JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 4, Number 5, 1985
Mary Ann Liebert, Inc., Publishers

6

Final Report on the Safety Assessment of Safflower Oil

Safflower Oil is a polyunsaturated edible seed oil consisting primarily of triglycerides of linoleic acid. The oil is used in cosmetics as an emollient in topical lotions and creams at concentrations normally between 0.1 and 5 percent. The pure oil produced slight to moderate comedogenicity. However, products containing up to 5 percent Safflower Oil were not comedogenic in rabbits. Results of animal tests indicated that Safflower Oil was not an eye or skin irritant or contact sensitizer. The oil increased the incidence of 12-dimethylbenz(a)anthracene in rats.

Safflower Oil has been used to treat human essential fatty acid deficiencies via oral and topical administration and is often applied to irritated and abraded skin. Products containing up to 5 percent Safflower Oil were negative for human skin irritation, sensitization, or photosensitization.

From the information presented in this report, it is concluded that Safflower Oil is safe as a cosmetic ingredient in the present practices of use.

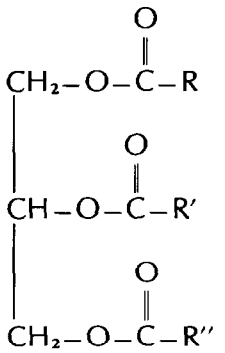
INTRODUCTION

Safflower Oil is an edible vegetable oil rich in linoleic acid. It is used in cosmetics for its oily emollient and moisturizing properties. Safflower Oil is used in a wide variety of products ranging from paints and varnishes to dietetic foods and shortening.

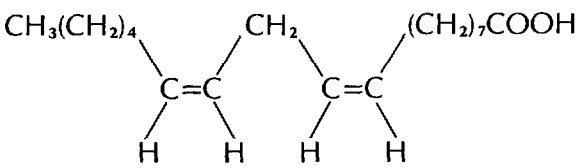
CHEMISTRY

Definition and Structure

Safflower Oil (CAS 8001-23-8) is the edible, oily liquid obtained from the seeds of *Carthamus tinctorius* and consists primarily of triacylglycerols of linoleic acid.[1]

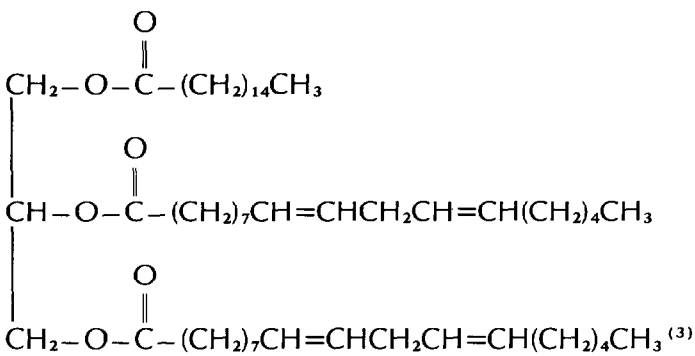


Triacylglycerol
(R, R', R'' are
usually $\geq C_{14}$)



Linoleic Acid
(cis, cis 9,12-octadecadienoic acid)[2]

An example of a typical triacylglycerol found in Safflower Oil is:



The composition of Safflower Oil used in cosmetics consists principally of about 68 percent linoleic, 26 percent oleic, 2 percent palmitic, and trace amounts of arachidic and linolenic acids.[4] The fatty acid composition of Safflower Oil can be experimentally manipulated and varies depending on the geographical location of the plants.[5] An unusual Safflower seed strain was first isolated in Australia. The oil from these seeds has a very high oleic acid content (74 to 80 percent), which makes this oil more resistant to oxidation than regular Safflower Oil.[6]

Safflower Oil is also known as *Carthamus tinctorius* oil.[1]

Physical and Chemical Properties

Safflower Oil is a golden yellow, edible drying oil that is liquid at room temperatures. It is miscible with ether, chloroform, benzene, and hexane and is slightly soluble in alcohol.[4,7] An infrared spectrum for Safflower Oil has been published.[4] The physical and chemical properties of Safflower Oil are presented in Table 1.

TABLE 1. Characteristics and Composition for a Number of High Linoleic Safflower Oils From Various Sources Reported During the Period 1945–1961[5]

Analysis	*United States*	*Africa*	*Range of Values*	*GLC*
Characteristic				
Iodine number	147–150	142.5	140–150	
Saponification number	–	191	189–194	
Refraction index at 25°C	1.4748–1.4752	1.4741	1.473–1.476	
Specific gravity at 25/25°C	–	–	0.919–0.924	
Unsaponifiable matter (%)	0.5	0.8	0.3–1.3	
Fatty acids (weight percent)				
Myristic	–	Trace	Trace	Trace
Palmitic	–	6.4	3–6	8
Stearic	–	3.1	1–4	3
Arachidic	–	0.2	Trace–0.2	Trace
TOTAL SATURATED	5.0–6.7	9.7	5–10	11
Oleic	14.7–17.3	13.4	13–21	13
Linoleic	76.6–79.0	76.9	73–79	75
Linolenic	0.04–0.13	–	Trace	1
TOTAL UNSATURATED	93.3–95.0	90.3	90–95	89

Reactivity

Safflower Oil is quite stable to atmospheric oxidation, and its stability increases as the oleic acid content increases.[3] Safflower Oil is relatively stable to oxidation; however, it thickens and becomes rancid on prolonged exposure to air.[7] Safflower Oil can be hydrolyzed under alkaline conditions, but very little Safflower Oil hydrolyzes under acidic conditions. Some grades of Safflower Oil contain an antioxidant.[8]

Safflower Oil has good drying properties and prevents after-yellowing in light-colored paints, varnishes and linoleum. It will polymerize into a stiff, elastic solid when heated to 307 to 310°C for approximately 2½ hours.[9]

Analytical Methods

The composition of Safflower Oil has been assayed using several analytical techniques. These analytical methods include nonpolar solvent extraction, drying, weighing, saponification and methylation,[10] gas phase chromatography,[11] silica gel column and thin-layer chromatography,[12] Raman spectroscopy,[13] and colorimetric and chromatographic analysis.[14] Slack et al.[15] and Swern[5] have published in-depth analyses of Safflower seeds and Safflower oils.

Method of Manufacture

Safflower Oil is obtained by pressing or solvent extraction of *Carthamus tinctorius* seeds. The seeds have an oil content of 25 to 37 percent.[5,16]

Impurities

The low acid value of Safflower Oil indicates a low content of unesterified fatty acids.[3] Hexabromide contamination of 0.4 to 1.6 percent has been reported by Jamieson.[9] Deosthale[17] has analyzed various oil seeds for trace element composition. Safflower Oil contained trace amounts of phosphorus, calcium, magnesium, iron, zinc, manganese, copper, molybdenum, and chromium.

In view of the fact that Safflower Oil is the product of a plant oilseed, there is a possibility for contamination from insecticides used on the Safflower plant.[18] Aflatoxin contamination of Safflower seeds and Safflower seed products from India has also been reported.[19,20] However, the possibility of aflatoxin contamination of Safflower seeds grown in the US is less likely, and no reports of aflatoxin contamination of US Safflower seed or products were found in the published literature.

USE

Purpose, Scope, and Extent of Use in Cosmetics

Safflower Oil is used as an emollient in topical skin care lotions, moisturizers, and bath preparations.[3,21,22] It has been reported to the FDA that Safflower Oil is an ingredient in 94 cosmetic formulations in concentrations ranging from ≤ 0.1 percent to >50 percent. The majority of these products contain 0.1 percent to 5 percent Safflower Oil. These products include moisturizing skin creams, suntan lotions, bath products, eye makeup removers and makeup bases and foundations.[22]

The FDA cosmetic product formulation listing is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations. Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration. See Table 2 for a list of cosmetic products containing Safflower Oil.

Surfaces, Frequency, and Duration of Contact

Cosmetics containing Safflower Oil are applied to all areas of the skin, including mucous membranes and nails. These cosmetics are frequently applied to the face and have the potential for coming into contact with the eye or being in-

TABLE 2. Product Formulation Data[22]

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations Within Each Concentration Range (%)						
			>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Safflower Oil									
Bath oils, tablets, and salts	237	1	–	–	–	–	–	1	–
Other bath preparations	132	2	–	–	–	–	–	2	–
Eye makeup remover	81	1	–	–	1	–	–	–	–
Other eye makeup preparations	230	1	–	–	–	–	–	1	–
Hair sprays (aerosol fixatives)	265	1	–	–	–	1	–	–	–
Makeup foundations	740	6	–	–	–	–	5	1	–
Lipstick	3319	4	–	–	–	–	2	–	2
Makeup bases	831	5	–	–	–	–	5	–	–
Other makeup preparations (not eye)	530	3	–	–	–	–	3	–	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	7	–	–	–	1	3	2	1
Face, body, and hand skin care preparations (excluding shaving preparations)	832	15	–	1	–	3	7	3	1
Moisturizing skin care preparations	747	28	1	–	5	2	8	10	2
Night skin care preparations	219	3	–	1	–	1	1	–	–
Paste masks (mud packs)	171	1	–	–	–	1	–	–	–
Skin fresheners	260	1	–	–	–	–	–	1	–
Wrinkle smoothers (removers)	38	1	–	1	–	–	–	–	–
Other skin care preparations	349	7	2	–	–	–	–	3	2
Suntan gels, creams, and liquids	164	7	3	–	–	–	2	2	–
1981 TOTALS		94	6	3	6	9	36	26	8

gested from the lips. Products containing Safflower Oil are applied up to several times a day and can remain in contact with the skin for long periods of time.

Noncosmetic Use

Safflower Oil has an extensive history of use in foodstuffs, and *Carthamus tinctorius* has, for many years, been extensively cultivated in India, Egypt, and Turkey. It is also grown in Russia and Europe on a more limited scale. During the first quarter of the 20th century, *Carthamus tinctorius* was introduced as an oilseed crop into the northwestern section of the United States by the Department of Agriculture.[9]

Safflower Oil is used in a variety of products, including alkyd resins, paints, varnishes, linoleum, medicines, dietetic foods, and hydrogenated shortening.[23] Safflower Oil is beginning to assume commercial importance as a vegetable oil. An estimated 90 million pounds of Safflower Oil were consumed in the United States during 1976.[5] Safflower Oil's use in resinous and polymeric coatings is regulated by the FDA as an indirect food additive.[24]

Safflower Oil is used clinically to treat a variety of conditions. It has been used to treat essential fatty acid deficiencies,[25-27] to control hypertension,[28] to treat lithium toxicity,[29] to treat Friedreich's ataxia,[30,31] and to alleviate debilitating hangovers in patients on antidepressant drug therapy.[32] Two emulsions commonly used for total parenteral nutrition of pediatric and adult patients contain 10 percent and 20 percent Safflower Oil.[33]

BIOLOGICAL PROPERTIES

Introduction: Oils and Linoleic Acid

The physical properties of such edible seed oils as Safflower Oil make them appropriate ingredients, bases, or vehicles for cosmetic and medicinal ingredients. They are light, nonocclusive, and capable of penetrating the pores of the skin. Natural seed oils generally do not contain skin irritants and sensitizers, making them appropriate for topical application.[3]

Oils and fats have several important functions in the body, such as serving as carriers for the fat-soluble vitamins A, D, E, and K and providing fatty acids. Linoleic acid, a major constituent of Safflower Oil, is considered to be an essential fatty acid. It is necessary for proper growth in children, to prevent drying and flaking of the skin, to maintain cell membranes, to regulate cholesterol metabolism, and in the synthesis of hormones and hormonelike substances.[3,4]

Skin Absorption

Safflower Oil is absorbed through the skin. Cutaneous application of Safflower Oil to rodents has reversed experimental essential fatty acid deficiencies (EFAD). Hartop and Prottey[35] administered pure fatty acid triacylglycerols to EFAD-rats and measured changes in transepidermal water loss and the composition of epidermal lecithin. The triacylglycerol of linoleic acid specifically was

found to have an important role in regulating the barrier function of the skin and may be metabolized by the skin and incorporated into complex lipids. Bohles et al.[36] studied the changes in plasma and erythrocyte phospholipid and plasma cholesterol ester and triacylglycerol levels of EFAD rats after treatment with Safflower Oil and concluded that cutaneous application of EFA-rich Safflower Oil reversed plasma biochemical manifestations of EFAD. Safflower Oil and triacylglycerols of linoleic acid are also absorbed through human skin, as illustrated by its effective clinical use for treatment of EFAD.[25,26,37]

Metabolism

Cholesterol Metabolism

Cholesterol concentrations in liver and serum are influenced by the proportion of saturated and polyunsaturated fatty acids in the diet. Diets with relatively higher amounts of polyunsaturated fat may result in lower serum cholesterol values. Cholesterol metabolism studies using Safflower Oil as the source of polyunsaturated fatty acids have been conducted using rats,[38-43] rabbits,[45] and cebus and squirrel monkeys.[46-49]

Lipid Metabolism

A multitude of studies has been performed to determine the relationship of dietary lipids on hepatic and adipose tissue lipogenesis. Species used for these studies included rats,[50-54] mice,[55] sheep,[56-58] rabbits and monkeys,[59] and man.[60] Safflower Oil was used as the dietary source of polyunsaturated fat (linoleic acid), and the observed trends were that as the proportion of polyunsaturated fat in the diet increased, lipogenesis decreased in the liver and increased in adipose tissue, and serum phospholipid and triacylglycerol concentrations increased.

Serum Components

The effects of dietary fatty acids (using Safflower Oil as the source of polyunsaturated fatty acids) on serum concentrations of various compounds have been investigated. Dietary Safflower Oil had no effect on serum concentrations of iron and copper in rats administered oral contraceptives.[61] Rats fed Safflower Oil had higher serum concentrations of free cholesterol, triacylglycerol, and lipoprotein (very low density lipoprotein, low density lipoprotein, and high density lipoprotein) than the corresponding control serum concentrations. However, serum total cholesterol concentrations were not altered.[62,63] Monkeys (*Macaca nigra* and *Ceropithecus aethiops*) fed Safflower Oil-containing diets had lower serum concentrations of free cholesterol, triacylglycerols, and lipoprotein than monkeys fed diets rich in saturated fats.[64,65]

Enzyme Assays

The effects of dietary fat upon enzyme activity in various tissues and organs have been studied using Safflower Oil as the source of polyunsaturated fat. The effects of various fats on in vitro lipase activity in cardiac tissue from the rat have been investigated by Friedman et al.[66] and Vajreswari and Tulpule.[67] Safflower Oil was hydrolyzed to a greater extent than mustard, rapeseed, or groundnut

oils. There was no difference in enzyme activity when cardiac cells were incubated in 100 percent medium or medium containing 20 percent serum derived from fasted rats. A 50 percent decrease in lipoprotein lipase activity was observed in cardiac tissue incubated in the presence of 20 percent serum from nonfasted rats. In vivo and in vitro desaturation of palmitic and stearic acid in the rat lung was inhibited by the presence of polyunsaturated fats.[68,69]

Numerous studies have been conducted to determine the effects of saturated vs. polyunsaturated fats on enzyme and enzyme system activity in the rat liver. Among the systems studied were oxidative phosphorylation in rat liver mitochondria,[70,71] acetyl-CoA carboxylase and fatty acid synthetase activity,[72–74] 3-hydroxy-3-methylglutaryl-CoA reductase and sterol synthesis,[75–79] glucose-6-phosphate dehydrogenase activity,[80] 5- and 9-desaturase activity,[81] and induction of tyrosine aminotransferase.[82]

Dietary Studies

Safflower Oil has been used in studies to investigate the role of dietary saturated and unsaturated fats on the induction of colon, mammary gland, and pancreatic cancers.

Roebuck et al.[83] investigated the effects of dietary fat on azasarine-induced pancreatic cancer. Twenty-one-day-old male Wistar/Lewis rats were given an intraperitoneal (IP) injection of 10 mg/kg azaserine in 0.9 percent NaCl once a week for 6 or 7 weeks. Test diets were fed to the rats either during the initiation period or for a 7.5 months postinitiation period. The test diets contained one of the following: 5 percent corn oil (control), 2 percent corn oil plus 18 percent hydrogenated coconut oil, 20 percent corn oil, 20 percent Safflower Oil, or 5 percent corn oil plus a low protein content. The test diets had no effect on the incidence of pancreatic cancer when they were fed during the initiation period. There was a significant increase in the incidence of pancreatic cancer in rats fed 20 percent corn oil or 20 percent Safflower Oil ($p < 0.05$) (Table 3). Coconut oil, low-protein, and restricted caloric intake diets did not affect the cancer incidence.

Dayton et al.[84] investigated the hypothesis that polyunsaturated fatty acids are cocarcinogenic using regular Safflower Oil as the source of polyunsaturated linoleic acid, Safflower Oil from a mutant plant strain as the source of monounsaturated oleic acid, and coconut oil as the source of saturated lauric acid. After receiving a single dose (by gavage) of 5 mg 7,12-dimethylbenz(a)anthracene (DMBA) in 0.2 ml sesame oil, groups of 20 female Sprague-Dawley rats were fed diets containing 20 percent oil with or without 100 mg/kg DL-α-tocopherol. Control groups were fed the various diets after receiving 0.2 ml sesame oil without DMBA. In control rats (no DMBA), no tumors were observed, and all rats survived the 22-week experiment. Mortality was low in the test groups, with 1 rat per group dying before the end of the study. There was no significant difference in the incidence of mammary gland tumors between rats fed standard Safflower Oil, high oleic acid Safflower Oil, or coconut oil (Table 4).

A statistical analysis of the relationship of 20 diets varying in fat composition to spontaneous mammary gland tumors in C3H mice indicated a significant, positive effect of linoleate (Safflower Oil was the dietary source of linoleic acid) on tumor incidence.[85]

TABLE 3. Postinitiation Diet and Pancreatic Cancer Incidence[83]

Postinitiation Diet	No. of Rats	Azaserine Induced	Pancreatic Adenomas and Adenocarcinomas		Incidence of Other Neoplasms
			Incidence	Neoplasms/Pancreas	
Control I	16	No	0	0	0
Control II	18	Yes	10 (56)*	0.9	2
Control and low protein	15	Yes	3 (20)	0.47	0
Control-restricted caloric intake	9	Yes	1 (11)	0.11	0
18% coconut oil + 2% corn oil	16	Yes	11 (69)	1.3	0
20% corn oil	17	Yes	16 (94)†	4.7	5
20% safflower oil	17	Yes	16 (94)†	5.9	2

*Numbers in parentheses indicate percent tumor-bearing animals.
†Compared to Control II, these groups had significantly higher incidences of neoplasms ($p < 0.05$).

TABLE 4. Dietary Fat and Tumor Incidence in Rats Fed DMBA[84]

Dietary Fat	DL-tocophol*	No. of Rats	No. of Rats With Tumors†	No. of Carcinomas/ No. of Tumors Examined‡
20% Safflower oil	–	19	15.5	6/15
20% Safflower oil	+	19	14.0	2/13
20% Safflower oil (high in oleic acid)	–	19	15.5	6/14
20% Safflower oil (high in oleic acid)	+	19	18.5	7/20
20% Coconut oil	–	19	15.0	6/14
20% Coconut oil	+	19	12.0	2/11

*100 mg/kg diet.
†Mean of 2 observations.
‡Only largest tumors were examined histologically.

Groups of 26 Sprague-Dawley male weanling rats were fed diets (2 groups per diet) consisting of 1 percent cholesterol and 5 percent or 20 percent Safflower Oil or coconut oil. After 1 week of feeding this diet, rats of each diet received an intramuscular injection of 10 mg/kg 1,2-dimethylhydrazine (DMH), a large bowel carcinogen, once a week for 20 weeks. The other 4 groups were controls. After 20 doses of carcinogen, all animals remained on the test diets for an additional 15 weeks. Tumor incidence was reported only for animals given DMH and fed 5 percent coconut oil, 20 percent coconut oil, and 20 percent Safflower Oil and were 50 percent, 85 percent and 100 percent, respectively. The only significant difference in tumor incidence was between groups fed 5 [illegible]

Tumor Transplant Studies

Safflower Oil has also been used in studies to investigate the effects of dietary and intraperitoneal (IP) injected fat on the fate of transplanted hepatoma and melanoma cells.

Adult, male Buffalo rats were used to determine the effects of IP administration of Safflower Oil and corn oil on the growth of transplanted hepatoma 7777 and 7800. The animals received daily IP injections of 0.6 ml Safflower Oil, corn oil, or saline for 14 days. Half of the animals in each group were given a single 40 to 50 mg intramuscular injection of hepatoma cells on Day 3, and the other half received the hepatoma cells on Day 8 of the 14-day treatment period. There were also groups of animals that did not receive any IP injections of fat or saline prior to, or after, tumor transplantation. Safflower Oil did not significantly reduce or enhance the growth of either strain of transplanted hepatoma.[87]

Erickson[88] manipulated the diets of mice before and after transplantation of melanoma cells to study the effects of dietary fat on melanoma growth and cytolysis. Mice were fed standard diets or diets supplemented with 8 to 20 percent coconut or Safflower Oil. Tumor latency periods were significantly reduced in animals fed 20 percent fat in the diet when compared to animals on standard diets. There was also a significant increase in tumor growth rates in mice fed Safflower Oil. In an additional experiment, Erickson et al.,[89] determined that dietary fat manipulation of offspring (mice) during prenatal and postnatal life could modulate the development of the immune system.

Therapeutic Use

Safflower Oil is used clinically as a source of linoleic acid. Disease conditions, such as essential fatty acid deficiency (EFAD), lithium toxicity, Friedreich's ataxia, and severe alcoholic hangovers, have been treated successfully with oral or cutaneous administration of Safflower Oil. Skolnik et al.[25] treated a 19-year-old man with severe EFAD with daily topical applications, on the thigh, of Safflower Oil containing 150 mg of linoleic acid. No adverse effects were observed during 3 months of therapy, and the cutaneous and serum biochemical signs of EFAD were alleviated.

Safflower Oil has been used as a source for polyunsaturated fats in investigating the relationships between dietary fat and cardiac disease, hypertension, and atherosclerosis. Studies have been conducted using rats,[90] rabbits,[91-93] and monkeys.[94,95] McCullagh et al.[96] reported that canine atherosclerosis can be induced by a diet containing 5 percent cholesterol and 16 percent hydrogenated coconut oil. Dogs can be completely protected against this atherogenic process by substituting 4 percent of the coconut oil with Safflower Oil.

Parenteral nutrition is regarded as a form of nutrition in some countries and as an extension of intravenous fluid therapy in others. Parenteral nutrition is now used extensively, and the underlying biochemical processes that determine the composition of parenteral nutrition fluids are well understood.[97] Fatty acid deficiency is common in patients receiving total parenteral nutrition, and vegetable oils, including Safflower Oil, are a constituent of parenteral feeding emulsions to prevent or treat EFAD. Clinical trials have established the safety and effectiveness of emulsions containing 10 and 20 percent Safflower Oil in the total parenteral

nutritional management of adults,[98-100] pediatric patients,[33,101,102] and newborn infants.[103]

Safflower Oil has been found ineffective in the treatment of some disease states. Safflower Oil therapy failed to correct aberrations in the fatty acid patterns or chloride concentrations of sweat of patients with cystic fibrosis.[104,105] In a clinical study involving neonates receiving total parenteral nutrition, topical application of Safflower Oil did not reverse or prevent EFAD.[106]

Animal Toxicology

Oral Toxicity

Acute Oral Toxicity

Five rats were given a single oral dose (by intubation) of 5.0 g/kg undiluted Safflower Oil. No animals died during the 7-day observation period, and the LD_{50} was greater than 5 g/kg. Safflower Oil was nontoxic by ingestion.[107]

The oral toxicity of a body cream containing 3 percent Safflower Oil was evaluated using 5 male and female Sprague-Dawley rats. Animals were fasted for 16 hours, then given 15.9 ml/kg of the undiluted product by gavage. Animals were then observed for general health and activity 1 hour after administration and daily for 14 days. All rats survived the study, and no signs of toxicity were observed.[108]

Subchronic Oral Toxicity

The effects of ingestion of autooxidized Safflower Oil were studied using groups of 45 weanling, male Sprague-Dawley rats. The autooxidized Safflower Oil had a peroxide value of 465 me/kg, and was obtained by aerating the Safflower Oil for 1 month at room temperature under fluorescent light. Rats were fed normal fat content diets, fat-free diets, fat-free diets plus 1 ml Safflower Oil per day (by intubation), or fat-free diets plus 1 ml autooxidized Safflower Oil. The normal fat diet was fed ad libitum, and all other diets were restricted to 10 g/day. Fifteen animals per group were killed after 3 days, 3 weeks, or 3 months of feeding. Tissues were evaluated by weight and by light and electron microscopy, and the blood and liver were chemically analyzed. Growth curves were calculated from monthly weights, and these curves were significantly different for the 4 dietary groups. The rats fed the normal fat diet had the best growth, followed by rats fed Safflower Oil-supplemented diets, then autooxidized Safflower Oil-supplemented diets. Rats fed unsupplemented fat-free diets had the poorest growth. Rats fed the autooxidized Safflower Oil for 3 days had changes in the endoplasmic reticulum and an increase in microbodies in hepatic cells. Plasma triglyceride concentrations and in vitro incorporation of ^{14}C into fatty acids in liver slices were increased. At 3 months, this same group of animals had an increased accumulation of lipofuscin-like substances in the liver, increased activity of serum glutamic-pyruvic transaminase (SGPT) and serum glutamic-oxalacetic transaminase (SGOT), and decreased values of plasma triglycerides and decreased in vitro ^{14}C incorporation into hepatic fatty acids.[109]

Ahlstrom et al.[110] heated Safflower Oil to 200°C (approximately 400°F) for 20 hours, then fed it to weanling male Sprague-Dawley rats (10 rats per group) for

8 weeks at dietary concentrations of 0, 1, 4, and 8 percent. The rats fed 1 and 8 percent Safflower Oil grew significantly faster and slower, respectively, than control animals. The 8 percent Safflower Oil group had diarrhea, and the livers were heavier in proportion to their body weight. The serum cholesterol values were elevated in rats fed 8 percent Safflower Oil, whereas in all other groups the serum cholesterol concentrations were comparable to control values. However, the control animals had significantly more hepatic cholesterol than test animals. There were no differences in total hepatic lipids or activities of SGOT and SGPT between test and control rats. Serum lipid values decreased and serum alkaline phosphatase activity increased as the concentration of Safflower Oil in the diet was increased.

Isocaloric diets containing 0, 2.5, 5.0, and 20 percent Safflower Oil were fed to Sprague-Dawley rats for 12 days to observe the effects of a diet rich in linoleic acid on lactating and nonlactating female rats and young (4 to 6 months) and old (8 to 10 months) male rats. Safflower Oil did not affect the feed intake of the animals, but as the dietary concentration of the Safflower Oil increased, the digestibility coefficient decreased. A decrease in dietary Safflower Oil was accompanied by increases in in vitro lipogenesis by hepatic and renal tissue and increased specific activities of lipogenic enzymes in young males and nonlactating females but had no effect on these parameters in old male and lactating female rats. Safflower Oil content of diet had no effect on milk fat content but caused a proportional increase in unsaturated fatty acids in the milk. Only minor dietary effects upon enzymatic patterns of mammary gland tissue and rates of in vitro lipogenesis were observed.[111]

Diets containing approximately 20 percent Safflower Oil or 20 percent tallow (high in saturated fatty acid content) were fed to rats (7 to 10 male Sprague-Dawley rats per group), chicks (8 male crossbred, 8- to 10-day-old chicks per group), and pigs (8 castrated male Yorkshire-Hampshire pigs per group) for 22 or 28 days. In comparing the animals (within species) fed Safflower Oil vs. tallow, there was no difference in body weight gain and feed intake or plasma free fatty acid and cholesterol values.[112]

Chronic Oral Toxicity

A lifetime feeding study was completed by Morin[113] using C3H/HeJ mice. Sixty male mice per group were fed diets containing 15 percent sucrose, hydrogenated coconut oil, or Safflower Oil. There was no significant difference between the groups in rate of weight gain, longevity, weight at death, or liver peroxide value.

Diets containing 20 percent soybean oil, corn oil, hydrogenated shortening, or Safflower Oil were fed to groups of 6 male rats for 27 weeks to determine the value of dietary fat in maintaining vitamin E nutrition. All animals had normal growth, plasma concentration of tocopherols, testicular development, and no muscle degeneration. The erythrocytes from animals fed Safflower Oil had slight, but definite, in vitro hemolysis.[114]

Six groups of 62 male Wistar rats were fed diets containing 15 percent coconut oil, 15 percent Safflower Oil, or 9 percent Safflower Oil plus 6 percent coconut oil. Each diet was fed ad libitum to 2 groups of rats and was further supplemented with either 2 mg/100 g or 200 mg/100 g dl-α-tocopherol. All of the rats eventually became moderately obese, and close to 100 percent of the animals

developed chronic nephropathy. Diet composition or age at initiation of feeding of test diets had no effect on age-dependent changes in organ weights, serum cholesterol values, or serum albumin:globulin ratios. Serum concentrations of vitamin E reflected the dietary concentrations of the vitamin. Rats fed Safflower Oil or the combined oil diet had increased rates in body weight gain during the first 9 to 12 months. There was a transient hypotriglyceridemia and hypophospholipidemia in rats fed Safflower Oil up to 24 months. There was no difference between the groups in mean and maximum life span. However, the 50 percent survival time (age when half of the animals were still alive) was significantly higher in animals fed Safflower Oil plus 200 mg/100 g vitamin E. The increased 50 percent survival time was related to postponement of onset and reduction of incidence of malignant neoplasms.[115]

Adult male and female squirrel monkeys were fed diets containing 5 g/kg cholesterol and 250 g/kg Safflower Oil (10 animals), coconut oil (13 animals), lard (10 animals), or butter for 2 years. A group of 6 control animals was maintained for 3 months on diets with no cholesterol and 250 g/kg lard. Serum cholesterol concentrations were assayed once a week in the last 2 months of the study. Control animals had the lowest serum cholesterol concentrations, followed by progressively higher values in animals fed Safflower Oil, coconut oil, and lard. Serum cholesterol concentrations were highest in animals fed butter. The body weights of animals in all groups remained stable over the 2-year study period.[116]

Ocular Toxicity

Six rabbits received a single ocular application of undiluted Safflower Oil and were scored for eye irritation using the Draize classification on Days 1, 2, 3, 4, and 7 after application. The eyes were not rinsed after treatment with Safflower Oil. One animal had conjunctival irritation and a score of 4 (maximum, 110) on Day 1, and all other animals had scores of 0 on Days 1, 2, 3, 4, and 7. The eye irritancy of Safflower Oil under these test conditions was minimal.[117]

A body cream containing 3 percent Safflower Oil was tested, undiluted, for ocular irritation in 3 female New Zealand rabbits. A single application of 0.1 ml product was instilled in the left eye, and the right eye served as an untreated control. Eyes were examined for irritation 1 hour after application, then daily until the eye was clinically normal (up to 7 days). No irritation of the cornea or iris was observed. One hour after application, all rabbits had scores of 4 (maximum, 20) for conjunctival irritation, which had resolved on Day 1 for 2 rabbits and on Day 2 for the third rabbit. This product was minimally irritating.[118]

Three products containing Safflower Oil were evaluated by modified Draize eye irritation studies using 6 rabbits per product. The moisturizer contained 3 percent Safflower Oil, and 2 night creams contained either 3 percent or 5 percent Safflower Oil. Under the conditions of the test, all 3 products met the Consumer Product Safety Commission requirements for classification as nonirritants to eyes.[119–121] See Table 5 for a summary of animal eye studies.

Skin Toxicity

Comedogenicity

Undiluted Safflower Oil was applied once daily, 5 times weekly, to the external ear of 3 New Zealand rabbits for a total of 14 applications. Individual applica-

TABLE 5. Animal Eye Studies

Test Type	*No. of Animals and Species*	*Vehicle or Product Type*	*Concentration of Safflower Oil/Dose*	*Observation Time or Length of Study*	*Comments*	*Reference*
Modified Draize	6 rabbits	None	100%/unspecified	7 days	Eyes were not washed. Ocular irritation score of 1 (max, 110). Minimal eye irritant	117
Modified Draize	3 female rabbits	Body cream	3%/0.1 ml	7 days	No irritation of cornea or iris. Slight conjunctival irritation which cleared by Day 2. Minimal eye irritant	118
Modified Draize	6 rabbits	Moisturizer	3%/unspecified	Unspecified	Nonirritant	119
Modified Draize	6 rabbits	Night cream	3%/unspecified	Unspecified	Nonirritant	120
Modified Draize	6 rabbits	Night cream	5%/unspecified	Unspecified	Nonirritant	121

tions ranged from 5 to 10 mg/cm^2. The animals were killed following the fourteenth application, and samples were taken from the treated sites and untreated control sites on the contralateral ear. Safflower Oil was a slight to moderate comedogenic agent, with a score of 1–2 on a 0 to 5 scale where 5 denoted maximal comedogenicity.[122]

A moisturizer and 2 night creams containing 3 percent, 3 percent, and 5 percent Safflower Oil, respectively, were tested for comedogenicity in a modified Kligman comedogenic assay. Daily 1 ml applications of the undiluted product were made to the right ear of 3 rabbits per product. The left ear served as the untreated control. A total of 15 applications were made over 3 weeks. Animals were observed daily for enlarged pores and comedone formation, and terminal biopsies were microscopically evaluated for hyperkeratosis of sebaceous ducts. All 3 cosmetics were noncomedogenic.[123–125]

Primary Skin Irritation

Undiluted Safflower Oil caused minimal primary skin irritation in a repeat open patch test. Eight rabbits received 8 daily open patch applications of 100 percent Safflower Oil to nonabraded skin. The cumulative PII was 0.50 (maximum, 4.0).[126]

Contact Sensitization

The sensitization and irritation potential of Safflower Oil was evaluated in a modified Magnusson-Kligman guinea pig maximization test. This procedure is divided into 4 phases: (1) induction phase, (2) dose range phase, (3) booster phase, and (4) challenge phase. Ten test animals and ten control animals went through

the induction, booster, and challenge phases, and a separate group of 10 guinea pigs was used for the dose range phase. In the induction phase, single 0.5 ml intradermal injections of 5 percent Safflower Oil in propylene glycol and 5 percent Safflower Oil in 50 percent aqueous Freund's complete adjuvant were administered to test animals, whereas control animals received injections of the vehicles only. The dose range phase consisted of a 24-hour occlusive patch of 25 percent, 50 percent, or 100 percent Safflower Oil in petrolatum. The test sites were graded to determine nonirritating and slightly irritating concentrations to be used in the booster and challenge phases. Safflower Oil was not irritating at any concentration. One week after the induction injections, a topical booster of a slightly irritating concentration of test material or petrolatum (for controls) was administered to the injection site, then wrapped occlusively for 48 hours. Since 100 percent Safflower Oil was not irritating to guinea pig skin in the dose range phase, test and control animals were treated with sodium lauryl sulfate in petrolatum 24 hours before booster application in order to slightly irritate the injection site. Two weeks after the topical booster, the animals were challenged with 24-hour occlusive patch applications of 50 percent (in petrolatum) and 100 percent Safflower Oil. The challenge sites were graded 24 and 48 hours after patch removal. Due to the large number of animals that escaped from their wrappings during the first challenge, a second occlusive challenge patch was applied. There were no reactors to the 50 percent and 100 percent Safflower Oil challenge patches. Safflower Oil was not a primary irritant or a sensitizer under these test conditions.[127] See Table 6 for a summary of animal skin studies.

Embryonic and Neonatal Toxicity

Female rats were fed 10 percent Safflower Oil diets 2 weeks before mating through the fourteenth day of gestation (average gestation is 23 days), then switched to diets containing 10 percent soybean oil, hydrogenated coconut oil, or Safflower Oil. Fetuses were then taken by cesarean section on Day 16, 18, or 21 of gestation, and brain tissue was analyzed for fatty acid content. The fatty acid content of the embryonic brains reflected the dietary fat available to the dam, indicating either increased placental transfer of fatty acids or increased fetal synthesis of these compounds during the last week of gestation.[128]

Safflower Oil was a negative control in a study investigating the teratogenic effects of cyclopropenoid fatty acids.[129]

Borgman et al.[130,131] investigated the effects of maternal dietary fat intake on completed gestations, maternal behavior, and neonatal brain size, physical development, and behavioral development. Female rats were fed standard commercial diets at all times except during gestation and lactation periods. Fourteen females were bred and fed the control diet throughout gestation and lactation; 11 of 14 litters were raised successfully. Eighteeen rats were bred, switched to a fat-free diet, and 14 of 18 litters were raised. Twelve litters were raised of 14 rats bred then fed 20 percent cocoa butter, and 10 of 15 animals fed 20 percent Safflower Oil raised litters. The dams fed cocoa butter were no different from controls in body weight, behavior during lactation, litter production, and dam and pup brain chemistry values. The dams fed Safflower Oil had fewer completed gestations and poorer maternal behavior during lactation with regard to nest construction, keeping young in the nest, and time spent with the young. The pups of dams

TABLE 6. Animal Skin Studies

Test Type	*No. of Animals and Species*	*Vehicle or Product Type*	*Concentration of Safflower Oil/Dose*	*Observation Time or Length of Study*	*Comments*	*Reference*
Comedogenicity	3 rabbits	None	100%/5–10 mg/cm²	14 days, daily applications	Comedogenic grade of 1–2 on 0–5 scale. Slight to moderate comedogenic potential	122
Primary irritation	8 rabbits	None	100%/unspecified	8 days, daily applications	Repeat open patch on nonabraded skin. Group primary irritation score of 0.50 (max, 4.0). Minimal skin irritant	126
Magnusson-Kligman maximization test	10 guinea pigs	Propylene glycol or 50% Freund's complete adjuvant	5%/0.5 ml induction injection	3 weeks	Single intradermal induction injection followed by an occlusive patch booster at 1 week, then occlusive challenge patch at 3 weeks. Dose range test to determine primary irritancy. "Not primary irritant or sensitizer"	127
		Petrolatum	25, 50, and 100% dose range irritancy test	72 hours		
		Petrolatum	100% booster skin patch	1 week after induction		
		Petrolatum	50 and 100% patch challenge	3 weeks after induction		
Comedogenicity	3 rabbits	Moisturizer	3%/1 ml	3 weeks, 15 daily applications	Noncomedogenic	123
Comedogenicity	3 rabbits	Night cream	3%/1 ml	3 weeks, 15 daily applications	Noncomedogenic	124
Comedogenicity	3 rabbits	Night cream	5%/1 ml	3 weeks, 15 daily applications	Noncomedogenic	125

fed Safflower Oil had smaller brains at birth. Dams on fat-free diets had reduced concentrations of RNA in the brain and low RNA:DNA ratios.[130]

This experiment was continued by weaning 4 pups (2 male and 2 female) from each litter to standard diets and observing their physical and behavioral development. Pups from dams fed Safflower Oil were similar to controls in physical development, behavioral development including exploratory activity and learning a T-maze, and concentrations of cholesterol, DNA, and RNA in the brain (pups killed at 8 weeks). Pups from dams fed cocoa butter had reduced exploratory activity coupled with rapid learning performance in the T-maze. Dams maintained on fat-free diets had pups with reduced growth rates, small brains at 8 weeks, and lower brain concentrations of cholesterol, DNA, and RNA.[131] Brain weight was decreased, and brain DNA and RNA concentrations of dams and offspring fed Safflower Oil were increased as compared to animals fed diets containing butter and lard.[132]

A similar experiment to study the effects of dietary fat on pup development was conducted by Lamptey and Walker.[133] Dams were fed either 10 percent Safflower Oil or 10 percent soybean oil (rich in linolenic acid) in their diet during gestation and lactation, and the offspring were subsequently weaned to the maternal diet. The physical, neuromotor, and reflex development of the pups was observed prior to weaning, and brain lipids were analyzed at birth, 21, or 210 days. Learning ability was assessed in mature progeny in a simple Y-maze test. The diets had no effect on physical development and onset of reflex responses and neuromotor coordination. The pups fed soybean oil performed better in the Y-maze tests and spent more time in neuromotor activities possibly associated with explorative drive. Brain lipid content reflected the dietary lipid intake.

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization Studies

Primary Skin Irritation Tests

A body cream containing 3 percent Safflower Oil was evaluated for primary irritation in a single insult patch test using 100 subjects. An occlusive patch with 0.1 ml of the undiluted product was applied to each subject's back and kept in place for 48 hours. The test site was then graded for erythema and edema 15 minutes and 24 hours after patch removal. No erythema or edema was observed. The body cream was not a primary irritant.[134]

A moisturizer and 2 night creams containing 3 percent, 3 percent, and 5 percent Safflower Oil, respectively, were tested for skin irritation in 21-day cumulative irritancy tests. Each product was tested on 21 subjects. The test products were applied under occlusion to the back of each subject once daily for 21 days. Before each application and after the last application, the test site was scored for irritation. The resultant scores were compared to scores for high and low irritation controls. Each product caused less irritation than the low control and was rated nonirritating.[135–137]

Repeat Insult Patch Test

Six products containing Safflower Oil were tested for irritation and sensitization by a modified Draize-Shelanski-Jordan repeat insult patch test (RIPT) according to the following procedure. Ten induction patches were applied to each subject over a 3-week period. All patches were occluded and remained in place for 24 hours, then removed, and sites were scored for erythema, edema, and eschar formation. After a 13-day nontreatment period, the product was reapplied under occlusion for 48 hours, and the sites were evaluated upon patch removal. Following a further 7-day nontreatment period, a second challenge patch was applied, and the site was evaluated at 48 and 72 hours after application. The results of the 6 tests were:

1. Irritation was observed during induction and challenge phase in 1 of 209 subjects tested with a moisturizer containing 3 percent Safflower Oil. Patching was discontinued on this subject. The reaction was considered nonspecific irritation. The product was neither an irritant nor a sensitizer.[138]
2. A night cream containing 3 percent Safflower Oil was not an irritant or sensitizer in 209 subjects. Irritation was observed in 1 panelist during induction and in another panelist during induction and challenge.[139]
3. No reactions were observed in induction or challenge phases of a 50-panelist RIPT on a night cream containing 5 percent Safflower Oil. The night cream was not an irritant or sensitizer.[140]
4. Two hundred seventeen volunteers were tested with a night cream containing 5 percent Safflower Oil. Five panelists had insignificant irritation during induction, and 1 panelist had slight irritation at the challenge patch. Results from repatching of this latter panelist indicated that the irritation was nonspecific. The product was neither an irritant nor a sensitizer.[141]
5. A night cream containing 5 percent Safflower Oil caused irritation in 2 of 217 subjects during the induction phase and 2 subjects during challenge. Results of repatching of these last 2 subjects indicated that the reactions were irritant in nature. The cream was not an irritant or sensitizer.[142]
6. A 200-member panel was used to test a night cream containing 5 percent Safflower Oil. Irritation was observed in 5 panelists during the induction phase. Slight irritation was observed in 1 panelist at challenge, but this reaction was considered nonspecific irritation. The product was not an irritant or sensitizer.[143]

Photosensitization

The photosensitization potential of a night cream containing 5 percent Safflower Oil was evaluated. Twenty-five subjects participated in the study, and individual mean erythemal doses (MED) were determined. Phototoxicity was determined at 3 sites on the back: 1 site was exposed to ultraviolet (UVA and UVB) light and not treated with the product, 1 site was treated with 0.01 to 0.02 ml product then exposed to UVA and UVB light, and 1 site was treated with the product and not exposed to UV light. All sites were evaluated 0, 1, 3, and 24 hours after irradiation. Product photosensitization was determined at 3 sites prepared as above. The sites were occluded for 24 hours prior to irradiation, then uncovered and irradiated with UVA light (excluding nonirradiated control). The

same sites were treated and irradiated for a total of 5 treatment/irradiations within 2.5 weeks. After a 10-day nontreatment period, a new site was selected, and the treatment/irradiation procedure was repeated as a challenge. Test sites were evaluated at 0, 24, and 48 hours following irradiation. The light source for these tests was a xenon plasma arc lamp (Hanovia Solar Simulator) emitting radiation between 280 and 1000 nm, with its peak output between 280 and 500 μm. UVA radiation (~6 MED equivalents) was obtained using a windowglass filter, and UVB radiation (~0.5 MED equivalents) was obtained by removing the filter. Within the confines of the test, the product was not a phototoxin or a photosensitizer.[144]

A night cream with 5 percent Safflower Oil was tested for photosensitivity as described above and was neither a phototoxin nor a photosensitizer.[145] Table 7 summarizes the clinical safety studies on products containing Safflower Oil.

SUMMARY

Safflower Oil is an edible seed oil consisting primarily of triglycerides of linoleic acid. It is a golden yellow liquid at room temperature and is soluble in the usual fat and oil solvents. Safflower Oil is relatively stable to oxidation. However, it thickens and becomes rancid on prolonged exposure to air.

Safflower Oil is used in cosmetics primarily as an emollient in topical lotions and creams. The majority of products in which Safflower Oil is an ingredient are moisturizing skin creams and suntan lotions. The usual concentration of Safflower Oil used in these products is 0.1 to 5 percent. Safflower Oil is used in resins and paints, medicines, dietetic food, and as a vegetable cooking oil.

The metabolism of linoleic acid has been studied in great detail. This knowledge is of great value in the study of Safflower Oil due to the latter's high content (~75 percent) of this polyunsaturated fatty acid. In many studies, Safflower Oil has been used as the dietary source of linoleic acid. Linoleic acid, an essential fatty acid, is an important carrier of vitamins A, D, K, and especially vitamin E. Linoleic acid is essential for proper growth in children, to prevent drying and flaking of the skin, to maintain cell membrane integrity, to regulate cholesterol metabolism, and for synthesis of hormones and hormonelike substances. The type and amount of fat in the diet can modify lipid metabolism in the liver and adipose tissue and may have long-term effects on the heart and cardiovascular system.

Safflower Oil is practically nontoxic when ingested. Single oral doses of 5 g/kg produced no signs of toxicity in rats. Subchronic and chronic feeding studies of Safflower Oil have been directed toward fatty acid metabolism rather than the toxic effects of Safflower Oil per se. However, oral administration of up to 20 percent dietary Safflower Oil was not toxic in these metabolism studies. Autooxidized and heated Safflower Oil (to simulate human consumption of the oil) has been fed to rats with no adverse effects.

Undiluted Safflower Oil was a minimal ocular irritant in rabbits. Several cosmetic products containing 3 percent Safflower Oil caused minimal to no ocular irritation in rabbits.

Pure Safflower Oil had slight to moderate comedogenicity and minimal skin irritancy in rabbits. Products containing up to 5 percent Safflower Oil were not

TABLE 7. Clinical Studies for Skin Irritation, Sensitization, and Photosensitization of Cosmetic Products Containing Safflower Oil

Test Type	*Product Type*	*% Safflower Oil*	*No. of Subjects*	*Comments*	*Reference*
Primary skin irritation	Body cream	3	100	Single insult, occluded 24-hour patch. No erythema or edema. Not a primary irritant	133
21-day cumulative irritancy test	Moisturizer[a]	3	21	Nonirritating	134
21-day cumulative irritancy test	Night cream[b]	3	21	Nonirritating	135
21-day cumulative irritancy test	Night cream	5	21	Nonirritating	136
RIPT	Moisturizer[a]	3	209	One irritant reaction during induction and challenge. Not an irritant or sensitizer	137
RIPT	Night cream[b]	3	209	One irritant reaction during induction; 1 irritant reaction at challenge. Not an irritant or sensitizer	138
RIPT	Night cream	5	50	No reactions. Not an irritant or sensitizer	139
RIPT	Night cream[c]	5	217	Five irritant reactions during induction; 1 irritant reaction at challenge. Not an irritant or sensitizer	140
RIPT	Night cream[d]	5	217	Two irritant reactions during induction; 2 irritant reactions at challenge. Not an irritant or sensitizer	141
RIPT	Night cream	5	200	Five irritant reactions during induction; 1 irritant reaction at challenge. Not an irritant or sensitizer	142
Phototoxicity	Night cream[d]	5	25	Product was applied, then test site exposed to UV light and evaluated. Not phototoxic	143
Phototoxicity	Night cream[c]	5	25	Product was applied, then test site exposed to UV light and evaluated. Not phototoxic	144
Photosensitization	Night cream[d]	5	10	Treated sites exposed to 5 exposures of UV over 2- to 3-week period. Not a photosensitizer	143
Photosensitization	Night cream[c]	5	10	Treated sites exposed to 5 exposures of UV over 2- to 3-week period. Not a photosensitizer	144

[a,b,c,d]Matching superscripts indicate the same product was tested.

comedogenic in rabbits. In a guinea pig maximization test, Safflower Oil was not a skin irritant or contact sensitizer.

Safflower Oil has been investigated in connection with the effects of maternal diet on prenatal and postnatal development, again with the main emphasis on fatty acid metabolism. The fatty acid content of brains of the rat pups reflected the fatty acid content of the maternal diet. Female rats fed Safflower Oil had fewer completed gestations and poorer maternal behavior as compared to dams fed control or coconut butter diets. The pups of dams fed Safflower Oil were similar to controls in physical and behavioral development. Pups of dams fed either Safflower Oil or soybean oil supplements had similar physical development and onset of reflexological responses and neuromotor coordination. However, the pups fed soybean oil performed better in Y-maze tests.

Studies on the role of polyunsaturated fatty acids in the induction of tumors have utilized Safflower Oil as a source of polyunsaturated fat. A 20 percent Safflower Oil diet increased the incidence of pancreatic cancer induced by azasarine in Wistar/Lewis rats. Safflower Oil diets also increased the incidence of mammary tumors induced by 7,12-dimethylbenz(a)anthracene, large bowel tumors induced by dimethylhydrazine, and reduced the latency period and increased the growth rate of transplanted melanomas as compared to rats fed control diets or saturated-fat diets. No data are available on Safflower Oil's mutagenic or carcinogenic activity.

No clinical skin irritation and sensitization studies have been published in connection with pure Safflower Oil. However, its effectiveness in the treatment of EFAD indicates a low toxicity. Safflower Oil has been used to treat EFAD via oral and topical administration and is often applied to irritated and abraded skin.

The clinical safety of Safflower Oil has been indirectly tested in several clinical studies with cosmetic products containing 3 to 5 percent Safflower Oil. The products were assayed for primary irritation, irritation and sensitization (RIPTs), and photosensitization. None of the products tested were irritants, sensitizers, or photosensitizers in humans.

DISCUSSION

Data are available indicating that Safflower Oil is not irritating to human skin at concentrations up to 5 percent. However, some cosmetic products contain over 50 percent Safflower Oil, and clinical safety at this concentration has not been established. Based on metabolic studies and the negative results from animal assays examining the ocular and cutaneous irritancy of 100 percent Safflower Oil, the Panel finds no cause for concern in the present uses of Safflower Oil in cosmetic products.

CONCLUSION

From information presented in this report, the CIR Expert Panel concludes that Safflower Oil is safe as a cosmetic ingredient in the present practices of use.

ACKNOWLEDGMENT

Lorraine E. Cathers, Scientific Analyst and writer, prepared the literature review and technical analysis used to develop this report.

REFERENCES

1. ESTRIN, N.F., CROSLEY, P.A., and HAYES, C.R. (eds.). (1982). *Cosmetic, Toiletry and Fragrance Association (CTFA) Cosmetic Ingredient Dictionary*, 3rd ed. Washington, DC: Cosmetic, Toiletry and Fragrance Association.
2. SOLOMON, T.W.G. (1978). *Organic Chemistry*. New York: Wiley.
3. KINSELLA, J. (1976). Properties of oil of grapeseed and other seeds in cosmetics. Cosmet. Toiletry **91,** 19–24.
4. ESTRIN, N.F., HAYNES, C.R., and WHELAN, J.M. (eds.). (1982). *CTFA Compendium of Cosmetic Ingredient Composition: Cosmetic Ingredient Descriptions*. Washington, DC: Cosmetic, Toiletry and Fragrance Association.
5. SWERN, D. (ed.). (1979). *Bailey's Industrial Oil and Fat Products*, 4th ed. New York: Wiley.
6. BERNHOLZ, W.F., and HOEN, R. (1975). Cosmetic applications of high oleic safflower oil. Cosmet. Perfum. **90,** 43–5.
7. WINDHOLZ, M. (ed.). (1976). *The Merck Index*, 9th ed. Rahway, NJ: The Merck Co.
8. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION. (CTFA). (1983). Submission of unpublished data by CTFA. Cosmetic ingredient chemical description of safflower oil. CTFA Code No. 2-28-25.*
9. JAMIESON, G.S. (1943). *Vegetable Fats and Oils*, 2nd ed. New York: Reinhold.
10. BRIGNOLI, C.A., KINSELLA, J.E., and WEIHRAUCH, J.L. (1976). Comprehensive evaluation of fatty acids in foods V. Unhydrogenated fats and oils. J. Am. Diet. Assoc. **68**(3), 224–9.
11. CASTANG, J. (1981). Composition of the sterol fraction of different oils and vegetable fats by gas phase chromatography on a column filled with OV17. Am. Falsif. Expert. Chim. Toxicol. **74**(803), 697–700.
12. SOHDE, K., IZUTANI, S., and MATSUSHITA, S. (1973). Preparation of triglyceride hydroperoxides. Agric. Biol. Chem. **37**(8), 1979–81.
13. KINT, S., LUNDIN, R.E., WAISS, A.C., JR., and ELLIGER, C.A. (1981). Analysis of cyclopropenoid fatty acids by Raman spectroscopy. Anal. Biochem. **118**(2), 364–70.
14. KARAWYA, M.S., KHAFAGY, S.M., HIFNAWY, M.S., and FARRAG, N.M. (1982). Colorimetric and chromatographic assay of fatty acids in sunflower and safflower seed oils. Egypt. J. Pharm. Sci. **20**(1–4), 121–30.
15. SLACK, C.R., BERTAUD, W.S., SHAW, B.D., HOLLAND, R., BROWSE, J., and WRIGHT, H. (1980). Some studies on the composition and surface properties of oil bodies from the seed cotyledons of safflower (*Carthamus tinctorius*) and linseed (*Linum ustatissimum*). Biochem. J. **190**(3), 551–61.
16. WINTERS, G. (1950). Safflower oil. J. Am. Oil. Chem. Soc. **27,** 82–84.
17. DEOSTHALE, Y.G. (1981). Trace element composition of common oilseeds. J. Am. Oil Chem. Soc. **58** (11), 988–90.
18. GOUD, K.B., KULKARNI, K.A., AND THONTADARYA, T.S. (1981). Residues of insecticides in safflower seed. Pesticides **15**(3), 12–3.
19. SUBRAHMANYAM, P., and RAO, A.S. (1974). A note on aflatoxin production by some Indian strains of *Aspergillus flavus*. Indian J. Microbiol. **14**(1), 31–4.
20. PATEL, P.M., NETKE, S.P., GUPTA, B.S., and DABADGHAO, A.K. (1981). Survey of oilcakes and some feeds for the presence of aflatoxin. Indian J. Anim. Sci. **51**(4), 402–7.
21. BALSAM, M.S., and SAGARIN, E. (eds.). (1972). *Cosmetics: Science and Technology*. New York: Wiley-Interscience.
22. FOOD AND DRUG ADMINISTRATION (FDA). (Dec. 22, 1981). Computer printout of voluntary submission of cosmetic ingredient data.

*Available upon request: Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Avenue, N.W., Washington, DC 20005.

23. HAWLEY, G.G. (ed.). (1971). *The Condensed Chemical Dictionary*, 8th ed. New York: Van Nostrand Reinhold.
24. CODE OF FEDERAL REGULATIONS (CFR). (1982). Title 21; Part 175.300. Washington, DC: US Government Printing Office.
25. SKOLNIK, P., EAGLESTEIN, W.H., and ZIBOH, V.A. (1977). Human essential fatty acid deficiency: treatment by topical application of linoleic acid. Arch. Dermatol. **113**(7), 939–41.
26. O'NEILL, J.A., JR., CALDWELL, M.D., and MENG, H.C. (1977). Essential fatty acid deficiency in surgical patients. Ann. Surg. **185**(5), 535–42.
27. MARTIN, D.J. (1981). Topical lotion for essential fatty acids. Nutr. Support Service **1,** 40.
28. RAO, R.H., RAO, U.B., and SRIKANTIA, S.G. (1981). Effect of polyunsaturate-rich vegetable oils on blood pressure in essential hypertension. Clin. Exp. Hypertension **3**(1), 27–38.
29. LIEB, J. (1980). Linoleic acid in the treatment of lithium toxicity and familial tremor. Prostaglandins Med. **4**(4), 275–9.
30. MELANCON, S.B., VANASSE, M., GEOFFROY, G., BARABE, L., PROULX, A., FONTAINE, G., DALLAIRE, L., and POTIER, M. (1982). Oral lecithin and linoleic acid in Friedreich's ataxia. II. Clinical results. Can. J. Neurol. Sci. **9**(2), 155–64.
31. MELANCON, S.B., DALLARIE, L., POTIER, M., CONSINEAU, J., VANASSE, M., GEOFFROY, G., FONTAINE, G., and GRIGNON, B. (1982). Oral lecithin and linoleic acid in Friedreich's ataxia. III. Biochemical results. Can. J. Neurol. Sci. **9**(2), 165–9.
32. LIEB, J. (1980). Prostaglandin-E_1 in affective disorders and alcoholism. Br. Med. J. **281**(9), 453.
33. CORAN, A.G., DRONGOWSKI, R., SARAHAN, T.M., and WESLEY, J.R. (1981). Comparison of a new 10 percent and 20 percent safflower oil fat emulsion in pediatric parenteral nutrition. JPEN **5**(3), 236–9.
34. LECOS, C. (March, 1983). A compendium on fats. FDA Consumer, p. 5–7.
35. HARTOP, P.J., and PROTTEY, C. (1976). Changes in transepidermal water loss with the composition of epidermal lecithin after applications of pure fatty acid triglycerides to the skin of essential fatty acid-deficient rats. Br. J. Dermatol. **95**(3), 255–64.
36. BOHLES, H., BIEBER, M.A., and HEIRD, W.C. (1976). Reversal of experimental essential fatty acid deficiency by cutaneous administration of safflower oil. Am. J. Clin. Nutr. **29**(4), 398–401.
37. PRESS, M., HARTOP, P.J., and PROTTEY, C. (1974). Correction of essential fatty acid deficiency in man by the cutaneous application of sunflower-seed oil. Lancet **1,** 597.
38. PAWAR, S.S., and TIDWELL, H.C. (1967). Cholesterol and lipid levels in blood and livers of rats fed unsaturated fats. Am. J. Physiol. **213**(6), 1350–2.
39. O'BRIEN, B.C., SKUTCHES, C.L., HENDERSON, G.R., and REISER, R. (1977). Interrelated effects of food lipids on steroid metabolism in rats. J. Nutr. **107**(8), 1444–54.
40. CARROLL, C., and WILLIAMS. L. (1977). Influence of dietary fat on fatty livers of choline-deficient rats. J. Nutr. **107**(7), 1263–8.
41. CARLSON, S.E., SHRIVER, C.N., and ARNRICH, L. (1978). Dietary fat and cholesterol metabolism in adult rats undergoing rapid tissue repletion. J. Nutr. **108**(7), 1170–9.
42. FELDMAN, E.B., RUSSELL, B.S., SCHNARE, F.H., MILES, B.C., DPYLE, E.A., and MORETTI-ROJAS, I. (1979). Effects of tristearin, triolein and safflower oil diets on cholesterol balance in rats. J. Nutr. **109**(12), 2226–36.
43. RAMESHA, C.S., PAUL, R., and GANGULY, J. (1980). Effect of dietary unsaturated oils on the biosynthesis of cholesterol and on biliary and fecal excretion of cholesterol and bile acids in rats. J. Nutr. **110**(11), 2149–58.
44. MERCER, N.J., and HOLUB, B.J. (1981). Measurement of hepatic sterol synthesis in the Mongolian gerbil in vivo using (3H) water: Diurnal variation and effect of type of dietary fat. J. Lipid Res. **22**(5), 792–9.
45. FIELD, F.J., and SALOME, R.G. (1982). Effect of dietary fat saturation, cholesterol and cholestyramine on acyl-CoA: Cholesterol acyltransferase activity in rabbit intestinal microsomes. Biochim. Biophys. Acta **712** (3), 557–70.
46. COREY, J.E., NICOLOSI, R.J., and HAYES, K.C. (1976). Effect of dietary fat on cholesterol turnover in old and new world monkeys. Exp. Mol. Pathol. **25**(3), 311–21.
47. TANAKA, N., PORTMAN, O.W., and OSUGA, T. (1976). Effect of type of dietary fat, cholesterol and chenodeoxycholic acid on gallstone formation, bile acid kinetics and plasma lipids in squirrel monkeys. J. Nutr. **106**(8), 1123–34.
48. TANAKA, N., and PORTMAN, O.W. (1977). Effect of type of dietary fat and cholesterol on cholesterol absorption rate in squirrel monkeys. J. Nutr. **107**(5), 814–21.
49. MELCHIOR, G.W., LOFLAND, H.B., and ST. CLAIR, R.W. (1978). The effect of polyunsaturated fats on bile acid metabolism and cholelithiasis in squirrel monkeys. Metabolism **27**(10), 1471–84.

50. SINCLAIR, A.J., and COLLINS, F.D. (1970). Effect of dietary essential fatty acids on the concentration of serum and liver lipids in the rat. Br. J. Nutr. **24**(4), 971–82.
51. DUNN, G.D., WILCOX, H.G., and HEIMBERG, M. (1975). Temporal relationships between dietary, plasma, hepatic and adipose tissue lipids after short-term feeding of safflower oil to rats. J. Lab Clin. Med. **86**(3), 369–77.
52. LANDES, D.R., and MILLER, J. (1975). Effects of several vegetable oils on lipid classes and very long chain polyenoic fatty acid content of rat liver and heart. J. Agric. Food Chem. **23**(3), 551–5.
53. AOYAMA, Y., YOSHIDA, A., and ASHIDA, K. (1977). Effects of dietary fats and fatty acids on the liver lipid accumulation induced by feeding a protein-repletion diet containing glycol to protein-depleted rats. J. Nutr. **107**(6), 1120–5.
54. AWAD, A.B. (1981). Effect of dietary lipids on composition and glucose utilization by rat adipose tissue. J. Nutr. **111**(1), 34–9.
55. SABINE, J.R., McGARTH, H., and ABRAHAM, S. (1969). Dietary fat and the inhibition of hepatic lipogenesis in the mouse. J. Nutr. **98**(3), 312–18.
56. VERNON, R.G. (1975). Effects of dietary safflower oil upon lipogenesis in neonatal lamb. Lipids **10**(5), 284–9.
57. VERNON, R.G. (1977). Development of perirenal adipose tissue in the neonatal lamb: Effects of dietary safflower oil. Biol. Neonate **32**(1–2), 15–23.
58. HOOD, R.L., COOL, L.J., MILLS, S.C., and SCOTT, T.W. (1980). Effect of feeding protected lipids on fatty acid synthesis in ovine tissues. Lipids **15**(9), 644–50.
59. PORTMAN, O.W., and ALEXANDER, M. (1978). Sequences of change in low density lipoprotein apoprotein concentrations and metabolism with changes in diet in monkeys and rabbits. J. Nutr. **108**(10), 1580–7.
60. TURNER, J.D., LE, N.A., and BROWN, M.V. (1981). Effect of changing dietary fat saturation on low-density lipoprotein metabolism on man. Am. J. Physiol. **241**(1), E57–63.
61. ONDERKA, H.L., and KIRKSEY, A. (1975). Influence of dietary lipids on iron and copper levels of rats administered oral contraceptives. J. Nutr. **105**(10), 1269–77.
62. DUNN, G.D., WILCOX, H.G., and HEIMBERG, M. (1975). Effects of dietary triglyceride on the properties and lipid composition of plasma lipoproteins: Acute experiments in rats fed safflower oil. Lipids **10**(12), 773–82.
63. LARKING, P.W., and SUTHERLAND, W.H. (1977). Lecithin:cholesterol acyltransferase activity in the serum of rats fed saturated and unsaturated fats. Atherosclerosis **26**(2), 225–32.
64. HOWARD, C.F., JR. (1979). Effects of quantity and unsaturation of dietary fat on serum components in normal and diabetic *Macaca nigra*. J. Nutr. **109**(5), 892–903.
65. RUDEL, L.L., REYNOLDS, J.A., and BULLOCH, B.C. (1981). Nutritional effects on blood lipid and HDL cholesterol concentrations in two subspecies of African green monkeys (Cercopithecus aethiops). J. Lipid Res. **22**(2), 278–86.
66. FRIEDMAN, G., STEIN, O., and STEIN, Y. (1979). Lipoprotein lipase of cultured mesenchymal rat heart cells. IV. Modulation of enzyme activity by VLDL added to the culture medium. Biochim. Biophys. Acta **573**(3), 521–34.
67. VAJRESWARI, A., and TULPULE, P.G. (1980). Activity of myocardial lipase using natural edible oils as substrates. Lipids **15**(11), 962–4.
68. BALINT, J.A., KYRIAKIDES, E.C., and BEELER, D.A. (1980). Fatty acid desaturation in lungs: Inhibition by unsaturated fatty acids. J. Lipid Res. **21**(7), 868–73.
69. BALINT, J.A., KYRIAKIDES, E.C., and BEELER, D.A. (1981). Desaturation of endogenous and exogenous palmitate in lung tissue in vitro. Lipids **16**(10), 767–70.
70. DIVARKARAN, P., and VENKATARAMAN, A. (1977). Effect of dietary fats on oxidative phosphorylation and fatty acid profile of rat liver mitochondria. J. Nutr. **107**(9), 1621–31.
71. DIVAKARAN, P. (1978). Essential fatty acids (EFA) deficiency and liver mitochondria. Experientia **34**(12), 1540–1.
72. FLICK, P.K., CHEN, J., and VAGELOS, P.R. (1977). Effect of dietary linoleate on synthesis and degradation of fatty acid synthetase from rat liver. J. Biol. Chem. **252**(12), 4242–9.
73. TOUSSANT, M.J., WILSON, M.D., and CLARKE, S.D. (1981). Coordinate suppression of liver acetyl-CoA carboxylase and fatty acid synthetase by polyunsaturated fat. J. Nutr. **111**(1), 146–53.
74. CLARKE, B.A., and CLARKE, S.D. (1982). Suppression of rat liver fatty acid synthesis by eicosa-5,8,11,14-tetranoic acid without a reduction in lipogenic enzymes. J. Nutr. **112**(6), 1212–19.
75. MITROPOULOS, K.A., VENKATESAN, S., and BALASUBRAMANIAM, S. (1980). On the mechanism of regulation of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase and of acyl coenzyme A: Cholesterol acyltransferase by dietary fat. Biochim. Biophys. Acta **619**(2), 247–57.

76. IDE, T., OKAMATSU, H., and SUGANO, M. (1978). Effects of dietary fats on the activity of 3-hydroxy-3-methylglutaryl-CoA reductase and sterol synthesis in the liver of fasted-refed rats. J. Nutr. Sci. Vitaminol. (Tokyo) **24**(5), 535–46.
77. IDE, T., OKAMATSU, H., and SUGANO, M. (1978). Regulation by dietary fats of 3-hydroxy-3-methylglutaryl-Coenzyme A reductase in rat liver. J. Nutr. **108**(4), 601–12.
78. IDE, T., TANAKA, T., and SUGANO, M. (1979). Dietary fat-dependent changes in hepatic cholesterogenesis and the activity of 3-hydroxy-3-methylglutaryl-CoA reductase in fasted-refed rats. J. Nutr. **109**(5), 807–18.
79. IDE, T., GOTOH, Y., and SUGANO, M. (1980). Dietary regulation of hepatic 3-hydroxy-3-methylglutaryl-CoA reductase and cholesterol synthetic activities in fasted-refed rats. J. Nutr. **110**(1), 158–68.
80. WILLIAMS, M.A., TINOCO, J., OJAKIAN, M.A., and CLARK, L. (1977). Influence of fasting-refeeding and dietary linoleate on liver glucose-6-phosphate dehydrogenase and phospholipid fatty acid composition in rats adapted to a purified diet. Lipids **12**(4), 386–92.
81. DE SCHRIJVER, R., and PRIVETT, O.S. (1982). Interrelationship between dietary trans fatty acids and the 6- and 9-desaturases in the rat. Lipids **17**(1), 27–34.
82. ZEPP, E.A., and YANNARELL, A. (1982). Effect of dietary fatty acid manipulation upon the inducibility of hepatic tyrosine aminotransferase by cortisol. Biochem. Biophys. Res. Commun. **108**(4), 1695–700.
83. ROEBUCK, B.D., YAGER, J.D., JR., LONGNECKER, D.S., and WILPONE, S.A. (1981). Promotion by unsaturated fat of azaserine-induced pancreatic carcinogenesis in the rat. Cancer Res. **41**(10), 3961–6.
84. DAYTON, S., HASHIMOTO, S., and WOLLMAN, J. (1977). Effect of high-oleic and high-linoleic safflower oil on mammary tumors induced in rats by 7,12-dimethylbenz(alpha)anthracene. J. Nutr. **107**(8), 1353–60.
85. TINSLEY, I.J., SCHMITZ, J.A., and WHANGER, P.D. (1980). Effect of dietary fatty acids on tumorigenesis (meeting abstract). Fed. Proc. **3**(part 1), 647.
86. BROITMAN, S.A., VITALE, J.J., VAVAROUSEK-JAKUBA, E., and GOTTLIEB, L.S. (1977). Polyunsaturated fat, cholesterol and large bowel tumorigenesis. Cancer [Suppl.] **40**(5), 2455–63.
87. GILBERTSON, J.R., GELMAN, R.A., OVE, P., and COETZEE, M.L. (1977). Inhibition of growth of Morris hepatomas 7777 and 7800 by corn oil. Oncology **34**(2), 62–4.
88. ERICKSON, K.L. (1980). Dietary fat influences on lymphocyte-mediated cytotoxicity and murine melanoma growth (meeting abstract). Fed. Proc. **40**(3), 947.
89. ERICKSON, K.L., McNEILL, C.J., GERSHWIN, M., and OSSMANN, J.B. (1980). Influence of dietary fat concentration and saturation on immune ontogeny in mice. J. Nutr. **10**, 1555–72.
90. McCUTCHEON, J.S., UMERMURA, T., BHATNAGER, M.K., and WALKER, B.L. (1976). Cardiopathogenicity of rapeseed oils and oil blends differing in erucic, linoleic, and linolenic acid content. Lipids **11**(7), 545–52.
91. KLOEZE, J., HOUTSMULLER, V.M.T., and VLES, R.O. (1969). Influence of dietary fat mixtures on platelet adhesiveness, atherosclerosis, and plasma cholesterol content in rabbits. J. Atheroscler. **9**(3), 319–34.
92. KENNEDY, M., BURSTYN, P.G., and HUSBANDS, D.R. (1978). Fat-induced hypertension in rabbits. Part 2. The effect of feeding diets containing high concentrations of safflower oil and palm oil. Proc. Nutr. Soc. **37**(3), 98A.
93. BURSTYN, P.G., and HUSBANDS, D.R. (1980). Fat-induced hypertension in rabbits. Effects of dietary fibre on blood pressure and blood lipid concentration. Cardiovasc. Res. **14**(4), 185–91.
94. CHAKRAVARTI, R.N., KUMAR, B.S., NAIR, C.R., and KUMAR, M. (1977). Reversibility of cholesterol-adrenaline-induced atherosclerosis in rhesus monkeys. Evaluation of safflower oil and low-fat low-calorie diet. Atherosclerosis **28**(4), 405–16.
95. ST. CLAIR, R.W., HENDERSON, G.R., HEASTER, V., WAGNER, W.D., BOND, M.G., and McMAHAN, M.R. (1980). Influence of dietary fats and an oral contraceptive on plasma lipids, high density lipoproteins, gallstones, and atherosclerosis in African green monkeys. Atherosclerosis **37**(1), 103–21.
96. McCULLAGH, K.G., EHRHART, A., and BUTKUS, A. (1976). Experimental canine atherosclerosis and its prevention. The dietary induction of severe coronary, cerebral, aortic, and iliac atherosclerosis and its prevention by safflower oil. Lab Invest. **34**(4), 394–405.
97. PHILLIPS, G.D., and ODGERS, C.L. (1982). Parenteral nutrition: Current status and concepts. Drugs **23**(4), 276–323.
98. BIVINS, B.A., RAPP, R.P., RECORD, K., MENG, H.C., and GRIFFEN, W.O., JR. (1980). Parenteral safflower oil emulsion (Liposyn 10 percent): Safety and effectiveness in treating or preventing essential fatty acid deficiency in surgical patients. Am. Surg. **191**(3), 307–15.
99. WONG, K.H., and DEITEL, M. (1981). Studies with a safflower oil emulsion in total parenteral nutrition. Can. Med. Assoc. J. **125**(12), 1328–34.

100. TABRETT, D.G., and PHILLIPS, G.D. (1982). A clinical evaluation of safflower oil emulsion in total parenteral nutrition. Anaesth. Intensive Care **10**(3), 258–64.
101. CONNORS, R.H., CORAN, A.G., and WESLEY, J.R. (1980). Pediatric TPN: Efficacy and toxicity of a new fat emulsion. J. Parenter. Enter. Nutr. **4,** 384–6.
102. CORAN, A.G., DRONGOWSKI, R., SARAHAN, T.M., and WESLEY, J.R. (1982). Studies on the efficacy of a new 20 percent fat emulsion in pediatric parenteral nutrition. JPEN **6**(3), 222–5.
103. MARCHILDON, H.B. (1982). Parenteral 20 percent safflower oil emulsion safety and effectiveness as a caloric source in newborn infants. JPEN **6**(1), 25–9.
104. LLOYD-STILL, J.D., SIMON, S.H., WESSEL, H.U., and GIBSON, L.E. (1979). Negative effects of oral fatty acid supplementation on sweat chloride in cystic fibrosis. Pediatrics **64,** 50–2.
105. LLOYD-STILL, J.D., JOHNSON, S.B., and HOLMAN, R.T. (1981). Essential fatty acid status in cystic fibrosis and the effects of safflower oil supplementation. Am. J. Clin. Nutr. **34**(1), 1–7.
106. HUNT, C.E., ENGEL, R.R., MODLER, S., HAMILTON, W., BISSEN, S., and HOLMAN, R.T. (1978). Essential fatty acid deficiency in neonates: Inability to reverse deficiency by topical application of EFA-rich oil. J. Pediatr. **92**(4), 603–7.
107. CTFA. (1982). Submission of unpublished data by CTFA. Acute oral toxicity of 100 percent safflower oil in rats. CTFA Code No. 2-28-3.*
108. CTFA. (1983). Submission of unpublished data by CTFA. Acute oral toxicity of a body cream containing 3 percent safflower oil. CTFA Code No. 2-28-27.*
109. NAKAMURA, M., TANAKA, H., HATTORI, Y., and WATANABE, M. (1973). Biological effects of autoxidized safflower oils. Lipids **8**(10), 566–72.
110. AHLSTROM, A., JARVINEN, R., PACKALEN, L., and MAKINEN, E. (1974). Nutritional properties of a fraction separated from heated safflower oil. Med. Biol. **52**(2), 343–9.
111. FARID, M., BALDWIN, R.L., YANG, Y.T., OSBORNE, E., and GRICHTING, G. (1978). Effects of age, diet and lactation on lipogenesis in rat adipose, liver, and mammary tissues. J. Nutr. **108**(3), 514–24.
112. WATERMAN, R.A., ROMSOS, D.R., TSAI, A.C., MILLER, E.R., and LEVEILLE, G.A. (1975). Influence of dietary safflower oil and tallow on growth, plasma lipids and lipogenesis in rats, pigs and chicks. Proc. Soc. Exp. Biol. Med. **150**(2), 347–51.
113. MORIN, R.J. (1967). Longevity, hepatic lipid peroxidation, and hepatic fatty acid composition of mice fed saturated or unsaturated fat-supplemented diets. Experimentia **23**(12), 1003–4.
114. BIERI, J.G., and EVARTS, R.P. (1975). Vitamin E adequacy of vegetable oils. J. Am. Diet Assoc. **66**(2), 134–9.
115. PORTA, E.A., JOUN, N.S., and NITTA, R.T. (1980). Effects of the type of dietary fat at two levels of vitamin E in Wistar male rats during development and aging. I. Life span, serum biochemical parameters, and pathological changes. Mech. Aging Dev. **13**(1), 1–39.
116. LOFLAND, H.B., JR., CLARKSON, T.B., and BULLOCK, B.C. (1970). Whole-body sterol metabolism in squirrel monkeys, *Saimiri sciureus*. Exp. Mol. Pathol. **13**(1), 1–11.
117. CTFA. (1982). Submission of unpublished data by CTFA. Draize eye irritation assay on 100 percent safflower oil. CTFA Code No. 2-28-2.*
118. CTFA. (1983). Submission of unpublished data by CTFA. Rabbit eye irritation study on a body cream containing 3 percent safflower oil. CTFA Code No. 2-28-26.*
119. APPLIED BIOLOGICAL SCIENCES LABORATORIES (ABSL). (1980). Submission of unpublished data by CTFA. Modified Draize eye irritation study on a moisturizer containing 3 percent safflower oil. CTFA Code No. 2-28-21.*
120. ABSL. (1980). Submission of unpublished data by CTFA. Modified Draize eye irritation study on a night cream containing 3 percent safflower oil. CTFA Code No. 2-28-5.*
121. ABSL. (1980). Submission of unpublished data by CTFA. Modified Draize eye irritation study on a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-12.*
122. MORRIS, W.E., and KWAN, S.C. (1983). Use of the rabbit ear model in evaluating the comedogenic potential of cosmetic ingredient. J. Soc. Cosmet. Chem. **34**(5), 215–225.
123. CONSUMER PRODUCT TESTING COMPANY (CPTC). (1980). Submission of unpublished data by CTFA. Modified Kligman comedogenic assay on a moisturizer containing 3 percent safflower oil. CTFA Code No. 2-28-20.*
124. CPTC. (1980). Submission of unpublished data by CTFA. Modified Kligman comedogenic assay on a night cream containing 3 percent safflower oil. CTFA Code No. 2-28-9.*
125. CPTC. (1981). Submission of unpublished data by CTFA. Modified Kligman comedogenic assay on a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-18.*

126. CTFA. (1982). Submission of unpublished data by CTFA. Primary skin irritation study on 100 percent safflower oil. CTFA Code No. 2-28-1.*
127. CTFA. (1982). Submission of unpublished data by CTFA. Modified Magnusson-Kligman guinea pig maximization test for contact sensitization potential. CTFA Code No. 2-28-4.*
128. SAMULSKI, M.A., and WALKER, B.L. (1982). Maternal dietary fat and polyunsaturated fatty acids in the developing foetal rat brain. J. Neurochem. **39**(4), 1163–8.
129. MILLER, A.M., SHEEHAN, E.T., and VAVICH, M.G. (1969). Prenatal and postnatal mortality of offspring of cyclopropenoid fatty acid-fed rats. Proc. Soc. Exp. Biol. Med. **131**(1), 61–6.
130. BORGMAN, R.F., BURSEY, R.G., and CAFFREY, B.C. (1975). Influence of dietary fat upon rats during gestation and lactation. Am. J. Vet. Res. **36**(6), 795–8.
131. BORGMAN, R.F., BURSEY, R.G., and CAFFREY, B.C. (1975). Influence of maternal dietary fat upon rat pups. Am. J. Vet. Res. **36**(6), 799–805.
132. BORGMAN, R.F., and LIGHTSEY, S.F. (1977). Influence in rats of dietary fats during the perinatal period: Effects upon brain chemistry in dams and offspring. Am. J. Vet. Res. **38**(10), 1661–3.
133. LAMPTEY, M.S., and WALKER, B.L. (1976). A possible essential role for dietary linolenic acid in the development of the young rat. J. Nutr. **106**(1), 86–93.
134. CTFA. (1983). Submission of unpublished data by CTFA. Single insult human patch test on a body cream containing 3 percent safflower oil. CTFA Code No. 2-28-29.*
135. CTFA. (1980). Submission of unpublished data by CTFA. Human cumulative dermal irritation study on a moisturizer containing 3 percent safflower oil. CTFA Code No. 2-28-22.*
136. CTFA. (1980). Submission of unpublished data by CTFA. Human cumulative dermal irritation study on a night cream containing 3 percent safflower oil. CTFA Code No. 2-28-6.*
137. CTFA. (1980). Submission of unpublished data by CTFA. Human cumulative dermal irritation study on a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-13.*
138. CTFA. (1980). Submission of unpublished data by CTFA. Repeat insult patch test on a moisturizer containing 3 percent safflower oil. CTFA Code No. 2-28-23.*
139. CTFA. (1980). Submission of unpublished data by CTFA. Repeat insult patch test of a night cream containing 3 percent safflower oil. CTFA Code No. 2-28-8.*
140. CTFA. (1982). Submission of unpublished data by CTFA. Repeat insult patch test on a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-19.*
141. CTFA. (1982). Submission of unpublished data by CTFA. Repeat insult patch test on a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-16.*
142. CTFA. (1982). Submission of unpublished data by CTFA. Repeat insult patch test on a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-14.*
143. CTFA. (1980). Submission of unpublished data by CTFA. Repeat insult patch test of a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-11.*
144. CTFA. (1982). Submission of unpublished data by CTFA. Phototoxicity/allergy patch test on a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-15.*
145. CTFA. (1982). Submission of unpublished data by CTFA. Phototoxicity/allergy patch test on a night cream containing 5 percent safflower oil. CTFA Code No. 2-28-17.*