6 ± 3.7	4.3 ± 4.1	Wax esters and cholesterol esters

Penetration Enhancement

Simmondsia Chinensis (Jojoba) Seed Oil

Schwarz et al. (1996) tested the effectiveness of Simmondsia Chinensis (Jojoba) Seed Oil, in the form of submicron particles of oil-in-water emulsion, for the delivery of diclofenac diethylammonium. The emulsion consisted of Simmondsia Chinensis (Jojoba) Seed Oil (20%) and diclofenac (diethyl ammonium salt; 1.16%) prepared by a proprietary high pressure homogenization process. Wistar rats (n = 6) were anaesthetized and iota-carrageenan (100 µl; 1%) was injected into the plantar region of a hind paw. The rats were then topically treated with the Jojoba emulsion, a commercial anti-inflammatory cream with the same concentration of diclofenac, or nothing. Edema volume was measured at 0, 0.5, 1, 2, 3, 4, and 6 h. There were no signs of skin irritation observed. Anti-inflammatory activity in the Jojoba emulsion was evident at 1 h. At 3, 4, and 6 h, the edema in the Jojoba emulsion group was less than that of the commercial cream ($p < .05$). The relative activity for the control, commercial cream, and the Jojoba emulsion were 100 ± 16%, 79 ± 14%, and 46 ± 18%. The authors concluded that the jojoba emulsion can be used to deliver moisturizing agents and lipids to the skin in cosmetics.

El laithy and El-Shaboury (2002) found that an emulsion of brij 96 (surfactant), capmul (cosurfactant), and Simmondsia Chinensis (Jojoba) Seed Oil with 40% water delivered fluconazole through new born mouse skin in a Franz diffusion cell at a greater rate than gel bases (cetyl palmitate; mixture of glyceryl stearate, cetearyl alcohol cetyl palmitate, and cocoglycerides; glyceryl stearate; and glyceryl monostearate) at 10% and 30%.

Wang et al. (2007) tested the dermal penetration enhancement properties of essential oils and plant oils including Simmondsia Chinensis (Jojoba) Seed Oil (10%). The oils were incorporated into microemulsions containing Span and Tween as emulsifying agents and aminophylline (5%). The attenuated total reflection was measured on the forearms (7 x 2 cm) of subjects (n = 6) before application and 30 and 60 min after application of the emulsion (~ 0.3 g). Simmondsia Chinensis (Jojoba) Seed Oil increased the permeability of the stratum corneum to aminophylline in comparison with treatment with aminophylline alone. The hierarchy of penetration enhancement of the plant and essential oils was: Simmondsia Chinensis (Jojoba) Seed Oil > peppermint > lilacin = rosemary = corn germ > ylang > olive. The authors concluded that the choice of proper combination of oil phase lipids may allow drug-controlled delivery from a topical oil/water microemulsion.

Shevachman et al. (2008) tested the enhancement of diclofenac sodium by microemulsions of Simmondsia Chinensis (Jojoba) Seed Oil/hexanol/Brij 96V/water and compared it with similar micoemulsions containing paraffin oil and isopropyl myristate. For comparison, an emulsion with Voltaren Emulgel (a commercial cream containing 1.16% diclofenac diethylammonium, corresponding to 1% diclofenac sodium) was used. The emulsions containing diclofenac sodium (0.5 ml) were applied to the trimmed abdominal area of anesthetized Sprague-Dawley rats in open containers glued to the skin. Blood samples were taken at 1, 2, 4, 6, and 8 h and analyzed for diclofenac. There was similar penetration of diclofenec with the Simmondsia Chinensis (Jojoba) Seed Oil emulsion as the commercial cream (C_{max} = 0.116 ± 0.031 and 0.106 ± 0.006 mg/ml and area under the curve = 0.601 ± 0.107 and 0.558 ± 0.172 µg/ml/h, respectively). The paraffin oil and isopropyl myristate emulsions had great penetrations (C_{max} = 0.962 ± 0.191 and 0.845 ± 0.005 mg/ml and area under the curve = 4.545 ± 0.615 and 4.067 ±0.482 µg/ml/h, respectively).

In an in vitro study, the abdominal skin of freshly killed rats was clipped, washed, and the subcutaneous fat removed. The skin was installed onto Franz diffusion cells with the stratum corneum facing upwards. Microemulsions or Voltaren Emulgel (0.5 g) were applied to the skin. Samples of the receptor cell were taken periodically. The microemulsions consisted of Simmondsia Chinensis (Jojoba) Seed Oil/hexanol at 1:1 wt ratio (60%) and Brij 96 or Tween 60 (40%) with diclofenac sodium (1%) added.

The Simmondsia Chinensis (Jojoba) Seed Oil emulsion had lower penetration of diclofenac than did paraffin oil or isopropyl myristate, which were similar. The drug permeability in the Simmondsia Chinenesis (Jojoba) Seed Oil was higher than the commercial cream, unlike the in vivo test. The authors suggest

that this could be due to the optimal perfusion and hydration of the skin in the diffusion cells compared to the skin in the animal study. The authors concluded that Simmondsia Chinensis (Jojoba) Seed Oil did not increase penetration of dicofenac through the skin and seemed to prevent active molecules from being freely diffused into the skin. The authors suggest that the 3-dimensional structure of the oil may result in delaying the diffusion of the drug (Shevachman et al. 2008).

Anti-inflammatory Effects

Jojoba Liquid Wax Habashy et al. (2005) investigated the anti-inflammatory effects of what the authors referred to as jojoba liquid wax in several experiments. In the first experiment, adult male Sprague-Dawley rats were used. The rats were fasted with free access to water for 16 h before treatment. Five groups (n = 6) of rats were treated. Groups I and II were administered saline by intubation; Groups III and IV were administered jojoba liquid wax (5 ml/kg (~4.35g) or 10 ml/kg (~8.7 g), respectively); and Group V was administered indomethacin (a standard anti-inflammatory drug; 10 ml/kg). Thirty min later, Group I was administered saline (0.05 ml) and Groups II through V were administered carrageenin (0.05 ml; 1% in saline) subcutaneously on the plantar surface of the right hind paw. The volume of the paw was immediately measured by water displacement and again 3 h later.

The right hind paws were removed after killing the rats. The eicosanoid-containing fluid was removed with the use of 10 µM indomethacin in 0.1 ml saline.

The carrageenin injection resulted in severe inflammation and increase in mean volume of the paw (162.3%) compared to untreated paws. Pretreatment with jojoba liquid wax at both doses (5 or 10 ml/kg) inhibited the carrageenin-induced increase in edema volume by 26.4% and 34%, respectively. Indomethacin treatment reduced inflammation by 43.4%.

Carrageenin injection resulted in a 5-fold increase in prostaglandin E_2 (PGE_2) concentration in Group II compared to the untreated Group I. Jojoba liquid wax reduced the PGE_2 concentration by 58.15% and 77.4%, respectively. The 10 ml/kg dose of jojoba liquid wax and the indomethacin lowered the PGE_2 to almost normal levels.

The authors conducted a chick's embryo chorioallantoic membrane (CAM) test. Fertile chicken eggs were incubated for 8 d then divided into 4 groups (n = 6). Filter paper discs (10 mm in diameter) were placed on the surface of the CAM after opening the shells with a dental drill. The shell pieces were replaced and sealed with paraffin wax. The filter paper in Group I was not treated (control); Groups II and III were treated with jojoba liquid wax (3.5 (~3.05 mg; 30%) and 7 µl (~6.1 mg; 50%), respectively) in saline. Group IV was treated with indomethacin (2.5 µg). The eggs were incubated for 4 d and opened by cutting the shells circumferentially along the longer perimeter. CAM membranes were eased out of the shell and the disc (with any adhering or infiltrating granulation tissue) were cut with fine scissors. The discs and tissue were dried overnight and weighed individually.

The administration of jojoba liquid wax at 30% and 50% decreased the granulation tissue weight by 15.8% and 38%, respectively, compared to the control.

The authors induced ear edema in rats to assess the effects of jojoba liquid wax. Five groups of rats (n = 6) were treated topically: Group I was treated with solvent; Group II was treated with irritant (4 parts croton oil, 10 parts ethanol, 20 parts pyridine, 66 parts ethyl ether) and solvent; Groups III and IV were treated with irritant, jojoba liquid wax (30% or 50%, respectively), and solvent; and Group V was treated with irritant, solvent, and indomethacin (12.5% w/v). Each solution was administered in a volume of 20 µl on both sides of the right ear. The left ear was left untreated and served as the control. One h after treatment, the right ears were treated again (Group I, solvent; Groups II through V croton oil solution). After 4 h, the rats were killed. An 8-mm cork borer was used to punch a disc out of each ear; the discs were weighed immediately.

The entire ear was homogenized in buffer and centrifuged and used to calculate myeloperoxidase (MPO) activity. Protein content was determined. Representative ear tissue was fixed, embedded, and sectioned for microscopic examination regarding leukocytic infiltration, edema, and extravasations.

Application of croton oil caused the ear disc to increase in size by 216% over the control. Pretreatment with jojoba liquid wax (30% and 50%) reduced the increase by 28% and 43.6%, respectively. MPO activity in ears treated with croton oil increased 83-fold. Pretreatment with jojoba liquid wax decreased MPO activity by 29% ($p < .05$) and 53.3% ($p < .05$), respectively, compared to ears not treated with jojoba liquid wax. Indomethacin treatment reduced MPO activity ($p < .05$). Ears treated with croton oil and no jojoba liquid wax had massive neutrophil infiltration with extraversion of red blood cells as well as edema in the dermal layer. Ears treated with jojoba liquid wax had less neutrophil infiltration and less hyperemia in a dose dependent manner.

The authors divided 30 rats into 5 groups (n = 6) and injected each of them with 20 ml sterile air in the suprascapular area of the back. Three days later, the pouches were re-inflated with 10 ml sterile air. After another 3 days, lipopolysaccharide from *E. coli* serotype 0111:B4 (LPS; 100 µg/ml) in physiological saline (1 ml/kg) was injected into the air-formed pouches of Groups II through V.

Group I was administered only saline. The rats were treated 30 min later: Groups I and II were administered only saline; Groups III and IV were administered jojoba liquid wax (5 and 10 mg/kg, respectively); and Group V was administered indomethacin (10 mg/kg). Eight h later, the pouches were lavaged using 1 ml sterile physiological saline. The lavage fluid was centrifuged and analyzed for nitric oxide (NO) and tumor necrosis factor-α (TNF-α).

The air pouch caused a 60-fold increase of NO production compared to untreated animals. Jojoba liquid wax injection at 5 and 10 ml/kg reduced NO levels by 31.4% ($p < .05$) and 32.8% ($p < .05$), respectively, compared to Group II. Indomethacin

lowered NO levels by 36.6% ($p < .05$). There was an 8-fold increase in TNF-α levels compared to untreated animals. Jojoba liquid wax treatment at 5 and 10 ml/kg lowered TNF-α levels by 62.2% ($p < .05$) and 75.8% ($p < .05$), respectively. Jojoba liquid wax (at 30% and 50%) reduced MPO activity by 29% and 53.3%, respectively.

The authors concluded that jojoba liquid wax exerted anti-inflammatory activity in several animal models; jojoba liquid wax combats inflammation via multilevel regulation of inflammatory mediators (Habashy et al. 2005).

Blood Cholesterol Effects

The effects of ingested Simmondsia Chinensis (Jojoba) Seed Oil on blood cholesterol concentrations were evaluated using 4 groups of female New Zealand white rabbits (4 months old; n = 4). The following diets (100 g of chow per diet) were provided daily for 30 days: (group 1) chow supplemented with 2% Simmondsia Chinensis (Jojoba) Seed Oil, (group 2) chow containing 1% cholesterol and 2% Simmondsia Chinensis (Jojoba) Seed Oil, (group 3) chow containing 1% cholesterol supplemented with 6% Simmondsia Chinensis (Jojoba) Seed Oil, (group 4) chow supplemented with 1% cholesterol (cholesterol control), and (group 5) untreated chow (negative control). Uneaten chow was discarded each day. The study was repeated using different groups of rabbits. Blood cholesterol concentrations were slightly increased in rabbits fed a cholesterol-free diet containing 2% Simmondsia Chinensis (Jojoba) Seed Oil. Rabbits fed an atherogenic diet consisting of 1% cholesterol and 2% Simmondsia Chinensis (Jojoba) Seed Oil had a 40% decrease in blood cholesterol over that of the cholesterol control. There was no further decrease in blood cholesterol concentrations in rabbits fed a diet containing 1% cholesterol and 6% Simmondsia Chinensis (Jojoba) Seed Oil for an additional 30-day period (Clarke and Yermanos 1981).

Miscellaneous Studies

Simmondsia Chinensis (Jojoba) Seed Oil

Week and Sevigne (1949a) reported that Simmondsia Chinensis (Jojoba) Seed Oil contains factors inhibiting the hydrolysis of vitamin A esters in chicks.

Week and Sevigne (1949b) reported that Simmondsia Chinensis (Jojoba) Seed Oil contains factors inhibiting the hydrolysis of vitamin A esters in rats to a greater extent than corn oil.

Acute Animal Oral Toxicity

Simmondsia Chinensis (Jojoba) Seed Oil

The oral toxicity of crude Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 80 5-week-old, dd Y-S mice. The average weights of 40 male and 40 female mice were 22.5 and 21.3 g, respectively. The animals were divided equally into 4 groups (10 males, 10 females/group), and Simmondsia Chinensis (Jojoba) Seed Oil was administered via gastric intubation at a single dose of 0.5, 0.75, 1.13, or 1.69 ml/10 g of body weight. Feed was withheld 6 h prior to intubation. At 7 d post-administration, the animals were killed and necropsied. Peritonitis was observed in 1 animal dosed with 1.69 ml/10 g, and discoloration of the renal capsule was observed among all groups. None of the gross alterations observed, including the single death, were attributed to the administration of Simmondsia Chinensis (Jojoba) Seed Oil. The actual causes of these deaths were not reported (Taguchi and Kunimoto 1977).

Following the administration of a single dose of Simmondsia Chinensis (Jojoba) Seed Oil (21.5 ml/kg) to male albino rats (number and weights not stated), fewer than 50% of the animals died (Wisniak 1977).

The acute oral toxicity of a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 10 Sprague-Dawley rats (5 males, 5 females; weights not stated). A single oral dose (5.0 g/kg) was administered to each animal via gavage. The animals were fasted during the night prior to dosing. None of the animals died during the 15-day observation period, and the product was classified as nontoxic (CTFA 1985a).

Simmondsia Chinensis (Jojoba) Seed Wax

The acute oral toxicity of a 50.0% solution of Simmondsia Chinensis (Jojoba) Seed Wax in corn oil (dose = 5.0 g/kg) was evaluated according to the procedure described above using 10 albino Sprague-Dawley rats (5 males, 5 females; 200-300 g). The only procedural variation was a 4-day observation period after dosing. Simmondsia Chinensis (Jojoba) Seed Wax was not classified as a toxic substance. Neither the mortality rate nor the results of macroscopic examinations were reported (Reinhardt and Brown 1990).

Jojoba Esters

Leberco Testing, Inc. (1988a) orally administered a single dose of Jojoba Esters 15 (5 g/kg) to white rats (n = 10; 5 male, 5 female) after 18 h of fasting as described in the Federal Hazardous Substances Act (Consumer Product Safety Commission 2007). The rats were observed for signs of toxicity for 14 d then necropsied. All the rats survived. There were no signs of toxicity.

Leberco Testing, Inc. (1988b) orally administered a single dose of Jojoba Esters 30 (5 g/kg) to white rats (n = 10; 5 male, 5 female) after 18 h of fasting. The rats were observed for signs of toxicity for 14 d then necropsied. All rats survived and there were no signs of toxicity.

Leberco Testing, Inc. (1988c) orally administered a single dose of Jojoba Esters 60 (5 g/kg) to white rats (n = 10; 5 male, 5 female) after 18 h of fasting. The rats were observed for signs of toxicity for 14 d then necropsied. All the rats survived. There were no signs of toxicity.

Leberco Testing, Inc. (1988d) orally administered a single dose of Jojoba Esters 70 (5 g/kg; 50% in corn oil) to albino Sprague Dawley rats (n = 10; 5 male, 5 female) after 18 h of fasting. The rats were observed for signs of toxicity for 14 d then necropsied. All the rats survived. There were no signs of toxicity.

In another study, the acute oral toxicity of 2 Jojoba Esters (iodine values 40 and 60) was evaluated using 2 groups of 10 white rats (5 males, 5 females per group). Animal weights ranged from 208 to 238 g in one group and from 212 to 238 g in the other group. Feed was withheld for 18 h, and the test substance (dose = 5.0 g/kg) was administered via a rigid stomach tube. The animals were then observed for signs of toxicity during a period of 14 days; all of the animals survived. At the conclusion of the observation period, the animals were killed and internal organs examined macroscopically. No gross abnormalities were observed in either test group (Reinhardt and Brown 1990).

Jojoba Alcohol

The acute oral toxicity of Jojoba Alcohol was evaluated using 3 groups of 20 mice of the dd Y-S strain (weights not stated). The test substance was administered via stomach tube to the 3 groups at doses of 32, 40, and 50 ml/kg, respectively. None of the animals in any of the 3 groups died (Taguchi no date).

Short-term Oral Toxicity

Simmondsia Chinensis (Jojoba) Seed Oil

The oral toxicity of refined Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 4 groups of 10 male Sprague-Dawley rats (avg. weight 80.6 g). Two of the groups were fed basal diets (5 g/feeding) containing 0.5 or 1.0 g of Simmondsia Chinensis (Jojoba) Seed Oil once daily for 7 days. The remaining 2 groups were fed basal diets containing 2.0 or 3.0 g of Simmondsia Chinensis (Jojoba) Seed Oil once daily for 4 d. The animals were given water ad libitum. Signs of toxicity were observed in 5 of the rats that were fed 1.0 g of Simmondsia Chinensis (Jojoba) Seed Oil (in diet) and all of the rats fed 2.0 and 3.0 g of Simmondsia Chinensis (Jojoba) Seed Oil. The mortality rate was 10% in each of these 3 groups. None of the rats fed 0.5 g of Jojoba Oil died (Hamm 1984).

Verschuren (1989) fed Simmondsia Chinensis (Jojoba) Seed Oil to male and female SPF Wistar rats (6 weeks old at acclimation) for 4 weeks. The rats were fed a purified diet with Simmondsia Chinensis (Jojoba) Seed Oil at 0 (n = 12), 2.2% (n = 10), 4.5% (n = 10), and 9% (n = 12). After 6 d on the diet, 2 of each sex in the control and high dose groups were killed and the hearts examined for fat deposition. After 3 weeks on the diet, blood was collected and analyzed. After 4 weeks on the diet, the feces were sampled and analyzed for lipid content. At the end of the experiment, the rats were killed and necropsied, blood collected and analyzed, and tissues were histologically examined.

No deaths occurred during the experiment. All the rats appeared to be in good health and no clinical signs were observed. There was a dose-dependent growth retardation in both sexes. Feed intake and water consumption did not differ between the groups. The amount of feces produced increased with Simmondsia Chinensis (Jojoba) Seed Oil intake. The lipid content of the feces had a dose-dependent increase (up to > 6-fold). There were no hematological differences except for the white blood cell count which increased in the high dose group in both males (13.6 ± 0.67 vs 16.9 ± 1.02) and females (13.7 ± 0.90 vs 21.0 ± 2.03). Serum analysis showed an increase enzyme activities (isocitrate dehydrogenase [ICDH], saccharopine dehydrogenase [SDH], alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], hydroxybutyrate dehydrogenase [α-HBDH], and creatine kinase [CK]). Urea concentrations increased in a dose dependent manner. A negative correlation was found for creatine and triacylglycerols and dose levels.

Animals fed Simmondsia Chinensis (Jojoba) Seed Oil had less body fat deposition. Absolute weights of the organs decreased for both sexes except for the spleen in the females. There was no evident adverse effect to the heart after 6 d of the Simmondsia Chinensis (Jojoba) Seed Oil diet. The stomachs of the rats fed Simmondsia Chinensis (Jojoba) Seed Oil were much fuller compared to the controls. The small intestines were distended and the contents were more fluid and non-homogenous compared to controls. The contents of the cecum were coarse and heterogenous compared to controls. The jejunum and ileum of the treatment groups were characterized by massive vacuolization of the enterocytes, distension of the lamina propria, and an increase in cellular components. There was increased cell turnover in the crypts of Lieberkuhn.

In a second experiment, 2 groups of rats (n = 5) were fed the diet with either 0 or 9% Simmondsia Chinensis (Jojoba) Seed Oil . After 3 weeks, the rats were killed and the small intestine removed and examined. The entire small intestine was affected except the anterior section of the duodenum and the posterior section of the ileum. There was an accumulation of fat in the vacuoles of the enterocytes in the upper region of the villi. The ALP activity was decreased. In the livers, there was a slight increase in intracellular acidophilic vacuoles, acidophilic bodies, and the number of mitoses (Verschuren 1989).

Dermal

Jojoba Alcohol

Taguchi (no date) evaluated the dermal toxicity potential of Jojoba Alcohol using 10 white male rabbits. Jojoba Alcohol was tested at concentrations of 12.5, 25.0, and 50.0% (in refined Simmondsia Chinensis (Jojoba) Seed Oil). Oleyl alcohol, also tested at concentrations of 12.5, 25.0, and 50.0% (in refined Simmondsia Chinensis (Jojoba) Seed Oil), served as the control.

In 15- and 30-day tests, there were no reactions to 12.5% Jojoba Alcohol that were grossly visible. However, the results of

microscopic examinations were that reactions ranged from very light to light incrassation of the germinative zone of the epidermis in 4 rabbits (15-day test), and reactions ranging from very light to medium incrassation of the germinative zone and very light to light dermal infiltration in 4 rabbits (30-day test). Also, in the 15-day test, 25.0% Jojoba Alcohol induced redness (2 rabbits), and redness and induration (1 rabbit); 50.0% Jojoba Alcohol induced redness (1 rabbit), redness and induration (2 rabbits), and redness, induration, and swelling (1 rabbit). In the 30-day test, 25.0% Jojoba Alcohol induced redness (2 rabbits); 50.0% Jojoba Alcohol induced redness (2 rabbits) and redness, induration, and swelling (2 rabbits). Histopathological evaluations in both the 15- and 30-day tests were negative for any reactions that were more severe than light incrassation of the germinative zone of the epidermis or very light dermal infiltration (Taguchi no date).

Subcutaneous

Simmondsia Chinensis (Jojoba) Seed Wax

The subcutaneous toxicity of Simmondsia Chinensis (Jojoba) Seed Wax was evaluated using 3 groups of 6-week-old male rats (10 rats/group). The 2 experimental groups received subcutaneous injections of Simmondsia Chinensis (Jojoba) Seed Wax (1 ml/kg of body weight) 6 days per week for 7 weeks. Refined olive oil was administered to the control group according to the same procedure. At the end of the seventh week, 10 experimental animals and 5 controls were killed. The remaining animals were killed 6 weeks later. Urine tests, blood tests, and gross and microscopic examinations were performed. There were no traces of bilirubin, ketones, glucose, or urobilinogen in the urine of any of the tested animals. Occult blood was detected in the urine of 7 experimental animals and 5 controls. Additionally all experimental animals and 5 controls had proteinuria. The urinary protein could have resulted from the contamination of urine with traces of feed. Most of the results from blood chemistry and blood cell analyses were similar in experimental and control groups. Except for a slight increase in liver weight relative to the increase in body weight (experimental animals), there were no significant differences in body weight or organ weight between experimental and control groups. Microscopic changes were not observed in the skin or in any of the other organs examined (Yaron et al 1982b).

Subchronic Dermal Toxicity

Simmondsia Chinensis (Jojoba) Seed Wax

The subchronic dermal toxicity of refined Simmondsia Chinensis (Jojoba) Seed Wax was evaluated using 32 DH guinea pigs (320 ± 25 g). The animals were divided into 4 groups (4 males, 4 females/group). In the first 2 groups, Simmondsia Chinensis (Jojoba) Seed Wax was applied to shaved dorsal skin in doses of 0.25 and 0.5 g/kg, respectively. Applications were made 6 days per week for a total of 20 weeks. The application sites were not covered. The 2 control groups received applications of olive oil (0.5 g/kg) and saline, respectively, according to the same procedure. At the end of the treatment period, the animals were killed and gross and microscopic examinations were performed. There were no differences in body weights or organ weights (liver, heart, kidneys, and testes) between the 4 groups of guinea pigs. Furthermore, lesions were not observed in tissues from the following organs (all groups): adrenal gland, thyroid gland, kidney, urinary bladder, spleen, liver, pancreas, heart, brain (2 sections), stomach, small and large intestine, and skin from treated and untreated areas (Yaron et al. 1982a).

Chronic Toxicity

No chronic toxicity data were available.

Dermal Irritation and Sensitization

Jojoba Alcohol

The primary skin irritation potential of Jojoba Alcohol (10.0% w/w in refined Simmondsia Chinensis (Jojoba) Seed Oil) was evaluated using 10 male and 10 female albino marmots with the Draize test (Taguchi no date). The test substance (0.5 ml) was applied, under a one-inch patch secured with adhesive tape, to each animal. The animals were immobilized in an animal holder, and the entire trunk of each animal was wrapped with rubberized cloth that remained throughout the 24 h exposure period. Reactions were scored at 24 and 48 h post-application according to the scales: 0 (no erythema) to 4 (severe erythema to slight eschar formation); 0 (no edema) to 4 (severe edema). Reactions to the test substance were not observed in any of the animals tested.

The skin sensitization potential of Jojoba Alcohol (10.0% w/w in refined Simmondsia Chinensis (Jojoba) Seed Oil) was evaluated according to the maximization test using 10 male and 10 female albino marmots. Two groups of male and female marmots (10 animals per sex) served as the untreated controls. Initially, each of the following substances (0.05 ml) was injected at different paired sites, to the right and left of the midline, on the back of each animal: complete adjuvant/water (1/1 mixture), Jojoba Alcohol solution, and complete adjuvant/Jojoba Alcohol solution (1/1 mixture). The Jojoba Alcohol solution consisted of Jojoba Alcohol dissolved in refined Simmondsia Chinensis (Jojoba) Seed Oil (1/10 mixture). After 1 week, patches containing the 10.0% Jojoba Alcohol solution (0.5 ml) were applied to the same injection sites. Two weeks later (challenge phase), a patch containing the solution was applied to a new site that was posterior to the injection sites. No sensitization reactions were observed 24 or 48 h after application of the challenge patch.

In an additional study connected with the SHORT-TERM TOXICITY study above, the dermal irritation potential of Jojoba Alcohol (12.5, 25.0, and 50.0%; in refined Simmondsia Chinensis (Jojoba) Seed Oil) using white male rabbits (n = 10) was tested. Each animal was simultaneously patch tested (6 patches per animal) with the 3 concentrations of both the test substance and control; patches were applied to the back. The 2 repeated patch

tests performed involved 15 days of patch testing (5 rabbits) and 30 days of continuous patch testing (5 rabbits), respectively. Naked eye observations of reactions were made, according to the method of Draize, on the last day of each test.

The average skin irritation scores during the 15-day test were as follows: 12.5% Jojoba Alcohol (no reactions), 25.0% Jojoba Alcohol (0.2-0.8), and 50.0% Jojoba Alcohol (0.4-1.80). During the 30-day skin irritation test, the average skin irritation scores were as follows: 12.5% Jojoba Alcohol (0.5), 25.0% Jojoba Alcohol (0.2 to 1.0), and 50.0% Jojoba Alcohol (0.6 to 1.25). The results of skin irritation tests on 12.5, 25.0, and 50.0% Jojoba Alcohol were not considered different from those for the controls, 12.5, 25.0, and 50.0% oleyl alcohol (Taguchi no date).

Simmondsia Chinensis (Jojoba) Seed Oil

The skin irritation potential of refined Simmondsia Chinensis (Jojoba) Seed Oil (100%) was evaluated using 10 male albino guinea pigs (weights = 350 g; strain not stated). Olive oil and light liquid paraffin served as controls. Half of the animals were simultaneously patch tested with Simmondsia Chinensis (Jojoba) Seed Oil (0.5 ml) and each control (0.5 ml) daily for 15 days. Applications were made to shaved skin. The remaining animals were patch tested (same procedure) daily for 30 days. Reactions were scored according to the Draize scale: 0 (no erythema or edema) to 4 (severe erythema to slight eschar formation, and edema). No significant reactions to Simmondsia Chinensis (Jojoba) Seed Oil or olive oil were observed. However, flare reactions to liquid paraffin were observed on the third day of the study. The results of microscopic examinations indicated no edema or cellular infiltration. However, swelling of the epidermis and hypertrophy at the roots of hairs were evident in all groups. Swelling of the epidermis may have been due, in part, to the shaving of application sites (Taguchi and Kunimoto 1977).

The skin irritation potential of a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 6 New Zealand white rabbits. A single 24 h application of the test substance (0.5 ml) was made to abraded and intact skin of the back. The test sites were covered with occlusive patches during the 24-h period. At 24 and 72 h post-application, reactions (erythema and edema) were scored according to the Draize scale: 0 to 4. The product was considered minimally irritating (mean primary irritation score = 0.33) (CTFA 1985b).

Simmondsia Chinensis (Jojoba) Seed Wax

The preceding experimental procedure was used to evaluate the skin irritation potential of Simmondsia Chinensis (Jojoba) Seed Wax (100%) in 6 albino rabbits (ages not stated). Positive skin irritation reactions were defined as primary irritation scores of 5 or greater. The mean primary irritation score for Simmondsia Chinensis (Jojoba) Seed Wax was 0.17 (Reinhardt and Brown 1990).

Jojoba Esters

Leberco Testing, Inc. (1988e) applied Jojoba Esters 15 to the intact and abraded skin of albino rabbits (n = 6). The rabbits were clipped of 10% their body hair; half of the exposed skin area was left intact and the other half was abraded so to penetrate the stratum corneum but not disturb the dermis. The Jojoba Esters 15 (0.5 ml) were applied to both sides of the exposed skin which were covered with a patch and polyethylene for 24 h. The sites were examined upon unwrapping and 48 h later. There was erythema for all the rabbits at the first reading and only 2 at the second reading but no edema formation. A score of ≥ 5 would indicate a positive irritant. The authors reported a mean score of 1.08.

Leberco Testing, Inc. (1988f) repeated the experiment with Jojoba Esters 30. There was erythema formation for all the rabbits at the first reading and only 2 at the second reading but no edema formation. A score of ≥ 5 would indicate a positive irritant. The authors reported a mean score of 0.42.

Leberco Testing, Inc. (1988g) repeated the experiment with Jojoba Esters 60. There was erythema formation for all the rabbits at the first reading and only 2 at the second reading but no edema formation. A score of ≥ 5 would indicate a positive irritant. The authors reported a mean score of 1.08.

Leberco Testing, Inc. (1988h) repeated the experiment with Jojoba Esters 70. There was erythema formation on 2 the rabbits at the first reading (1 on just intact skin and the other on both intact and abraded skin) and none at the second reading but no edema formation. A score of ≥ 5 would indicate a positive irritant. The authors reported a mean score of 0.17.

The skin irritation potential of 2 Jojoba Esters (iodine values = 40 and 60) was evaluated using 2 groups of 6 albino rabbits (ages not stated). Prior to application of the test substance, 10.0% of the body area of each animal was clipped free of hair. The test substance (0.5 ml) was applied to abraded and intact skin sites on the back. The Esters were applied as received. The application sites (abraded and intact) were covered with a 1 x 2 inch patch that was sealed with transparent tape. The entire treatment area was also wrapped with a sheet of polyethylene that was secured with tape. At 24 h post-application, the patches were removed and excess test material was wiped from each test site. Reactions were then scored at 24 and 72 h post-application according to the scales: 0 (no erythema) to 4 (severe erythema to eschar formation) and 0 (no edema) to 4 (severe edema). Primary irritation scores of 5 or greater were defined as positive skin irritation reactions. The mean primary irritation scores for the 2 esters were 0.42 and 1.08, respectively (Leberco Testing, Inc. 1988h).

Hydrolyzed Jojoba Esters

Celsis Laboratory Group (1999a) performed an in vitro Dermal Irritection test, which looks at changes in a biomembrane barrier to predict in vivo effects, on a sample of a mixture of Hydrolyzed Jojoba Esters and water (20:80 wt.%). The sample was found to be non-irritating at volumes of 25 to 125 µl. The researchers note that the pH of this sample was above the optimum range for the Irritection Assay System, thus there is a slight potential for irritation underestimation.

Simmondsia Chinensis (Jojoba) Butter

Brown (1984) evaluated the skin irritation potential of Jojobutter-51 using 6 male New Zealand white rabbits (2.3-3.0 kg). The test substance (0.5 ml, acid value = 2.8) was applied via gauze patches to abraded and intact sites (clipped free of hair) lateral to the midline of the back. The trunk of each animal was then wrapped with occlusive patches of polyethylene; patches and polyethylene coverings were secured with hypoallergenic tape for 24 h. Immediately after patch removal, excess test material was wiped from the skin with gauze. Reactions were scored at 24 and 72 h post-application according to the Draize scale: 0 (no erythema or edema) to 4 (severe erythema to slight eschar formation, and edema). At 24 h post-application, the following reactions were observed: no erythema (2 rabbits), very slight erythema (2 rabbits), and well-defined erythema (2 rabbits). Jojobutter-51 (acid value = 2.8) was classified as a mild irritant (Primary Irritation Index = 0.5). When samples of Jojobutter-51 with a reduced acid value (1.6) were applied to an additional 6 rabbits according to the same procedure, erythema was not observed. However, slight edema was observed at the abraded site of 1 rabbit at 24 h post-application. Jojobutter (acid value = 1.6) was classified as a nonirritant (Primary Irritation Index = 0.04).

Ocular Irritation

Simmondsia Chinensis (Jojoba) Seed Oil

The ocular irritation potential of refined Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 6 male white rabbits. Immediately after the oil (0.1 ml) was instilled into the conjunctival sac of the right eye of each animal, slight atretoblepharia was observed. Slight conjunctival hyperemia was observed 1 h after instillation. Ocular irritation did not increase in severity, and all reactions had cleared by 24 h post-instillation (Taguchi and Kunimoto 1977).

The ocular irritation potential of a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 6 New Zealand white rabbits. The test substance (0.1 ml) was instilled once into the conjunctival sac of one eye. The untreated eye served as the control. Reactions were scored at 24, 48, and 72 h post-instillation according to the Draize scale. At 24 h post-instillation, the mean ocular irritation score was 0.3 ± 0.8. No reactions were observed at 48 and 72 h. The product was classified as a nonirritant (CTFA 1985c).

Simmondsia Chinensis (Jojoba) Seed Wax

Reinhardt and Brown (1990) evaluated the ocular irritation potential of Simmondsia Chinensis (Jojoba) Seed Wax in 6 albino rabbits (ages not stated). The only procedural variation was the instillation of 0.05 ml of test substance. The following reactions were observed in 3 of the 6 rabbits tested: conjunctival chemosis, obvious swelling with partial eversion of lids (1 rabbit), and conjunctival redness, diffuse crimson red conjunctiva in which individual vessels were not discernible (2 rabbits). As the test ingredient did not produce a positive reaction in 4 or more test animals, it was not classified as an eye irritant.

Hydrolyzed Jojoba Esters

Celsis Laboratory Group (1999b) reported that a mixture of Hydrolyzed Jojoba Esters and water (20:80 wt.%) was non-irritating in a chorioallantoic membrane vascular assay for possible eye irritation. No further details were provided.

Jojoba Esters

Leberco Testing, Inc. (1988i) administered Jojoba Esters 15 (0.1 ml) to the right conjunctival sac of albino rabbits (n = 6). The left eye served as the control. The eyes were examined at 24, 48, and 72 h. Four of the treated eyes showed redness of the conjuctivae at 24 h that was resolved by 48 h. The authors concluded that Jojoba Esters 15 did not produce a positive reaction in 4 or more of the test rabbits so the test material was not classified as an eye irritant.

Leberco Testing, Inc. (1988j) repeated the experiment with Jojoba Esters 30 (0.1 ml). One of the treated eyes showed redness of the conjuctivae at 24 h that was resolved by 48 h. The authors concluded that Jojoba Esters 30 did not produce a positive reaction in 4 or more of the test rabbits so the test material was not classified as an eye irritant.

Leberco Testing, Inc. (1988k) repeated the experiment with Jojoba Esters 60 (0.1 ml). Four of the treated eyes showed redness of the conjuctivae at 24 h that was resolved by 48 h. The authors concluded that Jojoba Esters 60 did not produce a positive reaction in 4 or more of the test rabbits so the test material was not classified as an eye irritant.

Leberco Testing, Inc. (1988l) repeated the experiment with Jojoba Esters 70 (0.05 ml). Two of the treated eyes showed redness of the conjuctivae at 24 h that was resolved by 48 h. One of the treated eyes exhibited chemosis (swelling above normal) at 24 h that was resolved at 48 h. The authors concluded that Jojoba Esters 70 did not produce a positive reaction in 4 or more of the test rabbits so the test material was not classified as an eye irritant.

The ocular irritation potential of 2 Jojoba esters (iodine values 40 and 60, respectively) was evaluated using 2 groups of 6 albino rabbits (ages not stated) (Reinhardt and Brown 1990). The test substance (0.1 ml) was instilled, as received, into the right eye of each animal. Untreated eyes served as controls. Reactions were scored at 24, 48, and 72 h post-instillation according to the following scales: corneal opacity scores of 0 (no ulceration or opacity) to 4 (complete corneal opacity, iris not discernible); scores for the iris of 0 (normal) to 2 (no reaction to light, hemorrhage, gross destruction; any or all of these); conjunctival redness scores of 0 (vessels normal) to 3 (diffuse, beefy red); conjunctival chemosis scores of 0 (no swelling of the lids and/or nictitating membrane) to 4 (swelling with lids more than half closed); conjunctival discharge scores of 0 (no discharge) to 3 (discharge with moistening of the lids and hairs, and considerable area around the eye). Test results were classified as positive only if 4 or more animals had positive reactions in the cornea, iris, and conjunctiva and negative if only 1 animal had positive reactions in the cornea, iris or conjunctiva.

Of the 2 groups of rabbits tested, 1 of 6 had a reaction to one of

the esters (iodine value = 60) and 4 of 6 had reactions to the other ester (iodine value = 30). All of the reactions were classified as conjunctival redness (diffuse, crimson red; individual vessels not easily discernable). As the test ingredient did not produce a positive reaction in 4 or more test animals, it would not be classified as an eye irritant (Reinhardt and Brown 1990).

Leberco Testing, Inc. (1994a) performed the Eytex test on a sample of Jojoba Esters 15. The test substance was rated minimal for irritation level at 20 to 100 µl.

Leberco Testing, Inc. (1995a) performed the Eytex test on a sample of Jojoba Esters 20. The test substance was rated minimal for irritation level at 10 to 100 µl.

Leberco Testing, Inc. (1994b) performed the Eytex test on a sample of Jojoba Esters 30 (dose not provided). The test substance was rated minimal for irritation level.

Jojoba Mixtures

Leberco.Celsis Testing (1997) tested for the possibility of ocular irritation by a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (approximate weight % 35:35:30:0.1) using the chorioallantoic membrane vascular assay. The mixture (100%; 40 µl) did not cause slight/moderate hemmorrage, capillary injection, ghost vessels, or other abnormalities in 6 eggs after 30 min of contact time. The researchers concluded that this mixture was nonirritating.

Jojoba Alcohol

The ocular irritation potential of 12.5%, 25.0%, and 50% Jojoba Alcohol (in refined Simmondsia Chinensis (Jojoba) Seed Oil) was evaluated using 3 groups of 3 rabbits, respectively, according to the procedure by Draize. The test substance (0.05 ml) was instilled into the conjunctival sac of the right eye of each animal, and the untreated left eye served as the control. There were no reactions in the cornea or iris in any of the animals tested. Reactions in the conjunctiva were observed, but not beyond 24 h post-instillation. At concentrations of 12.5% and 50.0% Jojoba Alcohol, conjunctival reactions decreased in severity from Draize scores of 1.3 to 0.7 and from Draize scores of 4.0 to 0.7, respectively, up to 24 h post-instillation. At a concentration of 25.0%, reactions with a Draize score of 2 persisted up to 6 h post-instillation (Taguchi no date).

Comedogenicity

Simmondsia Chinensis (Jojoba) Seed Wax

Bio-Technics Laboratories, Inc. (1990a) evaluated the comedogenicity of Simmondsia Chinensis (Jojoba) Seed Wax. The comedogenicity score was 2.67, classifying the test substance as moderately comedogenic.

Jojoba Esters

Bio-Technics Laboratories, Inc. (1990b) evaluated the comedogenicity of a Jojoba Ester (iodine value = 60) using 4 young adult New Zealand white rabbits. Three animals were treated with the test substance and 1 animal was treated with the positive control, isopropyl myristate. The test substance (5 ml) was added to 45 ml of mineral oil, and the solution was heated to a temperature of 70°C. Liberal applications of the test solution were made to the right external ear canal via a cotton-tipped applicator 5 days per week (once per day) for a total of 14 applications. After each application, the solution was rubbed into the skin with a glass rod. The untreated left ear served as the negative control. At the end of the application period, the animals were killed and treated and untreated external ears were removed, fixed in 10.0% buffered formalin, and evaluated histopathologically. Comedone formation was graded according to the scale: 0 (negative) to 5 (severe: widely dilated follicles filled with packed keratin, follicular epithelial hyperplasia causing partial or total involution of sebaceous glands and ducts; possible inflammatory changes). The test solution was noncomedogenic (score = 0), whereas, the positive control caused marked superficial acanthosis and hyperkeratosis.

Bio-Technics Laboratories, Inc. (1990c) evaluated another Jojoba Ester (iodine value = 40) according to the same procedure. The comedogenicity score was 0.65, classifying the test substance as between non-comedogenic and slightly comedogenic.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No reproductive or developmental toxicity data were available.

GENOTOXICITY

Simmondsia Chinensis (Jojoba) Butter

The Ames test was used to evaluate the mutagenicity of 2 samples of Jojobutter-51 in strains TA97, TA98, TA100, and TA102 of *Salmonella typhimurium* (Marshall et al. 1983). The test substance (in tetrahydrofuran) was evaluated at concentrations ranging from 1 to 1000 µg/plate with and without metabolic activation. The concentration of rat liver homogenate used for metabolic activation in the bioassay was 84 µg protein per plate. Tetrahydrofuran served as the solvent control, and positive controls were as follows: sodium azide, 2-nitrofluorene, 9-aminoacridine, methyl methane sulfonate, and 2-aminofluorene. Jojobutter-51 was not mutagenic at any of the concentrations tested. All of the positive controls were mutagenic; the solvent control was not mutagenic. Jojobutter-51 also was not mutagenic in a second bioassay (same procedure and test concentrations) in which the concentration of rat liver homogenate was increased to 140 µg per plate, or in the absence of metabolic activation. With the exceptions of methyl methane sulfonate and 9-aminoacridine, results with negative and positive controls were similar to those reported in the first bioassay.

Jojoba Alcohol

The mutagenicity of Jojoba Alcohol was evaluated by Taguchi (no date) using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *E. coli* strain WP-2 (uvr A). All strains were tested with concentrations of Jojoba Alcohol ranging from 1.25 to 40.0 nl/plate both with and without metabolic activation. Untreated cultures of each strain tested served as negative controls. The following chemicals served as positive controls: N-ethyl-N-nitro-N-nitrosoguanidine (strains TA100, TA1535, and WP-2 (uvr A) without activation), benzo(a)pyrene

(strains TA98, TA100, TA1537, and TA1538 with activation), 2-aminoanthracene (strain WP-2 (uvr A) with activation), 2-nitroflourene (strain TA 98 without activation), 9-aminoanthracene (strain TA1537 without activation), and 4-nitro-o-phenylenediamine (strain TA1538 without activation).

The highest numbers of revertants per plate, compared with controls, in each strain tested without activation were as follows: TA98 (1.5 x control, dose = 10 nl/plate), TA100 (1.2 x control, 10 nl/plate), TA1535 (2.7 x control, 20 nl/plate), TA1537 (1.4 x control, 40 nl/plate), TA1538 (1.8 x control, 20 nl/plate), and WP-2 (uvr A) (1.8 x control, 1.25 and 20 nl/plate). The highest numbers of revertants per plate, compared with controls, in each strain tested with activation were as follows: TA98 (1 x control, 2.5 nl/plate), TA100 (1 x control, 40 nl/plate), TA1535 (1 x control, 1.25 and 20 nl/plate), TA1537 (1.5 x control, 10 nl/plate), TA1538 (1.2 x control, 2.5 nl/plate), and WP-2 (uvr A) (1.2 x control, 5.0 and 40 nl/plate). In positive control cultures, the number of revertants per plate ranged from 3.2 to 41.7 times that of control cultures. The authors concluded that Jojoba Alcohol was not mutagenic (Taguchi no date).

Jojoba Mixture

Celsis Laboratory Group (1999c) conducted an Ames mutagenicity assay on a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters, and tocopherol (35:35:30:0.1 wt%) on *S. typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538) and *E. coli* (WP2). The positive controls with S9 used 2-aminoanthracine. Positive controls without S9 used 2-nitrofluorene for TA98 and TA1538, sodium azide for TA100 and TA1535, 9-aminoacridene for TA1537, and methyl methone sulfate for *E. coli*. For concentrations ranging from 1 to 100 mg/plate, there was no mutagenicity observed. There was no sign of toxicity.

CARCINOGENICITY

No carcinogenicity data were available.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Simmondsia Chinensis (Jojoba) Seed Oil

Taguchi and Kunimoto (1977) evaluated the skin irritation potential of refined and crude Simmondsia Chinensis (Jojoba) Seed Oil using 26 patients (18-59 years old) with histories of eczema or dermatitis. Olive oil, safflower oil, and white petrolatum served as controls. The test substances were applied to the upper back for 48 h via adhesive bandages. Reactions were scored 30 min and 24 h after patch removal. Slight eczema, the only reaction reported, was observed in 1 of the patients patch tested with crude Simmondsia Chinensis (Jojoba) Seed Oil. This reaction was not observed 24 h after patch removal. In another skin irritation study (same procedure), both test substances and controls were applied to 20 patients (19-42 years old) with histories of eczema or dermatitis. Positive reactions to crude Simmondsia Chinensis (Jojoba) Seed Oil and olive oil (1 patient) were observed 30 min after patch removal. Positive reactions to refined Simmondsia Chinensis (Jojoba) Seed Oil, safflower oil, and white petrolatum (1 patient) were observed 30 min and 24 h after patch removal. Both patients were thought to have been inherently hyperallergic.

Scott and Scott (1982) tested a total of 6 patients who were suspected of being sensitive to Simmondsia Chinensis (Jojoba) Seed Oil in a contact dermatitis study. The patients were patch tested (muslin patches) with each of the following: (1) 20% Simmondsia Chinensis (Jojoba) Seed Oil mixed with 80% olive oil, (2) 20% Simmondsia Chinensis (Jojoba) Seed Oil mixed with 80% liquid petrolatum, (3) pure olive oil, (4) pure mineral oil, and (5) muslin only. Positive reactions (erythema or erythema and vesicles) to both Simmondsia Chinensis (Jojoba) Seed Oil mixtures were observed on the forearms of 5 patients within 24 or 48 h after patch application. None of the patients had reactions to olive oil, mineral oil, or muslin. When the patient with no reaction to Simmondsia Chinensis (Jojoba) Seed Oil mixtures subsequently used pure Simmondsia Chinensis (Jojoba) Seed Oil as a hairdressing, contact dermatitis of the scalp resulted. Reactions were not observed in a control group of 28 patients patch tested (muslin patches) with pure Simmondsia Chinensis (Jojoba) Seed Oil. These patients had no known sensitivities.

CTFA (1985d) submitted a clinical use test where a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was applied to the lips of 200 adult female subjects daily for 4 days. The subjects were evaluated at baseline and at 2 and 4 weeks post-application for signs of subjective/objective irritation. No adverse reactions were noted at any time during the study.

CTFA (1985e) submitted a report where the skin irritation and sensitization potential of a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 208 adult female subjects. The test substance (0.2 g) was applied for 24 h to the back of each subject, between the scapulae and waist (adjacent to the midline), via an occlusive patch. Applications were made 3 times per week for a total of 3 weeks. Patch removals on Tuesdays and Thursdays were followed by 24 h nontreatment periods, and those on Saturdays were followed by 48 h nontreatment periods. Reactions were scored prior to the next patch application according to the scale: 0 (no evidence of any effect) to 4 (deep red erythema with vesiculation or weeping). The application site was changed if a subject had a reaction of 2 (uniform, pink-red erythema) or greater during induction. If a 2+ reaction was observed at the new site, induction applications were discontinued. However, all subjects with induction reactions were patch-tested during the challenge phase. After a 10- to 19-day nontreatment period, a challenge patch was applied for 48 h to a new site. Reactions were scored at 48 and 72 h post-application. Mild, transient irritation, nonspecific in nature, was observed in 1 subject. The product was classified as a nonirritant and a nonsensitizer.

CTFA (1988) submitted a report where the skin irritation and sensitization potential of a topical oil product containing 0.5% Simmondsia Chinensis (Jojoba) Seed Oil was evaluated in the modified Draize-Shelanski repeat insult patch test using 152 normal subjects (38 males, 114 females; 18-65 years old). The

test substance (on occlusive patch) was applied to the upper back of each subject on Monday, Wednesday, and Friday for 3 consecutive weeks. Sites were scored 24 h after patch removal according to the scale: 0 (no reaction) to + + + + (bullae or extensive erosions involving at least 50% of the test area). After a 2-week nontreatment period, 2 challenge patches were applied consecutively to new sites (adjacent to old site) for 48 h. Sites were scored at 48 and 96 h. None of the subjects had allergic reactions. The product was neither a clinically significant irritant nor a sensitizer.

Hill Top Research, Inc. (1998b) performed a repeated insult patch test of Simmondsia Chinensis (Jojoba) Seed Oil. The test articles were 2 separate lots of Jojoba Oil (a yellow oil and a clear oil; 0.2 ml). They were repeatedly applied at 100% to the same site on the skin (site not specified) for 3 weeks to the subjects (100 men and women). After 2 weeks rest, the test articles were reapplied to different sites. The sites were read for sensitization at 48 and 96 h. One subject had a dermal response of grade 1 to both Oils at the 48-h observation which subsided by the 96-h observation. A second person had the same reaction to the clear Simmondsia Chinensis (Jojoba) Seed Oil which subsided by the 96-h observation. The researchers concluded that the Simmondsia Chinensis (Jojoba) Seed Oils showed no evidence of contact sentisization.

Consumer Product Testing Company (2003) conducted a repeated insult patch test of Simmondsia Chinensis (Jojoba) Seed Oil (100%) on 102 volunteers (males and females). The test material (0.2 ml) was applied to the upper back and covered by an absorbent pad held in place with a clear adhesive dressing (semi-occluded). Patches were applied 3 times/week for 3 weeks to the same location. Patches were removed by the volunteers 24 h after application and the test area was examined before each application for reaction. A challenge patch was applied 2 weeks after final induction patch to an area adjacent to the induction area. The patch was removed after 24 h and scored 24 and 72 h after application. All readings were negative throughout the test period. The authors concluded that Simmondsia Chinensis (Jojoba) Seed Oil does not have a potential for dermal irritation or allergic contact sensitization.

Hydrolyzed Jojoba Esters

International Research Services Inc. (2006) assessed the skin sensitization potential of a mixture of Hydrolyzed Jojoba Esters and water (20:80 wt.%). The test material (diluted to 10%) was applied to subjects (n = 104) Monday, Wednesday, and Friday for 8 applications. After a 10- to 14-day rest, the challenge patch was applied. The site was evaluated at 24 and 72 h. There were no adverse effects due to the test material. There was no evidence of sensitization. The researchers concluded that there was no evidence of potential clinical irritation under normal use conditions.

Jojoba Esters

Leberco Testing, Inc. (1995b) reported a repeated insult patch test of Jojoba Esters 70 (10% in mineral oil) to the upper back of subjects (n = 53) on Monday, Wednesday, and Friday for 3 weeks. The patches were left on for 24 h. After a 2-week rest, a new patch was applied to a new site on the upper back. After 24 h, the patch was removed and the site evaluated. The sites were evaluated again at 48 and 72 h. There were no reactions during the induction phase. One subject had a ± level reaction at the 24 and 48 h readings; it was resolved at the 72 h reading. The authors concluded that the sample of Jojoba Esters 70 demonstrated no potential for eliciting either dermal irritation or sensitization.

California Skin Research Institute (1997a) tested 4 Jojoba Esters (20, 30, 60, and 70) for irritation. The test materials (100%; 2 ml) were administered to the upper outer arm of the subjects (n = 15; ages 24 to 51 years) for 24 h under an occluded patch. The patch was removed and the test site observed at 15 min and 24 h after removal. There were no signs of irritant dermatittis.

Jojoba Alcohol

Taguchi (no date) evaluated the skin irritation potential of Jojoba Alcohol using 60 human subjects. Twenty subjects (healthy skin) were patch tested with 10.0 and 100.0% Jojoba Alcohol, and 40 subjects (contact dermatitis patients) were patch tested with 100.0% Jojoba Alcohol. Oleyl alcohol, at concentrations of 10.0% (normal subjects) and 100.0% (patients), served as the control. Patches containing the test substance were applied to the upper back for 48 h. Reactions were scored 30 min and 24 h after patch removal according to the scale: 0 to 4+. In the group of healthy subjects, one reaction (± reaction to 10.0% Jojoba Alcohol) was observed at 30 min; no reactions were observed at 24 h. There were no reactions to 100.0% Jojoba Alcohol in healthy subjects. In the group of patients, 1 reaction (± reaction to 100.0% Jojoba Alcohol) was observed at 30 min; no reactions were observed at 24 h. The reactions observed in the patient control group included one reaction (± reaction to 100.0% oleyl alcohol) at 30 min and no reactions at 24 h. There were no reactions to 10.0% oleyl alcohol in the healthy group of control subjects. Jojoba Alcohol was not a skin irritant.

Jojoba Mixtures

California Skin Research Institute (1997a) performed a test on a Jojoba product (a mixture of Jojoba Esters, isopropyl jojobate, and Jojoba Alcohol) for irritation. There were no signs of irritant dermatittis.

Hill Top Research, Inc. (1998a) performed a repeated insult patch test of a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (approximate weight % 35:35:30:0.1). The test substance (100%; amount not provided) was applied to the same site on the skin of subjects (n = 100; 18 years old or older) for ~3 weeks. After ~2 weeks rest, the test substance was applied to a new site on the skin. There were no adverse reactions reported during the course of this study.

Hill Top Research, Inc. (1998b) performed a repeated insult patch test of Jojoba Esters/Hydrogenated Jojoba Oil. The test article was one lot of Jojoba Esters/Hydrogenated Jojoba Oil (white crystals; 0.2 g). It was repeatedly applied at 100% to the same site on the skin (site not specified) for 3 weeks to the subjects (100 men and women). After 2 weeks rest, the test article was

reapplied to different sites. The sites were read for sensitization at 48 and 96 h. One subject had a dermal response of grade 1 to the Jojoba Esters/Hydrogenated Jojoba Oil at the 48-h observation which subsided by the 96-h observation. A second person had the same reaction to the Jojoba Esters/Hydrogenated Jojoba Oil at the 48-h observation both of which subsided by the 96-h observation. The researchers concluded that the Jojoba Esters showed no evidence of contact sentisization.

Phototoxicity

Simmondsia Chinensis (Jojoba) Seed Oil

CTFA (1985e) submitted a report where the phototoxicity of a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 10 subjects. In half of the subjects, ~0.2 g of the test substance was applied for 24 h to the inner aspect of the right forearm, and, in the remaining half, to the inner aspect of the left forearm. Similarly, the nonirradiated control site was on the inner aspect of the right or left forearm. After patch removal, reactions were scored according to the scale: 0 (no evidence of any effect) to 4 (deep red erythema with vesiculation or weeping). The test sites were then irradiated for 15 min with UVA light (dose = 4,400 µW/cm2) at a distance of approximately 10 cm. In each subject, the nonirradiated control site was shielded with aluminum foil during irradiation of the test site. Reactions were scored at the end of exposure and 24 and 48 h later. None of the subjects had reactions, and the product was classified as nonphototoxic.

CTFA (1985f) submitted a report where a total of 102 female subjects (18-49 years old) participated in an outdoor use test. Each subject used a sunscreen oil containing 0.5% Simmondsia Chinensis (Jojoba) Seed Oil for 2 h (in sunlight) on 2 consecutive days. The subjects were evaluated at 24 and 48 h post-exposure. Three subjects experienced slight, transient discomfort that was considered to be clinically insignificant.

Jojoba Alcohol

Taguchi (no date) evaluated the phototoxicity of Jojoba Alcohol using 60 subjects. Twenty subject (healthy skin) were patch tested with 10.0% and 100.0% Jojoba Alcohol, and 40 subjects (contact dermatitis patients) were patch tested with 100.0% Jojoba Alcohol. Oleyl alcohol, at concentrations of 10.0% (normal subjects) and 100.0% (patients), served as the control. Patches containing the test substance were applied to the upper back for 48 h. Each test site was then irradiated with the minimal erythema dose of black light. Neither the duration of exposure nor the intensity of the light source was stated. Reactions were scored at 24 h intervals according to the scale 0 and 4+. The only reaction was a ± reaction observed in one of the patients. Reactions were not observed in any of the normal subjects. No reactions were observed at control sites that had been treated with oleyl alcohol. The authors concluded that Jojoba Alcohol was not phototoxic.

Jojoba Mixtures

California Skin Research Institute (1997b) performed a phototoxicity study on a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (approximate weight % 35:35:30:0.1). The test substance (100%; 0.2 ml) and the control (distilled water) were applied to the paraspinal region of the subjects (n = 17; age 23 to 60) for ~24 h. The test sites with the test substance were exposed to UV radiation (16 J/cm^2 UVA) at each subject's minimal erythema dose and the controls sites were protected from the radiation. Visual evaluations were performed on all test sites 1, 24, 48, and 72 h after patch removal. There were no adverse effects during this study. There was 1 erythematous reaction at the 48-h evaluation which resolved by the 72-h evaluation. The researchers concluded that the mixture did not exhibit significant phototoxicity potential when compared to the negative control.

SUMMARY

Photoallergenicity

Simmondsia Chinensis (Jojoba) Seed Oil

CTFA (1985e) submitted a study that evaluated the photoallergenicity of a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil using 30 subjects. For half of the subjects, approximately 0.2 g of the product was applied for 24 h to the inner aspect of the left arm, and for the remaining half, to the inner aspect of the right arm. Likewise, sites on the inner aspect of the right or left arm served as control (nonirradiated) sites. Each application was made via an occlusive patch on Mondays, Wednesdays, and Thursdays for a total of 9 induction applications. If irritation was not observed, all applications were made to the same site.

After patch removal, each site was subjected to non-erythemogenic ultraviolet radiation for 15 min at a distance of 10 cm from the source. The dosage of UVA light was approximately 4,400 µW/cm^2. Each non-irradiated control site was covered during irradiation of the opposite arm. Irradiated sites were scored immediately after patch removal and 24 h after UV light exposure (72 h after irradiation on Friday) according to the scale: 0 (no evidence of any effect) to 4 (deep red erythema with vesiculation or weeping). After a 13- to 18-d nontreatment period, a challenge patch was applied for 48 h to a new site, and reactions were scored after patch removal. The test site was then irradiated and scored 24 h later. No reactions were observed, and the product was classified as non-photoallergenic.

Case Reports

Wantke et al. (1996) reported on a case of a 44-yr-old woman who applied moisturizing cream to her face daily for at least 5 yr. For the 3 months before presentation she had itching a few hours after application. The past 2 weeks there was dermatitis on her face. She was patch tested with the standard European ointment series, the cream she was using, and a related cream by the same manufacturer. She tested negative for everything except the moisturizing cream she had been using. She was then patch tested with all of the individual ingredients of the cream; 20 controls (10 men, 10 women) were also tested for irritation. The woman tested positive for "Jojoba Oil" (1.5%, ++), myristyl lactate (0.5%) and maleated soybean oil (1.5%, +), maleated soy bean oil (1.5%) not deodorized (?+), and glyceryl stearate (4.9%) and polyoxyethylene 23-lauryl ether (+). There was only 1

questionable reaction to glyceryl stearate (4.9%) and polyoxyethylene 23-lauryl ether by 1 male in the control group. Contact with the company revealed that the formulation had been changed about 2 years prior to the patient's presentation and there were 2 other suspected cases of contact dermatitis due to the cream.

SUMMARY

This safety assessment of the cosmetic ingredients Simmondsia Chinensis (Jojoba) Seed Oil (originally Jojoba Oil) and Simmondsia Chinensis (Jojoba) Seed Wax (originally Jojoba Wax) also includes Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil. Jojoba products (except Synthetic Jojoba Oil) are based on the esters from the fixed oil expressed or extracted from seeds of the desert shrub, Jojoba, *Simmondsia chinensis*. Simmondsia Chinensis (Jojoba) Seed Oil is composed almost completely (97%) of wax esters of monounsaturated, straight-chain acids and alcohols with high-molecular weights (C16-C26). These wax esters exist principally (83%) as combinations of C20 and C22 unsaturated acids and alcohols. Simmondsia Chinensis (Jojoba) Seed Oil is stable and resists oxidation. The amount and composition of the oil expressed from *S. chinensis* seeds varies with maturity of the seeds and somewhat with location and climate conditions surrounding the plant.

Impurities include lead up to 0.8 ppm and arsenic up to 0.1 ppm.

Simmondsia Chinensis (Jojoba) Seed Oil in cosmetic products has increased from 188 in 1989 (in concentrations up to 25%) to 1123 uses in 2007 at up to 100%. Simmondsia Chinensis (Jojoba) Seed Wax had no uses listed in 1989 and is currently reported to be used in 8 cosmetic products at up to 2%. Hydrogenated Jojoba Oil is reported to be used in 71 cosmetic products, Jojoba Esters in 121 cosmetic products, Simmondsia Chinensis (Jojoba) Butter in 18 cosmetic products, Jojoba Alcohol in 21 cosmetic products, and Synthetic Jojoba Oil in 6 cosmetic products at up to 31%, 44%, 6%, 1%, and 0.1%, respectively. Hydrolyzed Jojoba Esters are in 86 cosmetic products up to 2%. Isomerized Jojoba Oil is not reported as being used.

Simmondisia Chinensis (Jojoba) Seed Oil was detected in the feces of mice fed the ingredient at 0.5 to 1.69 mg/10 g.

Simmondsia Chinensis (Jojoba) Seed Oil penetrated nude mouse skin. The main route of penetration was the hair follicle. Simmondsia Chinensis (Jojoba) Seed Oil in an emulsion with Brij 96 and Capmul in 40% water delivered Fluconazole through new born mouse skin at a greater rate than gel bases. Only a small amount of radio-labeled Simmondsia Chinensis (Jojoba) Seed Wax injected subcutaneously into albino mice was absorbed into carcass and the lipid fractions of the brain and liver. Following the injection of the radio-labeled Simmondsia Chinensis (Jojoba) Seed Wax in mice, the greatest counts of radioactivity were in the liver, brain, lungs, and carcass lipids.

Simmondsia Chinensis (Jojoba) Seed Oil altered the penetration of aminophylline and Diclofenac when applied in a microemulsion.

Weanling rats fed Simmondsia Chinensis (Jojoba) Seed Wax had reduced weight gain. Digestibility of the Wax was 41%. Fecal matter contained 51% fat when the rats were fed 12% Simmondsia Chinensis (Jojoba) Seed Wax. Efficiency of energy conversion was half that of the control diets.

Orally administered jojoba liquid wax to rats inhibited carrageenin-induced edema at 5 and 10 ml/kg. In a chick's embryo chorioallantoic membrane test, jojoba liquid wax reduced the granulation tissue weight by 15.8% and 38% at 30% and 50%, respectively, compared to controls. Ear edema induced by a croton oil/ethanol/pyridine/ethyl ether solvent was reduced by 28% and 43.6% at 30% and 50%, respectively, with less neutrophil infiltration and hyperemia compared to controls. Jojoba liquid wax injected at 5 and 10 ml/kg reduced NO levels by 31.4% and 32.8%, respectively, after the injection of sterile air then lippolysaccharides from *E. coli* compared to controls. Croton oil-induced myeloperoxidase activity of rats' ears was decreased by jojoba liquid wax at 30% and 50% by 29% and 53.3%, respectively.

Simmondsia Chinensis (Jojoba) Seed Oil increased blood cholesterol levels in rabbits fed a cholesterol-free diet. Rabbits fed a diet consisting of 1% cholesterol and 2% Simmondisa Chinensis (Jojoba) Seed Oil was 40% lower compared with controls.

Simmondsia Chinensis (Jojoba) Seed Oil inhibits hydroysis of vitamin A esters in chicks and rats.

When tested for acute toxicity, Simmondsia Chinensis (Jojoba) Seed Oil was not toxic to mice at 1.69 ml/10 g. Fewer than 50% of rats died when administered 21.5 ml/kg Simmondsia Chinensis (Jojoba) Seed Oil. The acute oral toxicity of a lip balm with 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was greater than 5.0 g/kg. Simmondsia Chinensis (Jojoba) Seed Wax was not classified as a toxic substance in rats at 5.0 g/kg. Orally administered Jojoba Esters (15, 30, 60, 70) were not toxic to rats at 5 g/kg. Jojoba Esters (iodine values 40 and 60) were not toxic to white rats at 5.0 g/kg; the rats survived for 14 d after administration. Orally administered Jojoba Alcohol was not toxic to rats at 50 ml/kg.

Simmondisa Chinensis (Jojoba) Seed Oil administered in the diet of rats resulted in 10% mortality in all 3 exposures (1.0, 2.0, and 3.0 g/d). Simmondsia Chinensis (Jojoba) Seed Oil fed to rats reduced food consumption but did not affect food transit time. When rats in another study were fed up to 9% Simmondisa Chinensis (Jojoba) Seed Oil in their diet for up to 4 weeks, there were no deaths and no clinical signs. Lipid content in the feces and urea concentration increased dose-dependently. White blood cell counts increased in the high dose group.

Rats administered Simmondsia Chinensis (Jojoba) Seed Wax subcutaneously 6 d/week for 7 weeks at 1 ml/kg survived. Blood chemistry values were similar between controls and treatment groups. Simmondsia Chinensis (Jojoba) Seed Wax was not toxic when applied to the shaved backs of guinea pigs 6 d/week for 20 weeks up to 0.5 g/kg.

Simmondsia Chinensis (Jojoba) Seed Oil was not dermally

irritating when applied to guinea pigs at 0.5 ml for 15 d. When applied to intact and abraded skin of white rabbits in a lip balm at 20%, Simmondsia Chinensis (Jojoba) Seed Oil was minimally irritating with a mean score of 0.33 out of 4. Jojoba Esters (15, 30, 60, and 70) were not irritating to the intact and abraded skin of albino rabbits at 0.5 ml under an occluded patch for 24 h. When applied to the intact and abraded skin of albino rabbits, two Jojoba Esters (iodine values of 40 and 60) were non-irritating after 24 h under an occluded patch. Simmondsia Chinensis (Jojoba) Seed Wax was not irritating to albino rabbits. A Dermal Irritection test found Hydrolyzed Jojoba Esters and water (20:80 wt.%) to be non-irritating at 25 and 125 ml. Jojoba Alcohol was found to be non-irritating to the skin of albino marmots at 10.0% (in refined Simmondsia Chinensis (Jojoba) Seed Oil.

Simmondisa Chinensis (Jojoba) Butter was classified as a non-irritant when applied to the intact and abraded skin of New Zealand white rabbits at 0.5 ml for 24 h under an occluded patch. Jojoba Alcohol, up to 50% in refined Simmondsia Chinensis (Jojoba) Seed Oil, showed no signs of irritation at the macroscopic level when applied to the intact and abraded skin of white rabbits for 15 and 30 d. Microscopic evaluation revealed light to medium incrassation of the germinative zone of the epidermis and light dermal irritation. After 15 d, 25% Jojoba Alcohol induced redness, induration, and swelling. After 30 d, 25% Jojoba Alcohol induced redness; 50% induced redness, induration, and swelling. Histopathological examination was negative for other signs of irritation. The Draize test on albino marmots was negative at 10% Jojoba Alcohol, in refined Simmondsia Chinensis (Jojoba) Seed Oil.

Simmondsia Chinensis (Jojoba) Seed Oil was non- to slightly irritating when instilled into the eyes of white rabbits. Simmondsia Chinensis (Jojoba) Seed Wax was not classified as an ocular irritant when instilled into the eyes of white rabbits. Jojoba Esters (15, 30, 60, and 70) were not classified as ocular irritants when instilled into the eyes of albino rabbits. Jojoba Esters (iodine values of 40 and 60) were not classified as ocular irritants when instilled into the eyes of albino rabbits. In the Eytex test, Jojoba Esters (15, 20, and 30) were found to be non-irritating. Jojoba Esters in water (20:80 wt.%) was found to be non-irritating in a chorioallantoic membrane vascular assay. Jojoba Alcohol, at 12.5%, 25.5%, and 50% in refined Simmondsia Chinensis (Jojoba) Seed Oil, produced no reactions in the cornea or iris when instilled into the eyes of rabbits. Reactions in the conjuctivae did not last past 24 h. A mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (35:35:30:0.1 wt.%) was found to be non-irritating in a chorioallantoic membrane vascular assay.

Simmondsia Chinensis (Jojoba) Seed Wax was moderately comedogenic, score 2.67. Jojoba Esters was noncomedogenic, when tested on white rabbits. Jojoba Esters were found to be non- to slightly- comedogenic in mineral oil.

Simmondsia Chinensis (Jojoba) Butter was found to non-mutagenic in an Ames test using *S. typhimurium* (strains TA97, TA98, TA100, and TA 102) up to 1000 mg/plate with and without metabolic activation. Jojoba Alcohol was found to be non-mutagenic using *S. typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *E. coli* (strain WP-2) at 1.25 to 40.0 nl/plate, with and without metabolic activation. There was no mutgenicity observed in an Ames test of a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters, and tocopherol (35:35:39:0.1 wt.%) using *S. typhimurium* (strains TA98, TA100, TA1535, TA153, and TA1538) and *E. coli* (strain WP-2).

One of 26 patients, all with a history of either eczema or dermatitis, had a slight eczema reaction to refined and crude Simmondsia Chinensis (Jojoba) Seed Oil after 24 h of exposure. When repeated with 20 more patients, there was 1 patient with a reaction after patch removal. There were no reactions among the control group. In a contact dermatitis study of 6 patients suspected of sensitivity to Simmondsia Chinensis (Jojoba) Seed Oil, 5 had positive reactions to 20% Simmondsia Chinensis (Jojoba) Seed Oil in olive oil and 20% Simmondsia Chinensis (Jojoba) Seed Oil in liquid petrolatum. When applied to the person with no reaction, pure Simmondsia Chinensis (Jojoba) Seed Oil as a hair dressing resulted in contact dermatitis of the scalp. There were no reactions among the control group.

A lip balm with 20% Simmondsia Chinensis (Jojoba) Seed Oil was applied to the lips of 200 adults for 4 d, there was no irritation observed. The skin irritation and sensitization potential of this lip balm was tested on the backs of healthy subjects. One subject in 208 had mild, transient irritation in a non-specific nature. There were no other reactions.

In a modified Draize-Shelanski repeat insult patch test of Simmondsia Chinensis (Jojoba) Seed Oil, there were no allergic reactions in 152 normal subjects.

In a repeated insult patch test of Jojoba Esters 70 (10% in mineral oil) applied to the backs of subjects 3 d/week for 3 weeks, did not produce a reaction during the induction phase. When reapplied 2 weeks later, 1 subject had a low level reaction at the 24 h reading.

Jojoba Esters (20, 30, 60, and 70) and a Jojoba mixture (Jojoba Esters, isopropyl jojobate, and Jojoba Alcohol) applied to 15 subjects produced no signs of irritant dermatitis. In a repeated insult patch test of a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esers and tocopherol (35:35:30:0.1 wt.%) on 100 subjects, there were no adverse reactions.

In a repeated insult patch test of Simmondsia Chinensis (Jojoba) Seed Oil (2 separate lots, yellow and clear) and Jojoba Esters/Hydrogenated Jojoba Oil on 100 subjects there was 1 grade 1 reaction to all 3 test substances at 48 h which resolved by the 96-h reading. One other person had a similar reaction to the clear Simmondsia Chinensis (Jojoba) Seed Oil and another to the Jojoba Esters/Hydrogenated Jojoba Oil. In a repeated insult patch test of Simmondsia Chinensis (Jojoba) Seed Oil at 100% on 100 subjects, there were no dermal reactions during course of the study.

In a skin sensitization test of Hydrolyzed Jojoba Esters in water (20:80 wt.%) diluted to 10% there were no reactions nor evidence of sensitization.

In a patch test of Jojoba Alcohol at 10.0% and 100.0% on 20 healthy patients and 40 contact dermatitis patients, there were no reactions in the healthy test group. In the dermatitis patients, there was 1 mild reaction to the 100.0% Jojoba Alcohol at the 30 min observation.

Lip balm containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was applied to the forearms and irradiated with UVA for 15 min. There were no reactions and the lip balm was classified as non-phototoxic. Simmondsia Chinensis (Jojoba) Seed Oil in a sunscreen at 0.5% was administered to 102 subjects in sunlight for 2 consecutive days and found to be non-phototoxic. A mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (35:35:30:0.1 wt.%) was found to be non-phototoxic at 100%. In a photoallergenicity test of a lip balm containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil on 30 subjects, the lip balm was applied and irradiated with UVA to the inner arm 3 d/week for 3 weeks. After a 13- to 18-day rest, the lip balm was reapplied for 48 h. There were no reactions observed and the product was classified as non-photoallergenic. Jojoba Alcohol, at 10.0% and 100.0%, applied to healthy patients and contact dermatitis patients and irradiated with UVA, resulted in 1 mild reaction in one of the dermatitis patients.

There was a case history of a woman who had itching dermatitis after using a moisturizing cream. Patch tests were negative for the ingredients in the cream except for "jojoba oil" and other ingredients.

DISCUSSION

The Cosmetic Ingredient Review Expert Panel noted that there were new uses listed in baby and eye products. Since the original safety assessment did not break down the categories of use to the extent that is now in practice, it was considered likely that Simmondsia Chinensis (Jojoba) Seed Oil and Wax were used in these products. Simmondsia Chinensis (Jojoba) Seed Oil is used up to 100% in bath products, which would be diluted when used, and in body and hand creams, etc., which would not be diluted. The Expert Panel considered, therefore, that exposure to 100% use concentration was possible.

In the absence of inhalation toxicity data, the Panel determined that Simmondsia Chinensis (Jojoba) Seed Oil, Hydrogenated Jojoba Oil, Jojoba Esters, and Jojoba Alcohol can be used safely in hair sprays, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (~38 μm) and pump hair sprays (>80 μm) is large compared to respirable particulate sizes (≤10 μm).

The Expert Panel recognized that these ingredients can enhance the penetration of other ingredients through the skin (e.g. fluconazole and aminophylline). 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.

Based on the composition of these ingredients, there were no structural alerts for reproductive/developmental toxicity and these ingredients are not expected to easily penetrate skin. None of the tested ingredients were genotoxic and there were no structural alerts for carcinogenicity. The Expert Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients, including Jojoba derivatives. They stressed that the cosmetic industry should continue to use the necessary procedures to limit these impurities in the ingredients before blending into cosmetic formulations. It was noted that the Synthetic Jojoba Oil was actually produced in the laboratory and not processed from the actual Simmondsia Chinensis (Jojoba) Seed Oil or Wax.

The CIR Expert Panel recognized that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

CONCLUSION

Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil are safe as cosmetic ingredients in the practices of use and concentration as discussed in this safety assessment.[1]

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[1] 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 the group.

[2]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036.

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2011 FDA VCRP Raw Data

05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-10 HYDROGENATED CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-10 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-10 HYDROGENATED CASTOR OIL	1
12I - Skin Fresheners	PEG-10 HYDROGENATED CASTOR OIL	1
12J - Other Skin Care Preps	PEG-100 CASTOR OIL	1
03F - Mascara	PEG-2 HYDROGENATED CASTOR OIL	5
12A - Cleansing	PEG-20 HYDROGENATED CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-20 HYDROGENATED CASTOR OIL	3
12D - Body and Hand (exc shave)	PEG-20 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-20 HYDROGENATED CASTOR OIL	5
12J - Other Skin Care Preps	PEG-20 HYDROGENATED CASTOR OIL	1
03F - Mascara	PEG-20 HYDROGENATED CASTOR OIL TRIISOSTEARATE	3
04E - Other Fragrance Preparation	PEG-25 HYDROGENATED CASTOR OIL	4
05A - Hair Conditioner	PEG-25 HYDROGENATED CASTOR OIL	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-25 HYDROGENATED CASTOR OIL	19
05I - Other Hair Preparations	PEG-25 HYDROGENATED CASTOR OIL	1
10A - Bath Soaps and Detergents	PEG-25 HYDROGENATED CASTOR OIL	3
11A - Aftershave Lotion	PEG-25 HYDROGENATED CASTOR OIL	1
12D - Body and Hand (exc shave)	PEG-25 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-25 HYDROGENATED CASTOR OIL	3
12I - Skin Fresheners	PEG-25 HYDROGENATED CASTOR OIL	2
05F - Shampoos (non-coloring)	PEG-30 CASTOR OIL	1
06B - Hair Tints	PEG-30 HYDROGENATED CASTOR OIL	1
12A - Cleansing	PEG-30 HYDROGENATED CASTOR OIL	2
12F - Moisturizing	PEG-30 HYDROGENATED CASTOR OIL	1
03G - Other Eye Makeup Preparations	PEG-33 CASTOR OIL	2
05F - Shampoos (non-coloring)	PEG-33 CASTOR OIL	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-33 CASTOR OIL	2
05I - Other Hair Preparations	PEG-33 CASTOR OIL	1
12A - Cleansing	PEG-33 CASTOR OIL	4
12C - Face and Neck (exc shave)	PEG-33 CASTOR OIL	22
12D - Body and Hand (exc shave)	PEG-33 CASTOR OIL	5
12F - Moisturizing	PEG-33 CASTOR OIL	3

12H - Paste Masks (mud packs)	PEG-33 CASTOR OIL	3
12I - Skin Fresheners	PEG-33 CASTOR OIL	6
12J - Other Skin Care Preps	PEG-33 CASTOR OIL	2
02B - Bubble Baths	PEG-35 CASTOR OIL	1
03D - Eye Lotion	PEG-35 CASTOR OIL	1
03G - Other Eye Makeup Preparations	PEG-35 CASTOR OIL	1
05A - Hair Conditioner	PEG-35 CASTOR OIL	2
05D - Permanent Waves	PEG-35 CASTOR OIL	4
05F - Shampoos (non-coloring)	PEG-35 CASTOR OIL	5
10A - Bath Soaps and Detergents	PEG-35 CASTOR OIL	1
12A - Cleansing	PEG-35 CASTOR OIL	2
12C - Face and Neck (exc shave)	PEG-35 CASTOR OIL	10
12D - Body and Hand (exc shave)	PEG-35 CASTOR OIL	2
12J - Other Skin Care Preps	PEG-35 CASTOR OIL	3
13B - Indoor Tanning Preparations	PEG-35 CASTOR OIL	1
13B - Indoor Tanning Preparations	PEG-35 HYDROGENATED CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-36 CASTOR OIL	1
12D - Body and Hand (exc shave)	PEG-36 CASTOR OIL	1
12J - Other Skin Care Preps	PEG-36 CASTOR OIL	2
03E - Eye Makeup Remover	PEG-40 CASTOR OIL	1
03G - Other Eye Makeup Preparations	PEG-40 CASTOR OIL	1
05A - Hair Conditioner	PEG-40 CASTOR OIL	6
05F - Shampoos (non-coloring)	PEG-40 CASTOR OIL	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-40 CASTOR OIL	14
05I - Other Hair Preparations	PEG-40 CASTOR OIL	3
06A - Hair Dyes and Colors	PEG-40 CASTOR OIL	1
06G - Hair Bleaches	PEG-40 CASTOR OIL	1
07F - Makeup Bases	PEG-40 CASTOR OIL	1
07G - Rouges	PEG-40 CASTOR OIL	1
08C - Nail Creams and Lotions	PEG-40 CASTOR OIL	1
10E - Other Personal Cleanliness Products	PEG-40 CASTOR OIL	6
12A - Cleansing	PEG-40 CASTOR OIL	9
12C - Face and Neck (exc shave)	PEG-40 CASTOR OIL	5
12D - Body and Hand (exc shave)	PEG-40 CASTOR OIL	11
12F - Moisturizing	PEG-40 CASTOR OIL	11
12H - Paste Masks (mud packs)	PEG-40 CASTOR OIL	2
12J - Other Skin Care Preps	PEG-40 CASTOR OIL	9
13B - Indoor Tanning Preparations	PEG-40 CASTOR OIL	1

01A - Baby Shampoos	PEG-40 HYDROGENATED CASTOR OIL	1
01B - Baby Lotions, Oils, Powders, and Creams	PEG-40 HYDROGENATED CASTOR OIL	3
01C - Other Baby Products	PEG-40 HYDROGENATED CASTOR OIL	14
02A - Bath Oils, Tablets, and Salts	PEG-40 HYDROGENATED CASTOR OIL	3
02B - Bubble Baths	PEG-40 HYDROGENATED CASTOR OIL	17
02D - Other Bath Preparations	PEG-40 HYDROGENATED CASTOR OIL	12
03B - Eyeliner	PEG-40 HYDROGENATED CASTOR OIL	6
03C - Eye Shadow	PEG-40 HYDROGENATED CASTOR OIL	3
03D - Eye Lotion	PEG-40 HYDROGENATED CASTOR OIL	11
03E - Eye Makeup Remover	PEG-40 HYDROGENATED CASTOR OIL	6
03F - Mascara	PEG-40 HYDROGENATED CASTOR OIL	9
03G - Other Eye Makeup Preparations	PEG-40 HYDROGENATED CASTOR OIL	13
04A - Cologne and Toilet waters	PEG-40 HYDROGENATED CASTOR OIL	76
04B - Perfumes	PEG-40 HYDROGENATED CASTOR OIL	8
04E - Other Fragrance Preparation	PEG-40 HYDROGENATED CASTOR OIL	114
05A - Hair Conditioner	PEG-40 HYDROGENATED CASTOR OIL	36
05B - Hair Spray (aerosol fixatives)	PEG-40 HYDROGENATED CASTOR OIL	15
05D - Permanent Waves	PEG-40 HYDROGENATED CASTOR OIL	3
05E - Rinses (non-coloring)	PEG-40 HYDROGENATED CASTOR OIL	3
05F - Shampoos (non-coloring)	PEG-40 HYDROGENATED CASTOR OIL	68
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-40 HYDROGENATED CASTOR OIL	196
05H - Wave Sets	PEG-40 HYDROGENATED CASTOR OIL	12
05I - Other Hair Preparations	PEG-40 HYDROGENATED CASTOR OIL	146
06A - Hair Dyes and Colors	PEG-40 HYDROGENATED CASTOR OIL	53
06B - Hair Tints	PEG-40 HYDROGENATED CASTOR OIL	21
06D - Hair Shampoos (coloring)	PEG-40 HYDROGENATED CASTOR OIL	2
06G - Hair Bleaches	PEG-40 HYDROGENATED CASTOR OIL	1
06H - Other Hair Coloring Preparation	PEG-40 HYDROGENATED CASTOR OIL	1
07C - Foundations	PEG-40 HYDROGENATED CASTOR OIL	6
07D - Leg and Body Paints	PEG-40 HYDROGENATED CASTOR OIL	1
07E - Lipstick	PEG-40 HYDROGENATED CASTOR OIL	1
07F - Makeup Bases	PEG-40 HYDROGENATED CASTOR OIL	1
07I - Other Makeup Preparations	PEG-40 HYDROGENATED CASTOR OIL	6
08G - Other Manicuring Preparations	PEG-40 HYDROGENATED CASTOR OIL	3
09A - Dentifrices	PEG-40 HYDROGENATED CASTOR OIL	1
09B - Mouthwashes and Breath Fresheners	PEG-40 HYDROGENATED CASTOR OIL	3
10A - Bath Soaps and Detergents	PEG-40 HYDROGENATED CASTOR OIL	200
10B - Deodorants (underarm)	PEG-40 HYDROGENATED CASTOR OIL	28
10C - Douches	PEG-40 HYDROGENATED CASTOR OIL	1
10D - Feminine Deodorants	PEG-40 HYDROGENATED CASTOR OIL	1
10E - Other Personal Cleanliness Products	PEG-40 HYDROGENATED CASTOR OIL	80
11A - Aftershave Lotion	PEG-40 HYDROGENATED CASTOR OIL	110
11B - Beard Softeners	PEG-40 HYDROGENATED CASTOR OIL	1

11E - Shaving Cream	PEG-40 HYDROGENATED CASTOR OIL	2
11G - Other Shaving Preparation Products	PEG-40 HYDROGENATED CASTOR OIL	9
12A - Cleansing	PEG-40 HYDROGENATED CASTOR OIL	106
12B - Depilatories	PEG-40 HYDROGENATED CASTOR OIL	3
12C - Face and Neck (exc shave)	PEG-40 HYDROGENATED CASTOR OIL	133
12D - Body and Hand (exc shave)	PEG-40 HYDROGENATED CASTOR OIL	72
12E - Foot Powders and Sprays	PEG-40 HYDROGENATED CASTOR OIL	3
12F - Moisturizing	PEG-40 HYDROGENATED CASTOR OIL	88
12G - Night	PEG-40 HYDROGENATED CASTOR OIL	8
12H - Paste Masks (mud packs)	PEG-40 HYDROGENATED CASTOR OIL	32
12I - Skin Fresheners	PEG-40 HYDROGENATED CASTOR OIL	38
12J - Other Skin Care Preps	PEG-40 HYDROGENATED CASTOR OIL	76
13A - Suntan Gels, Creams, and Liquids	PEG-40 HYDROGENATED CASTOR OIL	1
13B - Indoor Tanning Preparations	PEG-40 HYDROGENATED CASTOR OIL	13
13C - Other Suntan Preparations	PEG-40 HYDROGENATED CASTOR OIL	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-40 HYDROGENATED CASTOR OIL PCA ISOSTEARATE	1
12A - Cleansing	PEG-40 HYDROGENATED CASTOR OIL PCA ISOSTEARATE	1
05A - Hair Conditioner	PEG-45 HYDROGENATED CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-50 CASTOR OIL	2
01C - Other Baby Products	PEG-60 HYDROGENATED CASTOR OIL	1
02A - Bath Oils, Tablets, and Salts	PEG-60 HYDROGENATED CASTOR OIL	3
02D - Other Bath Preparations	PEG-60 HYDROGENATED CASTOR OIL	1
03D - Eye Lotion	PEG-60 HYDROGENATED CASTOR OIL	3
03E - Eye Makeup Remover	PEG-60 HYDROGENATED CASTOR OIL	1
03F - Mascara	PEG-60 HYDROGENATED CASTOR OIL	1
03G - Other Eye Makeup Preparations	PEG-60 HYDROGENATED CASTOR OIL	1
04A - Cologne and Toilet waters	PEG-60 HYDROGENATED CASTOR OIL	1
04B - Perfumes	PEG-60 HYDROGENATED CASTOR OIL	3
04E - Other Fragrance Preparation	PEG-60 HYDROGENATED CASTOR OIL	3
05A - Hair Conditioner	PEG-60 HYDROGENATED CASTOR OIL	6
05C - Hair Straighteners	PEG-60 HYDROGENATED CASTOR OIL	3
05F - Shampoos (non-coloring)	PEG-60 HYDROGENATED CASTOR OIL	20
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-60 HYDROGENATED CASTOR OIL	10
05I - Other Hair Preparations	PEG-60 HYDROGENATED CASTOR OIL	6
07B - Face Powders	PEG-60 HYDROGENATED CASTOR OIL	5
07C - Foundations	PEG-60 HYDROGENATED CASTOR OIL	2
07D - Leg and Body Paints	PEG-60 HYDROGENATED CASTOR OIL	1
07E - Lipstick	PEG-60 HYDROGENATED CASTOR OIL	1

07F - Makeup Bases	PEG-60 HYDROGENATED CASTOR OIL	1
09B - Mouthwashes and Breath Fresheners	PEG-60 HYDROGENATED CASTOR OIL	1
10A - Bath Soaps and Detergents	PEG-60 HYDROGENATED CASTOR OIL	20
10B - Deodorants (underarm)	PEG-60 HYDROGENATED CASTOR OIL	2
10D - Feminine Deodorants	PEG-60 HYDROGENATED CASTOR OIL	1
10E - Other Personal Cleanliness Products	PEG-60 HYDROGENATED CASTOR OIL	3
11A - Aftershave Lotion	PEG-60 HYDROGENATED CASTOR OIL	37
11G - Other Shaving Preparation Products	PEG-60 HYDROGENATED CASTOR OIL	2
12A - Cleansing	PEG-60 HYDROGENATED CASTOR OIL	29
12C - Face and Neck (exc shave)	PEG-60 HYDROGENATED CASTOR OIL	60
12D - Body and Hand (exc shave)	PEG-60 HYDROGENATED CASTOR OIL	11
12F - Moisturizing	PEG-60 HYDROGENATED CASTOR OIL	53
12G - Night	PEG-60 HYDROGENATED CASTOR OIL	4
12H - Paste Masks (mud packs)	PEG-60 HYDROGENATED CASTOR OIL	10
12I - Skin Fresheners	PEG-60 HYDROGENATED CASTOR OIL	25
12J - Other Skin Care Preps	PEG-60 HYDROGENATED CASTOR OIL	28
13B - Indoor Tanning Preparations	PEG-60 HYDROGENATED CASTOR OIL	2
13C - Other Suntan Preparations	PEG-60 HYDROGENATED CASTOR OIL	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-7 HYDROGENATED CASTOR OIL	1
05I - Other Hair Preparations	PEG-7 HYDROGENATED CASTOR OIL	1
10E - Other Personal Cleanliness Products	PEG-7 HYDROGENATED CASTOR OIL	2
12D - Body and Hand (exc shave)	PEG-7 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-7 HYDROGENATED CASTOR OIL	2
12G - Night	PEG-7 HYDROGENATED CASTOR OIL	1
12J - Other Skin Care Preps	PEG-7 HYDROGENATED CASTOR OIL	1
13A - Suntan Gels, Creams, and Liquids	PEG-7 HYDROGENATED CASTOR OIL	3
13C - Other Suntan Preparations	PEG-7 HYDROGENATED CASTOR OIL	1
12D - Body and Hand (exc shave)	PEG-80 HYDROGENATED CASTOR OIL	2
12F - Moisturizing	PEG-80 HYDROGENATED CASTOR OIL	1
05B - Hair Spray (aerosol fixatives)	PEG-9 CASTOR OIL	1
02A - Bath Oils, Tablets, and Salts	APRICOT KERNEL OIL PEG-6 ESTERS	1
03D - Eye Lotion	APRICOT KERNEL OIL PEG-6 ESTERS	2
03G - Other Eye Makeup Preparations	APRICOT KERNEL OIL PEG-6 ESTERS	1
07E - Lipstick	APRICOT KERNEL OIL PEG-6 ESTERS	4
07I - Other Makeup Preparations	APRICOT KERNEL OIL PEG-6 ESTERS	11
12C - Face and Neck (exc shave)	APRICOT KERNEL OIL PEG-6 ESTERS	1
12F - Moisturizing	APRICOT KERNEL OIL PEG-6 ESTERS	1
12G - Night	APRICOT KERNEL OIL PEG-6 ESTERS	1
12J - Other Skin Care Preps	APRICOT KERNEL OIL PEG-6 ESTERS	1

05A - Hair Conditioner	PEG-10 COCONUT OIL ESTER	2
05F - Shampoos (non-coloring)	PEG-10 COCONUT OIL ESTER	4
12F - Moisturizing	PEG-10 COCONUT OIL ESTER	2
04E - Other Fragrance Preparation	GRAPE SEED OIL PEG-8 ESTERS	1
10A - Bath Soaps and Detergents	GRAPE SEED OIL PEG-8 ESTERS	2
10E - Other Personal Cleanliness Products	GRAPE SEED OIL PEG-8 ESTERS	3
12D - Body and Hand (exc shave)	GRAPE SEED OIL PEG-8 ESTERS	3
12F - Moisturizing	GRAPE SEED OIL PEG-8 ESTERS	3
12H - Paste Masks (mud packs)	GRAPE SEED OIL PEG-8 ESTERS	2
12J - Other Skin Care Preps	GRAPE SEED OIL PEG-8 ESTERS	2
03C - Eye Shadow	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
07C - Foundations	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
07I - Other Makeup Preparations	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
12F - Moisturizing	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
12I - Skin Fresheners	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
01B - Baby Lotions, Oils, Powders, and Creams	JOJOBA OIL PEG-8 ESTERS	1
01C - Other Baby Products	JOJOBA OIL PEG-8 ESTERS	2
02A - Bath Oils, Tablets, and Salts	JOJOBA OIL PEG-8 ESTERS	7
05A - Hair Conditioner	JOJOBA OIL PEG-8 ESTERS	3
05C - Hair Straighteners	JOJOBA OIL PEG-8 ESTERS	1
05F - Shampoos (non-coloring)	JOJOBA OIL PEG-8 ESTERS	2
07I - Other Makeup Preparations	JOJOBA OIL PEG-8 ESTERS	8
12A - Cleansing	JOJOBA OIL PEG-8 ESTERS	1
12C - Face and Neck (exc shave)	JOJOBA OIL PEG-8 ESTERS	2
12D - Body and Hand (exc shave)	JOJOBA OIL PEG-8 ESTERS	1
12F - Moisturizing	JOJOBA OIL PEG-8 ESTERS	12
01A - Baby Shampoos	OLIVE OIL PEG-7 ESTERS	1
05A - Hair Conditioner	OLIVE OIL PEG-7 ESTERS	2
05F - Shampoos (non-coloring)	OLIVE OIL PEG-7 ESTERS	8
05G - Tonics, Dressings, and Other Hair Grooming Aids	OLIVE OIL PEG-7 ESTERS	5
05I - Other Hair Preparations	OLIVE OIL PEG-7 ESTERS	4
10A - Bath Soaps and Detergents	OLIVE OIL PEG-7 ESTERS	16
10B - Deodorants (underarm)	OLIVE OIL PEG-7 ESTERS	1
10E - Other Personal Cleanliness Products	OLIVE OIL PEG-7 ESTERS	6
12A - Cleansing	OLIVE OIL PEG-7 ESTERS	12

12D - Body and Hand (exc shave)	OLIVE OIL PEG-7 ESTERS	13
12F - Moisturizing	OLIVE OIL PEG-7 ESTERS	5
12G - Night	OLIVE OIL PEG-7 ESTERS	1
12H - Paste Masks (mud packs)	OLIVE OIL PEG-7 ESTERS	1
12I - Skin Fresheners	OLIVE OIL PEG-7 ESTERS	4
12J - Other Skin Care Preps	OLIVE OIL PEG-7 ESTERS	5
13B - Indoor Tanning Preparations	OLIVE OIL PEG-7 ESTERS	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-75 MEADOWFOAM OIL	1