Final Report on the Safety Assessment of Sorbitan Caprylate, Sorbitan Cocoate, Sorbitan Diisostearate, Sorbitan Dioleate, Sorbitan Distearate, Sorbitan Isostearate, Sorbitan Olivate, Sorbitan Sesquiisostearate, Sorbitan Sesquistearate, and Sorbitan Triisostearate[1]

Sorbitan fatty acid esters are mono-, di-, and triesters of fatty acids and sorbitol-derived hexitol anhydrides. They function as surfactants in cosmetic formulations. Previously, the Cosmetic Ingredient Review (CIR) Expert Panel had reviewed the safety of several of these sorbitan fatty acid esters (Sorbitan Laurate, Sorbitan Oleate, Sorbitan Palmitate, Sorbitan Sesquioleate, Sorbitan Stearate, Sorbitan Trioleate, and Sorbitan Tristearate). This safety assessment is an addendum to that report that includes Sorbitan Caprylate, Sorbitan Cocoate, Sorbitan Diisostearate, Sorbitan Dioleate, Sorbitan Distearate, Sorbitan Isostearate, Sorbitan Olivate, Sorbitan Sesquiisostearate, Sorbitan Sesquistearate, and Sorbitan Triisostearate. Although concentrations of these ingredients up to 25% have been reported to be used, most commonly they are used at less than 10%. These esters may be hydrolyzed to the fatty acid and anhydrides of Sorbitol. Fatty Acids are absorbed and metabolized. Sorbitan fatty acid esters were relatively nontoxic via ingestion in acute and long-term studies. They were generally minimal to mild skin irritants in animal studies, except that Sorbitan Isostearate applied to the skin was a moderate irritant in one rabbit study and when injected intradermally caused mild to severe irritation in guinea pigs. Sorbitan fatty acid esters did not sensitize guinea pigs. The fatty acid component, tested alone, typically caused only slight irritation and sensitization, and was not photosensitizing. Sorbitan fatty acid esters were not ocular irritants. Fatty acids are normal components of diet for which no data were available concerning reproductive or developmental toxicity, but Sorbitol had no adverse effects on the reproduction of CD rats during a multigeneration feeding study and was not a reproductive toxin at doses of 3000 to 7000 mg/kg/day for 2 years. Overall these esters and their corresponding fatty acids were not mutagenic, but Sorbitan Oleate was reported to reduce DNA repair following ultraviolet radiation exposure in human lymphocytes in culture. Sorbitan Laurate and Sorbitan Trioleate were cocarcinogens in one mouse study, but Sorbitan Trioleate and Sorbitan Oleate were not tumor promoters in another study. In clinical tests, Sorbitan fatty acid esters were generally minimal to mild skin irritants and were nonsensitizing, but Sorbitan Sesquioleate did produce an allergic reaction in fewer than 1% of patients with suspected contact dermatitis and addition of Sorbitan Sesquioleate to the components of a fragrance mix used in patch testing increased both irritant and allergic reactions to the fragrance mix. Careful consideration was made of the data on the cocarcinogenesis of Sorbitan Laurate and Sorbitan Trioleate, but the high exposure levels, high frequency of exposure, and absence of a dose-response led to the conclusion that there was not a cocarcinogenesis risk with the use of these ingredients in cosmetic formulations. Accordingly, these ingredients were considered safe for use in cosmetic formulations under the present practices of use.

INTRODUCTION

Sorbitan Caprylate, Sorbitan Cocoate, Sorbitan Diisostearate, Sorbitan Dioleate, Sorbitan Distearate, Sorbitan Isostearate, Sorbitan Olivate, Sorbitan Sesquiisostearate, Sorbitan Sesquistearate, and Sorbitan Triisostearate are mono-, di-, and triesters of fatty acids and sorbitol-derived hexitol anhydrides.

The Cosmetic Ingredient Review (CIR) Expert Panel previously completed a safety assessment on other sorbitan fatty acid esters including Sorbitan Laurate, Sorbitan Oleate, Sorbitan Palmitate, Sorbitan Sesquioleate, Sorbitan Stearate, Sorbitan Trioleate, and Sorbitan Tristearate, concluding that these ingredients are safe as used in cosmetic formulations (Elder 1985). Summaries of selected data presented in that report, as well as new data on the ingredients previously reviewed, are included in this report.

This safety assessment completes the Panel's review of this family of sorbitan fatty acid esters.

As part of this safety assessment, the CIR Expert Panel considered its previous assessments of a number of related ingredients with findings as described below.

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Rebecca S. Lanigan and Torill A. Yamarik, former Cosmetic Ingredient Review staff, prepared this report. Address correspondence to F. Alan Andersen, Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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Coconut Oil, Coconut Acid, Hydrogenated Coconut Oil, and Hydrogenated Coconut Acid are safe for use as cosmetic ingredients (Elder 1986).

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are safe in the present practices of use and concentration in cosmetics (Elder 1987).

Isostearic Acid is safe as a cosmetic ingredient in the present practices of use (Elder 1983).

Summaries of data from those reports and other published sources are included as a further basis for assessing the safety in cosmetics of the Sorbitan Fatty Acid Esters.

CHEMISTRY

Definition and Structure

The Sorbitan Fatty Acid Esters are mono- and diesters of fatty acids and hexitol anhydrides derived from sorbitol. They conform to the formulas given in Figure 1, but can be depicted using a six-membered ring—shown as the tetrahydropyran form. Formulas were not available for Sorbitans Sesquiisostearate and Sesquistearate, which are mixtures of mono- and diesters of isostearic and stearic acids. These ingredients have no CAS numbers and are also known as Sorbitan, Monohexadecanoate and Anhydrosorbitol Sesquistearate, respectively (Wenninger and McEwen 1997).

The ingredients of this safety assessment are esters of caprylic, coconut, oleic, isostearic, and stearic acids, as well as fatty acids derived from refined olive oil, with hexitol anhydrides derived from sorbitol. The ingredients of the previous safety assessment (Elder 1985) are mono- and triesters of lauric, stearic, oleic, and palmitic acids, or mixtures of oleic acid esters, with sorbitol anhydrides (Wenninger and McEwen 1997). Table 1 provides a complete list of ingredients previously reviewed and ingredients addressed in this addendum.

"Sorbitan" is a generic name for anhydrides (cyclic ether tetrahydric alcohols) derived from sorbitol by removal of one molecule of water. Sorbitol is a crystalline hexahydric alcohol that occurs naturally in berries, plums, cherries, pears, apples, seaweed, and algae. In mammals, it is formed from glucose and then converted to fructose. Sorbitol is also found in deposits of the lens of patients with diabetes mellitus (Taylor 1988; Lewis 1993).

Chemical and Physical Properties

Sorbitan Caprylate has an acid value <6.00 mg KOH/g, a saponification value of 250 to 280 mg KOH/g, and an iodine value of <5 g I_2/100 g (Gattefossé S.A. 1998).

Sorbitan Olivate is an ivory-colored, waxy solid at 20°C with a slight, characteristic odor. It consists of 99.0% (minimum) of the active substance, and contains a maximum of 1.0% moisture. The melting point is 52°C to 55°C. Sorbitan Olivate has acid, iodine, and saponification values of 10 to 12, 3.0 (maximum), and 155 to 165, respectively. It is soluble in ethanol, almost soluble in vegetable oils, and dispersible in warm water (B&T Srl 1998).

Sorbitan fatty acid esters are waxy solids or viscous liquids that are soluble in organic solvents. For Sorbitans Stearate, Laurate, Sesquioleate, Oleate, Tristearate, Palmitate, and Trioleate, the maximum moisture contents were 1% to 2%, and the specific gravities (at 25°C) were generally 0.95 to 1.05. The acid values were 5 to 15, the saponification values were 135 to 190, and the hydroxyl values ranged from 55 to 80 for Sorbitans Trioleate and Tristearate to 182 to 360 for Sorbitans Stearate, Laurate, Sesquioleate, Oleate, and Palmitate.

Reactivity

Undiluted Sorbitan Fatty Acid Esters, as well as neutral, mildly alkaline, or mildly acidic solutions of these esters are stable at room temperature and within a pH range of 2 to 12. Hydrolysis occurs in the presence of water at high or low pH conditions (Elder 1985).

Analytic Methods

Commercially available (food-grade) Sorbitan Fatty Acid Esters have been analyzed using high-performance liquid chromatography (Garti et al. 1983). Sorbitan Palmitate consisted of 52% monoesters, 39% diesters, and 9% triesters. Sorbitan Stearate consisted of 45% to 56% monoesters, 33% to 40% diesters, and 9% to 17% triesters. Sorbitan Tristearate consisted of 38% monoesters, 31% diesters, and 31% triesters. Sorbitan Oleate consisted of 44% to 52% monoesters, 34% to 38% diesters, and 14% to 18% triesters. Sorbitan Trioleate consisted of 31% to 35% monoesters, 32% to 33% diesters, and 32% to 37% triesters. Sorbitan Sesquioleate was comprised of 36% monoesters, 38% diesters, and 26% triesters. Sorbitan Isostearate consisted of 44% monoesters, 33% diesters, and 23% triesters.

Sorbitan Stearate was also analyzed using gas chromatography (Tsuda et al. 1984; Brüschweiler and Hautfenne 1990). Confectionery products contained 0.1% to 0.63% Sorbitan Stearate, and average recoveries from samples spiked with 1.0% of the ester were 91% to 96% for isosorbide, 83% to 99% for 1,4-sorbitan, and 92% to 98% for D-sorbitol. Sorbitan Stearate content was calculated using the formula:

$$C = (W1 + W2 + W3)/(10{,}000 \times W \times f)$$

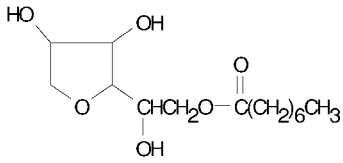
where C is the Sorbitan Stearate content (%); $W1$, $W2$, and $W3$ are isosorbide, 1,4-sorbitan, and D-sorbitol contents (μg), respectively; W is the sample weight (g); and f is a conversion factor of 0.27 (Tsuda et al. 1984).

Method of Manufacture

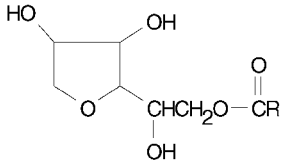
In general, Sorbitan Fatty Acid Esters are prepared by the dehydration of sorbitol (Figure 2) to form a hexitan, which is then esterified with the desired fatty acid (Gennaro 1990; Canterbery 1997).

Sorbitan Caprylate is produced by the esterification of sorbitol with caprylic acid (Gattefossé S.A. 1998) and Sorbitan

SORBITAN CAPRYLATE
No CAS No. or Synonyms

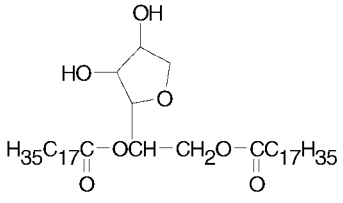


SORBITAN COCOATE
CAS No. 68154-36-9
Synonyms: Anhydrosorbitol Monococoate
Fatty Acids, Coco, Monoesters with Sorbitan
Sorbitan Monococoate

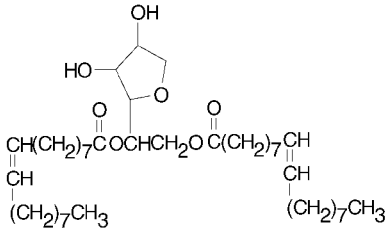


where RCO- represents the fatty acids
derived from coconut oil

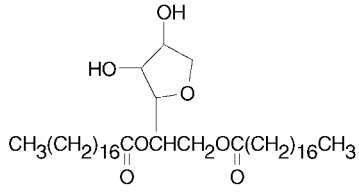
SORBITAN DIISOSTEARATE
CAS No. 68238-87-9
Synonym: Anhydrohexitol Diisostearate



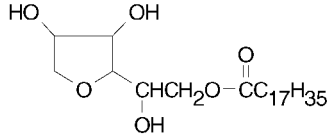
SORBITAN DIOLEATE
CAS No. 29116-98-1
Synonyms: Anhydrosorbitol Dioleate
Sorbide Dioleate
Sorbitan, Di-9-Octadecanoate



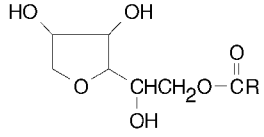
SORBITAN DISTEARATE
CAS No. 36521-89-8
Synonyms: Anhdrosorbitol Distearate
Sorbitan Dioctadecanoate



SORBITAN ISOSTEARATE
CAS No. 54392-26-6
Synonyms: 1,4-Anhydro-D-Glucitol, 6-Isooctadecanoate
Anhydrosorbitol Monoisostearate
D-Glucitol, 1,4-Anhydro-, 6-Isooctadecanoate
Sorbitan, Monoisooctadecanoate
Sorbitan Monoisostearate

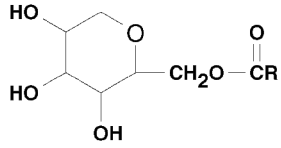


SORBITAN OLIVATE
No CAS No.
Synonyms: Anhydrosorbitol Monoolivate
Fatty Acids, Olive, Monoesters with Sorbitan
Sorbitan Monoolivate



where RCO- represents the fatty acids
derived from olive oil

GENERIC STRUCTURE - TETRAHYDROPYRAN FORM



where RCO⁻ equals the fatty acid moiety

FIGURE 1
Formulas for specific sorbitan esters, including a generic structure for the tetrahydropyran form.

TABLE 1
Ingredients previously reviewed by CIR and ingredients addressed in this report

New ingredients reviewed (this report)	Ingredients previously reviewed	Reference
Sorbitan Caprylate	Sorbitan Laurate	Elder 1985
Sorbitan Cocoate	Sorbitan Oleate	
Sorbitan Diisostearate	Sorbitan Palmitate	
Sorbitan Dioleate	Sorbitan Sesquioleate	
Sorbitan Distearate	Sorbitan Stearate	
Sorbitan Isostearate	Sorbitan Trioleate	
Sorbitan Olivate	Sorbitan Tristearate	
Sorbitan Sesquiisostearate		
Sorbitan Sesquistearate	Coconut acid	Elder 1986
Sorbitan Triisostearate	Hydrogenated Coconut acid	
	Isostearic acid	Elder 1983
	Oleic acid	Elder 1987
	Lauric acid	
	Palmitic acid	
	Myristic acid	
	Stearic acid	

Olivate is formed by the esterification of sorbitan with the wax obtained by partial hydrogenation of olive oil (B&T Srl 1998).

Impurities

Impurities such as free acid and alcohol, arsenic (<3 ppm), lead (<10 ppm), and water may be found in the Sorbitan Fatty Acid Esters (Elder 1985).

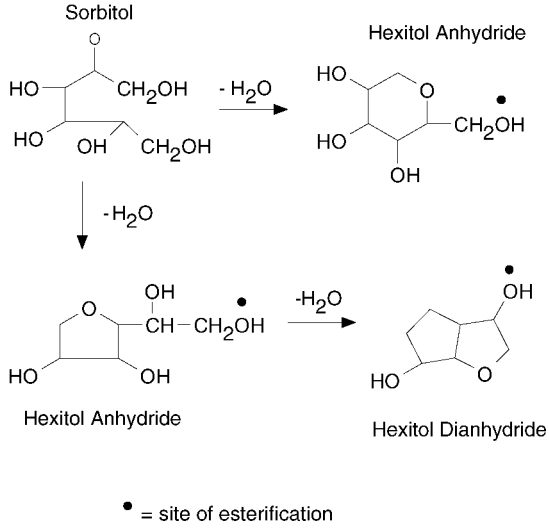


FIGURE 2
Mechanisms of Hexitol Anhydride Derivation (Canterbery 1997).

Polycyclic aromatic hydrocarbons and aflatoxins have been found as contaminants of copra and crude Coconut Oil; these impurities are removed by conventional refining processes (Elder 1986).

Cosmetic grade fatty acids occur as mixtures of several fatty acids, the content varying with method of manufacture and source. Fatty acid preparations can include up to 1.5% unsaponifiable matter, glyceryl monoesters of fatty acids, and butylated hydroxytoluene (Elder 1987).

Ultraviolet Absorption

Sorbitan Laurate at a concentration of 26,244 mg/l (in absolute ethanol) had maximum absorbance (2.0) at 230 nm; the absorbance was 0.1/2.0 at a wavelength of 350 nm. Sorbitan Sesquioleate (8,397 mg/l) had an absorbance of 1.98/2.0 at 245 nm and 0.1/2.0 at 320 nm. Sorbitan Palmitate (27,982 mg/l) had maximum absorbance at 220 nm and an absorbance of 0.1 at 350 nm. Sorbitan Trioleate (8,093 mg/l) had maximum absorbance at 250 nm and an absorbance of 0.1 at 320 nm (Elder 1985).

USE

Cosmetic

The Sorbitan Fatty Acid Esters function as surfactants—emulsifying agents in cosmetics (Wenninger and McEwen 1997). It was also reported that Sorbitan Isostearate functions as a pigment dispersant in creams (Unichema International 1996). In 1998, Sorbitan Isostearate, Sorbitan Laurate, Sorbitan Oleate, Sorbitan Palmitate, Sorbitan Sesquiisostearate, Sorbitan Sesquioleate, Sorbitan Stearate, Sorbitan Trioleate, and Sorbitan Tristearate were reported to the Food and Drug Administration (FDA) as used in 37, 93, 68, 39, 16, 170, 308, 20, and 8 product formulations, respectively (Table 2). Sorbitans Caprylate, Cocoate, Dioleate, Diisostearate, Distearate, Olivate, Sesquistearate, and Triisostearate were not reported used in cosmetics (FDA 1998).

In 1984, Sorbitan Isostearate was used at concentrations of 1% to 5%; Sorbitan Laurate was used at concentrations of 5% to 10%, but was mostly used at 1% to 5%; Sorbitan Oleate was used at concentrations of 10% to 25%, but was mostly used at 0.1% to 1%; Sorbitan Palmitate was used at concentrations of 0.1% to 5%; Sorbitan Peroleate was used at concentrations of 0.1% to 1%; Sorbitan Sesquiisostearate was used at concentrations of up to 5%; Sorbitan Sesquioleate was used at concentrations up to 5% to 10%, but was mostly used at concentrations of 0.1% to 1%; Sorbitan Stearate was used at concentrations up to 10% to 25%, but was mostly used at concentrations of 1% to 5%; Sorbitan Trioleate was used at concenrations up to 1% to 5%; and Sorbitan Tristearate was used at concentrations up to 5% to 10%, but was mostly used at 0.1% to 1% (FDA 1984).

Data submitted by industry indicated that Sorbitan Isostearate was used in concealers at concentrations up to 2.5% and in eye creams at concentrations of 4% (Cosmetic, Toiletry, and

TABLE 2
Product formulation data (FDA 1998)

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Sorbitan Isostearate		
Baby lotions, oils, powders, and creams	53	3
Eyebrow pencil	91	1
Eyeliner	514	1
Eye shadow	506	12
Other eye makeup preparations	120	2
Tonic, dressings, and other hair-grooming aids	549	1
Blushers (all types)	238	7
Foundations	287	2
Makeup bases	132	5
Other personal cleanliness products	291	1
Body and hand preparations (excluding shaving)	796	1
Other skin care preparations	692	1
1998 Sorbitan Isostearate total		**37**
Sorbitan Laurate		
Eyeliner	514	2
Eye lotion	18	2
Mascara	167	3
Other eye makeup preparations	120	2
Other fragrance preparations	148	5
Shampoos (noncoloring)	860	1
Other hair preparations	276	1
Foundations	287	14
Lipstick	790	15
Makeup bases	132	5
Makeup fixatives	11	2
Other makeup preparations	135	3
Aftershave lotion	216	2
Other shaving preparation products	60	2
Cleansing preparations	653	5
Body and hand preparations (excluding shaving)	796	7
Moisturizing preparations	769	10
Paste masks (mud packs)	255	4
Other skin care preparations	692	5
Suntan gels, creams, and liquids	136	2
Indoor tanning preparations	62	1
1998 Sorbitan Laurate total		**93**
Sorbitan Palmitate		
Bath oils, tablets, and salts	124	1
Eyebrow pencil	91	5
Eyeliner	514	3
Other eye makeup preparations	120	2
Other fragrance preparations	148	1
Hair conditioners	636	1
Hair straighteners	63	1
Lipstick	790	3
Other makeup preparations	135	3
Aftershave lotion	216	1

(Continued on next page)

TABLE 2
Product formulation data (FDA 1998) *(Continued)*

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Cleansing preparations	653	7
Body and hand preparations (excluding shaving)	796	1
Moisturizing preparations	769	3
Night preparations	188	1
Paste masks (mud packs)	255	3
Other skin care preparations	692	1
Suntan gels, creams, and liquids	136	1
Indoor tanning preparations	62	1
1998 Sorbitan Palmitate total		**39**
Sorbitan Oleate		
Eyeliner	514	1
Eye shadow	506	3
Eye makeup remover	84	1
Other fragrance preparations	148	4
Hair conditioners	636	2
Permanent waves	192	1
Tonics, dressings, and other hair-grooming aids	549	1
Other hair preparations	276	1
Blushers (all types)	238	2
Foundations	287	8
Lipstick	790	1
Makeup bases	132	2
Makeup fixatives	11	1
Other makeup preparations	135	2
Nail creams and lotions	17	1
Other manicuring preparations	61	2
Cleansing preparations	653	3
Body and hand preparations (excluding shaving)	796	4
Moisturizing preparations	769	18
Night preparations	188	3
Paste masks (mud packs)	255	2
Skin fresheners	184	3
Other skin care preparations	692	1
Other suntan preparations	38	1
1998 Sorbitan Oleate total		**68**
Sorbitan Sesquiisostearate		
Eye shadow	506	5
Other eye makeup preparations	120	1
Face powders	250	3
Foundations	287	6
Other makeup preparations	135	1
1998 Sorbitan Sesquiisostearate total		**16**
Sorbitan Sesquioleate		
Baby lotions, oils, powders, and creams	53	2
Other bath preparations	159	1
Eyebrow pencil	91	1
Eyeliner	514	3
Eye shadow	506	11

(Continued on next page)

TABLE 2
Product formulation data (FDA 1998) *(Continued)*

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Eye lotion	18	1
Eye makeup remover	84	1
Mascara	167	20
Other eye makeup preparations	120	5
Tonics, dressings, and other hair-grooming aids	549	1
Other hair preparations	276	1
Blushers (all types)	238	4
Face powders	250	10
Foundations	287	19
Lipstick	790	16
Makeup bases	132	1
Rouges	12	1
Other makeup preparations	135	5
Nail creams and lotions	17	1
Other manicuring preparations	61	1
Aftershave lotion	216	1
Cleansing preparations	653	11
Face and neck preparations (excluding shaving)	263	3
Body and hand preparations (excluding shaving)	796	6
Moisturizing preparations	769	12
Night preparations	188	10
Other skin care preparations	692	12
Suntan gels, creams, and liquids	136	8
Other suntan preparations	38	1
1998 Sorbitan Sesquioleate total		**170**
Sorbitan Stearate		
Baby lotions, oils, powders, and creams	53	4
Other baby products	29	1
Eyebrow pencil	91	15
Eyeliner	514	5
Eye shadow	506	3
Eye lotion	18	2
Eye makeup remover	84	1
Mascara	167	12
Other eye makeup preparations	120	3
Other fragrance preparations	148	9
Hair conditioners	636	4
Tonics, dressings, and other hair-grooming aids	549	4
Other hair preparations	276	1
Foundations	287	8
Makeup bases	132	2
Other makeup preparations	135	5
Cuticle softeners	19	3
Deodorants (underarm)	250	5
Other personal cleanliness products	291	1
Aftershave lotion	216	2
Shaving cream	139	1
Cleansing preparations	653	24

(Continued on next page)

TABLE 2
Product formulation data (FDA 1998) *(Continued)*

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Face and neck preparations (excluding shaving)	263	19
Body and hand preparations (excluding shaving)	796	57
Foot powders and sprays	35	2
Moisturizing preparations	769	56
Night preparations	188	11
Paste masks (mud packs)	255	11
Other skin care preparations	692	29
Suntan gels, creams, and liquids	136	3
Indoor tanning preparations	62	4
1998 Sorbitan Stearate total		**308**
Sorbitan Trioleate		
Eye shadow	506	1
Tonics, dressings, and other hair-grooming aids	549	1
Blushers (all types)	238	5
Face powders	250	1
Foundations	287	2
Makeup bases	132	2
Other makeup preparations	135	2
Cleansing preparations	653	2
Body and hand preparations (excluding shaving)	796	1
Moisturizing preparations	769	1
Night preparations	188	1
Other skin care preparations	692	1
1998 Sorbitan Trioleate total		**20**
Sorbitan Tristearate		
Makeup bases	132	1
Face and neck preparations (excluding shaving)	263	1
Moisturizing preparations	769	2
Paste masks (mud packs)	255	2
Other skin care preparations	692	1
Other suntan preparations	38	1
1998 Sorbitan Tristearate total		**8**

Fragrance Association [CTFA] 1998a). Sorbitan Caprylate functioned as an antistatic agent and was used at concentrations of 1% to 5% (Gattefossé S.A. 1998) and 2.5% to 7.5% Sorbitan Olivate served as an emulsifier (B&T Srl 1998).

Further data submitted by industry reported that Sorbitan Isostearate was used at a maximum concentration of 1% in eyebrow pencils, eyeliner, eye shadow, and all types of blushers, of 0.5% in other makeup preparations, 0.8% in moisturizing creams, lotions, powders, and sprays and at a maximum concentration of 0.2% in suntan gels, creams and liquids. Reported uses of Sorbitan Sesquiisostearate indicate maximum concentrations of 1% in eye shadow and all types of blushers and 3% in foundations, depilatories, and face powders (CTFA 1998d, 1999a).

The Sorbitan Esters of Fatty Acids and the Sorbitans Distearate, Isostearate, Cocoate, Isostearate, Laurate, Oleate, Palmitate, Stearate, Sesquiisostearate, Sesquioleate, Sesquistearate, Trioleate, and Tristearate are listed in the Japanese *Comprehensive Licensing Standards of Cosmetics by Category* (CLS) (Rempe and Santucci 1997).

Sorbitans Isostearate, Laurate, Oleate, Palmitate, Stearate, Sesquiisostearate, Sesquioleate, Sesquistearate, Trioleate, and Tristearate, which conform to the specifications of the *Japanese Standards of Cosmetic Ingredients* (JSCI) and *Japanese Cosmetic Ingredient Codex* (JCIC), have precedent for use without restriction in all CLS categories. Sorbitan Distearate and Sorbitan Trioleate, which conform to the specifications of the JCIC and JSCI, respectively, have precedent for use without restriction

in all CLS categories except Eyeliner Preparations, for which there is no precedent for use. Sorbitan Cocoate, which conforms to the specifications of the JCIC has precedent for use without restriction in all CLS categories except Eyeliner Preparations, Lip Preparations, Oral Preparations, and Bath Preparations, for which there is no precedent for use.

Sorbitan Isostearate and Sorbitan Sesquiisostearate are used in Japan at concentrations less than 5% (CTFA 1998b).

Noncosmetic

Polyalcohol isostearate esters, including Sorbitan Stearate, are used as lubricants or ingredients in lubricants, but "are not allowed to be used in any application implying (possible) food contact." These ingredients are not listed in any pharmacopoeia or national formulary (Unichema International 1996).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Sorbitan fatty acids were reported to affect the metabolism and excretion of other materials.

The Sorbitans Laurate, Palmitate, Stearate, Oleate, Sesquioleate, and Trioleate at concentrations of 50% and 100% increased the cumulative urinary excretion of pirenzepine dihydrochloride after oral administration to rats (dose = 2 mg/kg) within 24 hours of treatment. In this study, rats of the control group (12 rats) had cumulative urinary excretion of 2.7% pirenzepine dihydrochloride, whereas rats given Sorbitan Fatty Acid Esters (3–6/group) excreted 3.8% to 15.7% of the drug (Nakagawa et al. 1988).

When applied daily for 81 days to the skin of rabbits at test concentrations of 1% to 60%, Sorbitans Laurate, Stearate, Oleate, and Trioleate caused two- to threefold increases in oxygen consumption of the skin and increased numbers of inflammatory cells were observed in the dermis. In another study, treatment for 4 days with 10% Sorbitan Trioleate resulted in a 27% to 58% increase in phosphorus content using DNA content as a reference standard. After 10 days of treatment, phosphorus content increased 18% to 35%, suggesting that damage to the biological membranes had occurred. During a third study, 10% Sorbitan Trioleate increased the rate of water loss from rabbit skin, compared to control water loss time, but no significant difference in water content (Elder 1985).

Coconut Oil was used as a saturated fat control for metabolism studies and caused slight increases in serum cholesterol concentrations. The longevity of experimental animals in metabolism studies was not affected by diets containing Coconut Oil (Elder 1986).

Although data were unavailable on the absorption, distribution, and excretion of the Sorbitans Caprylate, Cocoate, Dioleate, Diisostearate, Distearate, Isostearate, Olivate, Sesquiisostearate, Sesquistearate, and Triisostearate, information from earlier safety assessments is provided below.

Sorbitan Stearate was hydrolyzed to stearic acid and anhydrides of sorbitol when ingested. Approximately 90% of the Sorbitan Stearate was absorbed and hydrolyzed when fed to rats in oil solution, and 50% was absorbed and hydrolyzed when fed as a water emulsion. Sorbitan Stearate did not accumulate (<0.5%) in the fat stores of the rat (Elder 1985).

Results of dietary studies suggest that 95% to 98% of ingested Coconut Oil is absorbed. No specific data were available indicating the extent of percutaneous absorption of Coconut Oil (Elder 1986).

Fatty acids are absorbed, digested, and transported in animals and humans. Radioactivity from labeled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph. β-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl coenzyme A (CoA). Although placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied, no studies on the teratogenicity of Oleic, Lauric, Palmitic, Myristic, or Stearic Acids were found. High intake of dietary saturated fatty acids has been associated with the incidence of atherosclerosis and thrombosis (Elder 1987).

Results of studies with rat liver homogenate have suggested that Isostearic Acid is readily metabolized following ingestion (Elder 1983).

Cytotoxicity

The cytotoxicity of Sorbitan Oleate was investigated using in vitro skin recombinants and primary cultures of human keratinocytes (Roguet, Dossoe, and Rougier 1992). These recombinants were comprised of human epidermal cells cultured at the air-medium interface on dead de-epidermized dermis. After a 24-hour exposure, 10% aqueous Sorbitan Oleate induced mild to no change in morphology of the skin recombinant. The ester (at concentrations up to 200 mg/ml) had only a small effect on membrane integrity of the keratinocytes, as measured by the amount of lactic dehydrogenase leakage to the media.

In addition, Sorbitan Oleate had no effect on mitochondrial activity, which was assessed by measuring the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to a MTT-formazan precipitate. The IC_{50} in the MTT assay was 2 mg/ml for the monolayer keratinocytes, and >200 mg/ml for the skin recombinants. In contrast, the IC_{50} values for 6% aqueous sodium dodecyl sulfate (SDS) were 1 and 0.07 mg/ml, respectively, and SDS induced a complete separation of the epidermis from the dermis.

ANIMAL TOXICOLOGY

The no-effect dose of Sorbitan Stearate was 7.5 g/kg/day after rats were treated with the ester for up to 2 years. Rats were fed Sorbitan Stearate concentrations of up to 25.0 g/kg/day and dogs were fed 5.0 g/kg/day of the ester. No adverse effects were noted after 24 months of treatment, with the exception of

retarded growth in rats of the high-dose group (Fitzhugh et al. 1959).

Five female ddY mice were treated with a single oral dose of Sorbitan Sesquiisostearate at a volume of 10 ml/kg body weight. The acute oral LD_{50} was 25 ml/kg, which was considered "practically nontoxic" under the conditions of the study (CTFA 1998c).

The results of oral toxicity studies of the Sorbitan Fatty Acid Esters indicated that these Sorbitans at low concentrations were relatively nontoxic via ingestion. The lowest LD_{50} for the rat in the 20 Sorbitan Ester studies was 31 g/kg for Sorbitan Stearate.

Prolonged feeding (8 weeks) of Sorbitan Stearate to rats did not affect growth, and other studies indicated that Sorbitan Stearate had nutritive value for rats and dogs. In subchronic feeding experiments of Sorbitan Laurate in a variety of species (chickens, rats, monkeys, and hamsters), no toxic effects were noticed when the ester concentration in the feed was less than 10%. When the feed concentration was $\geq$10%, growth depression, decreased organ weights, diarrhea, unkempt appearance, hepatic and renal abnormalities, and gastrointestinal tract irritation were generally observed. Subchronic feeding of Sorbitan Oleate to rats produced no abnormalities until the ester comprised at least 10% of the diet. At this concentration, the same types of abnormalities were observed that occurred in the Sorbitan Laurate–fed animals.

Chronic feeding studies have been conducted using Sorbitans Stearate, Laurate, and Oleate. At a 5% dietary concentration, Sorbitan Laurate and Sorbitan Oleate had no adverse effects on rats over a 2-year period. Dogs fed 5% Sorbitan Stearate for 20 months had no compound-related changes. A feed concentration of $\geq$10% Sorbitan Stearate was required to produce depressed growth and hepatic and renal abnormalities. Mice appeared more sensitive to toxic effects of Sorbitan Stearate than rats. In other studies, a 0.5% dietary concentration produced growth abnormalities in male rats, and a 4% dietary concentration produced renal abnormalities (Elder 1985).

Coconut Oil and Hydrogenated Coconut Oil are relatively nontoxic when ingested. Administered as a single 5-g/kg dose to rats, neither compound caused deaths over a 7-day observation period. In a 90-day subchronic feeding study, rats fed a diet containing 25% Coconut Oil had slight fatty change of the liver. The results of a chronic lifetime study in which mice were fed diets supplemented with 15% Hydrogenated Coconut Oil indicated no effect on life spans of the test animals (Elder 1986).

Little acute toxicity was observed when Oleic, Lauric, Palmitic, Myristic, or Stearic Acid, or cosmetic formulations containing these fatty acids at concentrations of 2.2% to 13% were given to rats orally at doses of 15 to 19 g/kg body weight. In subchronic oral toxicity studies, Oleic, Palmitic, and Stearic Acids were fed to rats at concentrations ranging from 5% to 50%. Thrombosis, aortic atherosclerosis, anorexia, and deaths were observed. In a subchronic study, no signs of toxicity were observed in chicks fed 5% dietary Stearic and Oleic Acids. Rats fed 15% Oleic Acid in a chronic study had normal growth and general health, but the reproductive capacity of female rats was impaired (Elder 1987).

In rats, the acute oral LD_{50} of Isostearic Acid is estimated to be greater than 32 ml/kg (Elder 1983).

Dermal Irritation and Sensitization

Sorbitan Isostearate was classified as a moderate irritant (primary irritation index, PII = 2.8/8.0) when applied to the skin of rabbits. Sorbitan Isostearate also had very low sensitization potential when tested in four Magnusson-Kligman guinea pig maximization studies. The induction concentrations were 1% to 2% (intradermal injection) and 50% to 100% (topical application), and the challenge concentrations were 10% to 25%. In addition, in a Landsteiner guinea pig test the intradermal injections of 0.2% Sorbitan Isostearate in propylene glycol caused mild to severe irritation in all animals, but did not cause sensitization reactions (Unichema International 1996).

Sorbitan Isostearate was described as nonirritating, nonsensitizing, noncomedogenic in repeat-insult patch test (RIPT) and comedogenicity protocols, and in the chorioallantoic membrane vascular assay (details unavailable) (CTFA 1998a).

The primary skin irritation potentials of Sorbitan Isostearate and Sorbitan Sesquiisostearate (both 10.0% in squalene) were evaluated using eight male Japanese white rabbits. The test materials were added to abraded and intact skin sites of the clipped back, and the sites were covered for 24 hours using patch-test plaster. The test sites were evaluated at 24 and 72 hours after administration of the test material. The PIIs were 0.3/8.0 and 0.5/8.0, respectively, which corresponded to a grade of non- to weak irritant.

Sorbitan Isostearate and Sorbitan Sesquiisostearate were weak cumulative irritants in a study using three male Hartley guinea pigs. A 0.05-ml volume of each test substance (10.0% in squalene) was applied to the clipped and shaved skin of the flank, once daily for 3 consecutive days. The treatment sites were examined for irritancy 24 hours after each application. The cumulative scores were 1.1/4.0 and 1.7/4.0, respectively (CTFA 1998c).

Data on the dermal irritation and sensitization potential of Sorbitans Caprylate, Cocoate, Dioleate, Diisostearate, Distearate, Olivate, Sesquistearate, and Triisostearate were not available.

Numerous skin irritation studies in animals indicate that the Sorbitan Fatty Acid Esters are minimal to mild irritants. Acute skin irritation tests with rabbits involving Sorbitan Stearate (1% to 60%) resulted in mild irritation. Sorbitan Laurate (1% to 100%) was mildly irritating to rabbit skin, causing dose-dependent erythema and edema. The rabbit dermal toxicity and irritation potential of Sorbitan Sesquioleate (3%) were minimal. Sorbitan Oleate (5% to 100%) was minimally irritating to rabbit skin. When solutions of Sorbitan Oleate were applied to rabbit skin, erythema and edema developed. Sorbitan Palmitate (4% to 50%) was tested for acute dermal irritation in the

rabbit and produced no irritation. A subchronic dermal study was negative for any systemic toxicity. Sorbitan Tristearate (30%) was nonirritating when applied to the skin of rabbits. Sorbitan Trioleate (1% to 100%) was a skin irritant in rabbits and produced erythema, edema, and thickening. No systemic toxicity was observed (Elder 1985).

Hydrogenated Coconut Oil was nontoxic when applied dermally. A single 3-g/kg dose applied to guinea pigs caused no deaths during a 7-day observation period. It was nonirritating to the skin in three single-insult occlusive patch tests. A primary irritation index of 0.11/8.0 indicating minimal irritation was reported in a fourth study. Hydrogenated Coconut Oil was not a sensitizer in guinea pigs when applied to the skin in a modified Buehler test. Coconut Oil did not cause skin irritation when applied to rabbit skin in a 24-hour single-insult occlusive patch test. It was nonsensitizing to the skin in a Magnusson-Kligman maximization test. Coconut Acid caused minimal irritation in rabbits when assayed in a 24-hour single-insult occlusive patch test. PIIs of 0.13/4.0 and 0.17/4.0 were reported for 10% Coconut Acid in corn oil and undiluted Coconut Acid, respectively. These scores were indicative of minimal skin irritation (Elder 1996).

Results from topical application of Oleic Acid (at concentrations from 50% Oleic Acid to commercial grade Oleic Acid) to the skin of mice, rabbits, and guinea pigs ranged from no toxicity to signs of erythema, hyperkeratosis, and hyperplasia. Intradermal administration to guinea pigs of 25% commercial grade Oleic Acid resulted in local inflammation and necrosis. A formulation containing 2.2% Palmitic Acid was considered nontoxic to rabbits. A topically applied dose of 5 g/kg commercial grade Stearic Acid was not toxic to rabbits. Intradermal administration of 10 to 100 mM Stearic Acid to guinea pigs and rabbits resulted in mild erythema and slight induration. Eighteen millimole percent concentrations of the fatty acids topically applied to the skin of the external ear canals of albino rabbits for 6 weeks produced a range of responses, varying from no irritation with Stearic Acid to slight irritation with Myristic and Palmitic Acids to defined erythema, desquamation, and persistent follicular keratosis with Oleic and Lauric Acids. Slight local edema and no deaths were observed among New Zealand white rabbits after 4 weeks of topical administration of product formulations containing 2.0% Stearic Acid.

In 13-week dermal toxicity studies, two cosmetic product formulations containing, at most, 5% Stearic Acid produced moderate skin irritation in rats receiving 4.0 ml/kg and 227 mg/kg doses. All other physiological parameters were normal. In single-insult occlusive patch tests for primary irritation, commercial grades of all five fatty acids (Myristic, Stearic, Lauric, Oleic, and Palmitic Acids), at doses of 35% to 65% in vehicles (Stearic Acid only) and at 1% to 13% in cosmetic product formulations (other fatty acids), produced no to moderate erythema and slight, if any, edema in the skin of rabbits. Slight increases in irritation were observed in the short-term repeated patch tests (daily for 3 to 14 days) of Oleic and Myristic Acids. In maximization studies with two cosmetic product formulations containing 5.08% Oleic Acid and 1.0% Stearic Acid, slight reactions were observed to challenge patches. These formulations were considered weak, grade I sensitizers. In another maximization study, after intradermal induction and booster injections of a formulation containing 3.5% Stearic Acid, reactions to topical challenge applications of the formulation were few and minimal in severity. Skin lotion formulations containing 2.8% Stearic Acid were not photosensitizing to the skin of Hartley guinea pigs. Oleic Acid and its ultraviolet A (UVA)-induced peroxides were associated with increased comedo formation in the skin of the treated external ears of two species of rabbits (Elder 1987).

Raw Isostearic Acid produced no significant skin irritation in Draize rabbit irritation tests, whereas variable degrees of irritation were produced by product formulations containing Isostearic Acid. A product formulation both with and without 2.5% Isostearic Acid was tested in a rabbit external ear comedogenicity assay. The formulation without Isostearic Acid was irritating but did not produce comedones; however, the formulation with Isostearic Acid was both irritating and comedogenic (Elder 1983).

Ocular Irritation

Sorbitan Isostearate was nonirritating to the eyes of rabbits during two studies (Unichema International 1996). When 0.1 ml (10.0% in squalene) was tested using three male Japanese White rabbits, the average total score was 4.0/110.0, which corresponded to a grade of minimal irritant. Using the same procedure, Sorbitan Sesquiisostearate (10.0% in squalene) was a minimal irritant to the eyes of rabbits, with an average total score of 6.7/110.0 (CTFA 1998c). Data on the ocular irritancy potential of Sorbitans Caprylate, Cocoate, Dioleate, Diisostearate, Distearate, Olivate, Sesquistearate, and Triisostearate were not available.

Ocular irritation studies using rabbits were performed with Sorbitan Fatty Acid Esters: one study using a concentration of 30% Sorbitan Stearate was negative for ocular irritation, and low concentrations (4%) in products caused slight conjunctival irritation. High concentrations of Sorbitan Sesquioleate (3.0% to 100%) produced no ocular irritation. One study with Sorbitan Laurate (30%), and two studies each using Sorbitans Oleate (5% to 100%), Tristearate (30% to 40%), and Palmitate (4.0% to 30%) were negative for ocular irritation in the rabbit (Elder 1985).

Results of several studies suggested that the ocular irritation potential of Coconut Oil and Hydrogenated Coconut Oil was low. Coconut Oil in Draize ocular tests scored a maximum of 2/110, indicating minimal irritation. Hydrogenated Coconut Oil was assayed in 10 Draize ocular tests. In nine tests, ocular irritation ($\leq$2/110) was minimal, and in one test, it was mild (6/110) (Elder 1986).

In ocular irritation studies, the fatty acids alone and at concentrations ranging from 1% to 19.4% in cosmetic product formulations produced no to minimal irritation after single and

multiple (daily, 14-day) instillations into the eyes of albino rabbits. Irritation was primarily in the form of very slight conjunctival erythema. A single instillation of Lauric Acid also produced corneal opacity and iritis (Elder 1987).

Raw Isostearic Acid produced no significant ocular irritation in Draize rabbit irritation tests, whereas variable degrees of irritation were produced by product formulations containing Isostearic Acid (Elder 1983).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No data were available on the reproductive and developmental toxicity of Sorbitan fatty acid esters.

MacKensie et al. (1986) performed a multigeneration feeding study to determine the reproductive and developmental effects of Sorbitol. Twelve male and 24 female Charles River CD (SD) BR rats per group were fed a diet containing 2.5%, 5.0%, or 10% Sorbitol (replacing the sucrose content of the basal feed) during a 96-week multigeneration study. The two high concentrations were "built up in 2.5% steps at weekly intervals." The F_0 rats were mated to produce the F_{1a} and F_{1b} litters. The F_{1b} rats were treated and mated to produce the F_{2a} and F_{2b} litters. The F_{2b} rats were treated and mated to produce the F_{3a} litters. Twelve rats/sex/group were fed the test diets for 4 weeks, then were killed. Gross examinations were performed on all mated animals and two rats/sex of the F_{1a} and F_{2a}. Gross and microscopic examinations and biochemical analyses were performed on the F_{3a} rats. In this study, the feeding of up to 10% Sorbitol to rats had no significant adverse clinical, behavioral, or reproductive effects, and no significant gross or microscopic changes were observed.

The safety of hydrogenated starch hydrolysates (HSH), which are mixtures of polyhydric alcohols such as ~7.0% Sorbitol, was investigated using a 2-year ingestion study (50 Sprague-Dawley rats/sex/group), a multigeneration reproduction study (20 rats/sex/group), and a teratology study (30 dams/group). At a concentration of 18% in drinking water (3000 to 7000 mg/kg/day), HSH did not produce reproductive or developmental effects (Modderman 1993).

GENOTOXICITY

Data on the mutagenicity of the Sorbitan fatty acids in this report were not available.

Inoue, Sunakawa, and Takayama (1980) reported that Sorbitan Stearate at concentrations of 0.01 to 300 μg/ml (in dimethyl sulfoxide, the vehicle control) did not induce in vitro transformation of hamster ovary cells. Sorbitan Stearate was not mutagenic in *Salmonella typhimurium* strains TA100 and TA98, with or without metabolic activation, when the ester was tested at concentrations up to 2000 μg/plate.

An unspecified Sorbitan Fatty Acid Ester (maximum dose = 5.0 mg/plate, in DMSO) was tested for mutagenicity in the Ames test using *S. typhimurium* strains TA92, TA94, TA98, TA100, TA 1535, and TA1537. In the chromosomal aberration test using Chinese hamster fibroblasts, a maximum dose of 0.3 mg/ml of the test compound (in DMSO) resulted in 5.0% polyploid cells and 8.0% structural aberrations 48 hours after treatment. The results were considered equivocal, and polyploidization effects were observed (Ishidate et al. 1984).

After being fed to adult *Drosophila*, Sorbitol was negative for whole chromosome loss and did not cause clastogenic effects or nondisjunction. In these studies, Sorbitol did not appear to cause sex-linked recessive lethals; however, it could not be classified as either positive or negative for mutagenic activity due to an inadequate sample size (Abbott and Bowman 1976)

Chinese hamster ovary cells in medium made hyperosmotic with Sorbitol had significant increases in the incidence of chromosomal aberrations. The test concentrations were 300 to 450 mM. The cells were harvested for aberration analysis 24 to 26 hours after the beginning of the 4-hour treatment period. Cells treated with 300 to 350 mM Sorbitan had 100% survival, and cells treated with 400 and 450 mM had 40% and 15% survival, respectively. Survival was measured after 6 days of colony formation, as a percentage of the untreated control value. The numbers of aberrations per 100 cells were 2 (control), 26 (300 mM; one cell was excluded), 11 (350 mM), 29 (400 mM), and 27 (450 mM; only 30 scoreable cells). The incidences of cells with aberrations were 2% (control), 8% (300 mM), 7% (350 mM), and 17% (400 and 450 mM). The investigators concluded that the increase in aberrations represented an indirect effect on the cells (Galloway et al. 1987).

The addition of sugars such as Sorbitol reduced the mutagenicity of smoke condensates of high- and low-tar cigarettes, as tested using *S. typhimurium* strains TA98 and TA100, with metabolic activation. Cigarettes treated with Sorbitol yielded more tar than untreated cigarettes. When 0.51 g Sorbitol was added to each high-tar cigarette, the percent mutagenicity per mg smoke condensate was 66% (TA100) and 37% (TA98), relative to cigarettes without added sugars. The percent mutagenicity per cigarette was 77% (TA100) and 46% (TA98). When 0.70 g Sorbitol was added to low-tar cigarettes, the percentages were 65% (TA100) and 23% (TA98) per mg smoke condensate and 184% (TA100) and 66% (TA98) per cigarette. The addition of sugars without metabolic activation had no effect on mutagenicity of the cigarette smoke condensates (Sato et al. 1979). In a study examining the role of inhibition of DNA repair as a mechanism in cocarcinogenesis, Sorbitan Oleate, at a concentration of 0.01%, was found to inhibit the repair of UV-irradiated DNA extracted from normal human lymphocytes (Gaudin et al. 1971).

Sorbitan Stearate was not mutagenic in bacteria with or without metabolic activation systems. Sorbitan Stearate did not transform primary Syrian golden hamster embryo cells in vitro (Elder 1985).

Although Oleic and Lauric Acids induced mitotic aneuploidy during in vitro mutagenicity tests, both were considered inhibitors of mutagenicity (produced by positive controls, such

TABLE 3
Macroscopic effects of Sorbitan Fatty Acid Ester on hepatocarcinogenesis (Yanagi et al. 1985)

		No. of rats with neoplasms		Neoplasms/group		Neoplasms/rat	
Treatment	No. of rats	All size neoplasms	Neoplasms ≥10 mm	All size neoplasms	Neoplasms ≥10 mm	All size neoplasms	Neoplasms ≥10 mm
Control	15	0	0	0	0	0	0
10% sorbitan ester	16	0	0	0	0	0	0
3′-Me-DAB	20	7 (35%)	4 (20%)	16	5	0.80	0.25
3′-Me-DAB + 5% sorbitan ester	21	15[a] (71.4%)	6 (28.6%)	35	13	1.67	0.62
3′-Me-DAB + 10% sorbitan ester	21	15[a] (71.4%)	9 (42.9%)	40	14	1.90	0.67
3′-Me-DAB + 0.1% phenobarbital	20	17[b] (85.0%)	11[b] (55.0%)	49	33	2.45	1.65

[a]Significantly different from group given 3′-Me-DAB alone; $p < .5$ (χ^2 test).
[b]Significantly different from group given 3′-Me-DAB alone; $p < .005$ (χ^2 test).

as *N*-nitrosopyrrolidine and sodium azide) in other tests. Stearic Acid was inactive in aneuploidy induction tests and in the Ames test, and it did not inhibit mutagenicity, as did Oleic and Lauric Acids. No increase of mitotic crossing-over events was induced by Oleic, Lauric, or Stearic Acids. Oleic Acid did not increase the number of sister chromatid exchanges over background (Elder 1987).

CARCINOGENICITY

Yanagi, Sakamoto, and Nakano (1986) noted that chemicals that enhanced formation of hyperplastic nodules in the rat liver also caused marked increases of pyruvate kinase (PK) activity. PK activity in rats was typically decreased during feeding of hepatic promoters and the extent of the decrease was inversely correlated with the doses. When an unspecified Sorbitan Fatty Acid Ester (55% palmitic acid) was added to the basal diet of male Wistar rats at a concentration of 10% for 2 to 4 weeks, a marked, persistent decrease in PK activity was observed in the liver.

During the second week of the study, the PK activities of five rats fed a basal diet alone were 169.2±3.7 and 100.0 μmol/min/g liver. During week 4, the activities were 164.2±6.5 μmol/min/g liver and 100.0 μmol/min/g liver. For four rats fed the Sorbitan Ester, PK activity was decreased from 128.5 to 75.9 μmol/min/g liver during week 2, and from 87.9 ± 1.6 to 53.5 μmol/min/g liver during week 4. The initial values for both weeks 2 and 4 were significantly different than those for the control group ($p < .01$ in week 2; $p < .001$ in week 4). The Sorbitan Ester was the only compound tested that decreased PK activity at both weeks 2 and 4.

Yanagi et al. (1985) fed the hepatocarcinogen 3′-methyl-4-dimethyl-aminoazobenzene (3′-Me-DAB) at a concentration of 0.06% for 6 weeks to male Wistar rats (15–21/group). The rats were then fed basal diet for two weeks, then were fed 5% to 10% of the Sorbitan Ester or 0.1% phenobarbital for the remaining 43 weeks of the study. The macro- and microscopic effects of treatment are described in Tables 3 and 4.

Thirty-five percent of the rats treated with the carcinogen alone had neoplasms. The incidence of neoplasms in rats fed

TABLE 4
Microscopic effects of Sorbitan Fatty Acid Ester on hepatocarcinogenesis (Yanagi et al. 1985)

	No. of rats with specific hepatic lesions				
Treatment	Large HN[a] (≥1 mm)	HCC[a]	BDF[a]	CF[a]	H[a]
Control	0	0	0	0	0
10% sorbitan ester	0	0	0	0	0
3′-Me-DAB	6 (30.0%)	6 (30.0%)	2 (10.0%)	11 (55.0%)	3 (15.0%)
3′-Me-DAB + 5% sorbitan ester	15 (71.4%)[b]	9 (42.9%)	3 (14.3%)	9 (42.9%)	4 (19.0%)
3′-Me-DAB + 10% sorbitan ester	18 (85.7%)[c]	10 (47.6%)	1 (4.8%)	10 (47.6%)	5 (23.9%)
3′-Me-DAB + 0.1% phenobarbital	19 (95.0%)[c]	13 (65.0%)[c]	6 (30.0%)	5 (25.0%)	3 (15.0%)

[a]HN = hyplastic nodules; HCC = hepatocellular carcinomas; BDF = bile duct proliferation; CF = cholangiofibrosis; H = hemangioma.
[b]Significantly different from group given 3′-Me-DAB alone; $p < .5$ (χ^2 test).
[c]Significantly different from group given 3′-Me-DAB alone; $p < .005$ (χ^2 test).

3′-Me-DAB plus the Sorbitan Ester at a concentration of 5% was 76.2%; for the group given the carcinogen and fed the 10% ester diet, the incidence was 90.5%. No neoplasms were observed in rats fed either the basal diet or the 10% Sorbitan Ester diet alone. The incidence of large hyperplastic nodules and/or hepatocellular carcinomas in rats fed the carcinogen alone was 45.0% at the end of 51 weeks. Metastatic lesions and cholangiocarcinomas were not observed in any group, and no differences in morphological characteristics were noted among the groups.

In addition, the investigators assayed the PK activity of the treated rats. Hepatic PK activities were approximately 100%, 60%, 50%, and 46% for rats (five/group) fed 0%, 5%, 10%, and 15% of the ester for 4 weeks, respectively. The relative promoting activity (RPA) of each test compound was determined. The RPA was the ratio of numbers of hyperplastic nodules or γ-glutamyltranspeptidase–positive foci per cm^2 between the experimental group and the control group; it was expressed as a ratio of percentages of tumor-bearers in the experimental and control groups. The investigators classified compounds with RPAs >1 as promoters. The RPA of the Sorbitan Ester was 2.0, compared to 107 for 3′-Me-DAB, which caused the formation of hyperplastic nodules. The investigators concluded that the Sorbitan Ester had an enhancing effect on hepatocarcinogenesis, but this effect was weak compared to that of up to 0.1% phenobarbital.

Sorbitan Stearate was fed to 48 male and 48 female TO strain mice at doses of 0%, 0.5%, 20%, or 40% of the diet for 80 weeks. Tumor type and incidence were two of the parameters studied. A majority of the tumors found in this study occurred either with comparable frequency in the test and control groups or more frequently in the control groups (Hendy et al. 1978).

The Sorbitan Fatty Acid Esters had no antitumor activity against Ehrlich ascites tumors in mice (Kato et al. 1970). In this study, one million tumor cells were inoculated intraperitoneally to 5-week-old ddY mice. A saline solution or suspension of the samples was administered once daily for 5 successive days. Tumor growth and body weight gain were determined after day 7, and the life span was observed (Table 5).

TABLE 5
Antitumor activity against Ehrlich ascites tumor cells (Kato et al. 1970)

Test compound	Dose (mg/mouse/day)	Tumor growth	Body weight gain (g)	Survival time (days)
Sorbitan Stearate	10.0	+++	+2.1	10
	2.5	+++	+3.6	12
Sorbitan Palmitate	10.0	+++	+5.2	11
	2.5	+++	+4.8	16
Sorbitan Laurate	6.0	++	+3.7	17
	1.5	+++	+4.2	18
Control	—	+++	+8.4	16

Carcinogenicity studies have been performed with Sorbitans Stearate and Laurate. Mice fed low concentrations of Sorbitan Stearate for 80 weeks had no difference in tumor type and incidence as compared to control animals. Sorbitan Laurate was inactive as a carcinogen or tumor promoter when painted on mouse skin for 70 weeks. However, in another study, Sorbitan Laurate was a tumor promoter when applied twice daily to mouse skin after initiation by 7,12-dimethylbenz(a)anthracene (DMBA). In the same study, Sorbitan Oleate and Sorbitan Trioleate were inactive as tumor promoters. In undiluted form, Sorbitan Laurate and Sorbitan Trioleate were active as cocarcinogens on mouse skin when applied with 0.003% DMBA (Elder 1985).

Coconut Oil was reported less effective than polyunsaturated fat as a tumor promoter for mammary tumors in rats induced by DMBA (Elder 1986).

In carcinogenicity studies, no malignant tumors were induced by repeated subcutaneous injections of 1 to 16.5 mg Oleic Acid in two species of mice. Intestinal and gastric tumors were found in mice receiving dietary Oleic Acid at daily concentrations up to 200 mg/mouse. Treatment of mice with repeated subcutaneous injections of 25 and 50 mg Lauric Acid was not carcinogenic. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of 25 and 50 mg Palmitic and up to 82 mg Stearic Acid. Feeding of up to 50 g/kg/day dietary Stearic Acid to mice was not carcinogenic (Elder 1987).

At a concentration of 18% in drinking water (3000 to 7000 mg/kg/day), hydrogenated starch hydrolysates (mixtures of polyhydric alcohols such as ~7.0% Sorbitol) did not produce evidence of carcinogenicity after 2 years of treatment. This study used 50 Sprague-Dawley rats/sex/group. No significant clinical signs of toxicity were observed (Modderman 1993).

In studies using rats, high dietary concentrations of Sorbitol caused enlargement of the cecum, increased absorption of calcium from the gut, increased urinary excretion of calcium, pelvic and corticomedullary nephrocalcinosis, acute tubular nephropathy, urinary calculus formation, and hyperplasia and neoplasia of the adrenal medulla. The investigator concluded that adrenal neoplasms observed in mice fed 20% Sorbitol were laboratory artifacts, and not indicative of human risk exposed to normal concentrations of Sorbitol in the diet (Roe 1984).

Cocarcinogenicity

Saffiotti and Shubik (1963) tested Sorbitan Laurate for both tumor-promoting activity and carcinogenicity in the skin using 50 male Swiss mice. Sorbitan Laurate was applied to a 2 × 2-cm area of the interscapular region kept free of hair by periodic clipping. During the carcinogenicity experiment, Sorbitan Laurate was applied twice weekly to the skin for 73 weeks. All animals were checked twice weekly for skin lesions. No carcinogenic effect was detected, with one animal out of 50 developing one papilloma. Control groups of 240 male and female mice from the same colony were kept untreated and observed over their lifespan. One papilloma appeared and regressed in one control

female and one skin papilloma and a carcinoma of skin appendages were each found in a control male.

Additional control groups of 100 males and 100 females were observed for over 100 weeks and had no signs of skin tumors. In the test of Sorbitan Laurate as a promoting agent, a single application of DMBA as a 1% solution in mineral oil was applied 1 week after the single application of the ester (dose not given) and thereafter the ester was applied twice weekly for 75 weeks. Five of the 50 animals developed eight tumors, one of which regressed. One of the eight tumors was a carcinoma. Two nonconcomitant control groups received the DMBA and no further treatment. One of the 100 control mice developed five tumors.

Setälä (1956) evaluated the promoting and cocarcinogenic activity of a variety of nonionic-lipophilic-hydrophilic agents, including Sorbitan Laurate, Oleate, and Trioleate. An initial single dose of 150 μg of DMBA (0.3% in paraffin) was painted on the backs of male mice (50 mice per group). The hair was cut from the treatment site twice weekly. The promoting agents were applied to the test site in doses that ranged between 51 and 87 mg once or twice daily, 6 days per week for 52 weeks.

Animals receiving Sorbitan Laurate once or twice daily after initiation had 10 tumors in 9 animals and 33 tumors in 21 animals, respectively. The Sorbitan Oleate group had five tumors in four animals. No tumors were observed in animals that received Sorbitan Trioleate after initiation. Additional details are available in Table 6.

Sorbitan Oleate and Trioleate were inactive as tumor promoters. Sorbitan Laurate was considered an active tumor promoter on mouse skin apparently based on the finding that doubling the frequency of application, without increasing the dose of carcinogen, increased significantly the mean incidence of tumor-bearing mice.

Setälä (1956) also investigated the cocarcinogenic activity of Sorbitans Laurate, Oleate, and Trioleate (exact dose not specified). DMBA of either 0.3% (150 μg), 0.03% (15 μg), or 0.003% (1.5 μg) was dissolved into the various Sorbitans and applied to the backs of mice (50 per group) three times per week. The hair was cut from the treatment site twice weekly. At the 0.3% DMBA dose the results were: Sorbitan Laurate, 240 tumors in 46 animals after 30 weeks; Sorbitan Oleate, 1 tumor in 1 animal after 10 weeks; Sorbitan Trioleate, 17 tumors in 8 animals after 17 weeks; and controls (DMBA in liquid paraffin), 200 tumors in 46 animals after 26 weeks.

The results for the 0.03% dose were: Sorbitan Laurate, 155 tumors in 31 animals after 30 weeks; Sorbitan Oleate, 168 tumors in 30 animals after 36 weeks; Sorbitan Trioleate, 130 tumors in 41 animals after 41 weeks; and controls (DMBA in liquid paraffin), 215 tumors in 39 animals after 34 weeks. At the 0.003% carcinogen dose, the results were: Sorbitan Laurate, 155 tumors in 35 animals after 52 weeks; Sorbitan Oleate, 25 tumors in 16 animals after 52 weeks; Sorbitan Trioleate, 57 tumors in 27 animals after 52 weeks; and controls (DMBA in liquid paraffin), 18 tumors in 13 animals after 52 weeks. Sorbitan Laurate and Sorbitan Trioleate were active on mouse skin as cocarcinogens when used as the solvent for 0.003% DMBA. Carcinomas did not develop on mouse skin when Sorbitan Oleate was used as a solvent for 0.003% DMBA.

TABLE 6
Mean incidence of tumor-bearing mice during a 10-week period (Setälä 1956)

Compound tested for tumor-promoting capacity	Mean incidence of tumor-bearing mice (%)
PEG Sorbitan Stearate	63
PEG Sorbitan Palmitate	48
PEG Sorbitan Trioleate	37
PEG Sorbitan Oleate (Tween 80)	27
Sorbitan Laurate	2.9
Sorbitan Oleate	1.5
PEG Sorbitan Laurate	1.1
PEG Sorbitan Oleate (Tween 81)	0
Sorbitan Trioleate	0
PEG Sorbitol Tetraoleate	0

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation and Sensitization

Frosch et al. (1995) reported a multicenter study using 709 patients with suspected contact dermatitis. The patients were tested with two fragrance mixes (one with Sorbitan Sesquioleate and one without), the mix components plus 1% Sorbitan Sesquioleate, the mix components alone, and 20% Sorbitan Sesquioleate in petrolatum, and petrolatum alone (control). The test series was applied for 2 days to the back with Finn Chambers on adhesive tape, and readings were made at two and three days. In some patients, repeated open application tests (ROATs) were performed to validate patch test results; in the ROAT, 0.2 ml of the test material was applied to a 10 × 10-cm area of the antecubital fossa or the external aspect of the upper arm, twice daily for 7 days.

Seven patients (0.98%) reacted to 20% Sorbitan Sesquioleate; five of the seven had "clearly allergic" reactions and two had "doubtful" or "irritant" reactions. Five patients had allergic reactions to the fragrance mix containing Sorbitan Sesquioleate and four had allergic reactions to the mix without the sorbitan ester. All five patients with a definite allergic reaction to 20% Sorbitan Sesquioleate reacted to the mix containing the ester, but not all reacted to at least one of the components, even when the ester was added at a concentration of 1%. When tested with the components without the ester, 41.5% of the patients had allergic reactions, compared to 54.7% of patients tested with the components plus ester.

If irritant and allergic reactions were considered, 38.3% of 73 patients had a positive "breakdown" result without Sorbitan Sesquioleate, versus 54.8% with the sorbitan ester. Allergic

reactions were increased by Sorbitan Sesquioleate, but the rank order of the top three sensitizers was not changed. The investigators concluded that the addition of Sorbitan Sesquioleate to the components of a fragrance mix increased both irritant and allergic reactions.

Tosti et al. (1990) patch-tested 737 patients with contact dermatitis with a series of emulsifiers commonly found in topical preparations, including Sorbitan Sesquioleate (20% in petrolatum), PEG-20 Sorbitan Palmitate (10% in petrolatum), and PEG-20 Sorbitan Oleate (10% in petrolatum). Of the 737 patients, 39 had positive results to one or more of the emulsifiers. Seven patients reacted to Sorbitan Sesquioleate, five reacted to PEG-20 Sorbitan Palmitate, and four reacted to PEG-20 Sorbitan Oleate.

Of the patients that reacted to Sorbitan Sesquioleate, one was sensitized to PEG-20 Sorbitan Oleate, one reacted to an antimycotic cream containing 2% Sorbitan Sesquioleate, and one reacted positively in a use test of a topical steroid containing 0.5% Sorbitan Sesquioleate, but gave a negative patch test to the preparation. Two patients reacted to PEG-20 Sorbitan Palmitate alone, one reacted to PEG-20 Sorbitan Oleate alone, and three reacted to both Polysorbates. Three patients were sensitized by leave-on cosmetics, and one was sensitized by an antimycotic cream containing 0.1% PEG-20 Sorbitan Oleate, 1.5% PEG-20 Sorbitan Stearate, and 2% Sorbitan Stearate.

Pache-Koo et al. (1994) tested a group of 47 patients with chronic or recurrent inflammatory skin diseases (leg ulcers, contact dermatitis, atopic dermatitis, psoriasis) and a group of 10 healthy subjects with a series of emulsifiers using Finn Chambers on Scanpor tape. Sorbitans Stearate, Oleate, and Sesquioleate, PEG-20 Sorbitan Oleate (Polysorbate 80), PEG-20 Sorbitan Palmitate (Polysorbate 40), and an unspecified PEG Sorbitol Lanolin derivative were tested. The test concentration for each Sorbitan Ester and Polysorbate was 10% in petrolatum, and the PEG Sorbitol Lanolin derivative was tested at a concentration of 20% in petrolatum.

One patient had a positive reaction (+) to Sorbitan Oleate, one patient had a (+) reaction to Sorbitan Stearate and a (++) reaction to Sorbitan Oleate, one patient had a (+) reaction to Sorbitan Sesquioleate, one patient had a (++) reaction to both Sorbitan Oleate and Sorbitan Sesquioleate, and one patient had a (+++) reaction to Sorbitan Oleate and a (++) reaction to Sorbitan Sesquioleate. No patients reacted to PEG-20 Sorbitan Palmitate, and one patient had a (+) reaction to both PEG-20 Sorbitan Oleate and the PEG Sorbitol Lanolin derivative. Positive reactions were also observed when the patients were treated with wound dressings or topical preparations containing emulsifiers. The majority of patients who reacted to the emulsifier series had leg ulcers. The healthy subjects and the remainder of the patients had no positive reactions to any of the emulsifiers tested.

Hannuksela, Kousa, and Pirilä (1976) tested common emulsifiers, including Sorbitan Stearate, Sorbitan Oleate, and Sorbitan Sesquioleate, for contact sensitization potential using 1206 patients with eczema. Epicutaneous tests were performed using the chamber method; the test sites were covered for 24 hours. The skin sites were evaluated 20 minutes, 1 day, and 3 to 4 days after removal of occlusion.

Of the patients, six (0.5%) had "allergic reactions" to 20% Sorbitan Sesquioleate in petrolatum, and five (0.4%) reacted to a mixture of 5% Sorbitan Oleate and 5% Stearate in petrolatum. Five (0.4%) and four (0.3%) patients had "toxic reactions" (irritant reactions) to Sorbitan Sesquioleate and Sorbitan Oleate/Sorbitan Stearate, respectively. Five patients sensitive to Sorbitan Sesquioleate had cross-sensitivity to the other two Sorbitan Esters, and one also reacted to PEG-20 Sorbitan Oleate and PEG-20 Sorbitan Palmitate. The irritation reactions were strongest on the first day and faded by day 5 of the study.

A 24-hour occlusive patch test was performed using 56 subjects. A 0.05-ml volume of Sorbitan Isostearate (10.0% in squalene) was applied to the intact skin of the forearm for 24 hours, when the treatment site was examined for signs of primary irritation. None of the subjects reacted to Sorbitan Isostearate under the conditions of this study. Sorbitan Sesquiisostearate (10.0% in squalene) was evaluated similarly using 10 subjects, none of whom reacted to the test material (CTFA 1998c).

Sorbitan Isostearate (2.5%) was tested in an RIPT using 201 subjects. During the induction period 48- to 72-hour occlusive patches containing 0.2 g of the test material were applied to the upper arm or back. Patches were applied three times per week for 3 weeks. After a 2-week nontreatment period, a 72-hour challenge patch was applied to a previously unexposed sight. Reactions were scored at 96 hours post application. Sorbitan isostearate did not induce a sensitization response (CTFA 1998a).

The Sorbitan Fatty Acid Esters are minimal to mild skin irritants in humans. Results from three RIPTs (involving a total of 420 subjects) indicated that Sorbitan Stearate was not a sensitizer. Products containing low concentrations of Sorbitan Stearate were mild irritants in 21-day cumulative irritation studies. A Schwartz prophetic patch test with Sorbitan Laurate produced no irritation. Human skin tests for sensitivity to Sorbitan Sesquioleate indicated that the compound was a nonsensitizer. Two Schwartz prophetic patch tests (60 subjects total) utilizing high concentrations of Sorbitan Sesquioleate produced no reactions. In five RIPTs involving 352 subjects, results indicated that none of the five products containing 1% to 3% Sorbitan Sesquioleate was a sensitizer; however, some subjects experienced mild irritation. Several products containing 1.75% to 2.0% Sorbitan Oleate have been tested on human subjects. In four 21-day cumulative irritation studies, the products tested were mildly irritating. In the tests using entire product formulations, the specific ingredient(s) causing irritation was not determined. Four RIPTs involving 339 subjects classified the Sorbitan Oleate–containing products as nonsensitizers (Elder 1985).

No irritation was observed in maximization tests. A product usage test on 53 subjects produced mild irritation in two individuals. A Schwartz prophetic patch test using Sorbitan Tristearate

produced no irritation in 211 panelists. Sorbitan Palmitate–containing skin products were found to be slightly irritating in humans in 21-day cumulative irritation tests (34 subjects total). In a Shelanski/Jordan RIPT (206 subjects), a skin care product containing Sorbitan Palmitate was nonirritating and nonsensitizing. Several products containing 5% Sorbitan Trioleate were tested on human subjects. Sorbitan Trioleate–containing products were slightly irritating in 21-day cumulative irritation tests, Shelanski/Jordan RIPT, Modified Schwartz-Peck predictive patch tests, and in a 4-week usage test (Elder 1985).

Clinical assessment of cosmetic products containing Coconut Oil has used a variety of assays. Bar soaps containing 13% Coconut Oil, when tested using standard Draize procedures, produced very minimal skin reactions. In a 2-week normal use test, bar soaps caused no unusual irritation responses. The results of soap chamber tests of bar soaps were minimal irritation in one study and mild irritation in another. No phototoxicity or photosensitivity was produced by these same bar soap formulations. A tanning butter containing 2.5% Coconut Oil did not cause erythematous reactions in a 6-week repeat insult predictive patch test. Lipstick containing 10% Hydrogenated Coconut Oil was tested using Schwartz-Peck prophetic patch procedures. No evidence of primary irritation was observed after a single patch application and no indication of sensitization was observed in retests performed 14 days later (Elder 1986).

In clinical primary and cumulative irritation studies, Oleic, Myristic, and Stearic Acids at concentrations of 100% or 40% to 50% in mineral oil were nonirritating. Mild to intense erythema in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies were produced by cosmetic product formulations containing 2% to 93% Oleic, Palmitic, Myristic, or Stearic Acid and were generally not related to the fatty acid concentrations in the formulations (Elder 1987).

In clinical RIPTs (open, occlusive, and semiocclusive), maximization tests, and prophetic patch tests with cosmetic product formulations containing Oleic, Lauric, Palmitic, and Stearic Acids at concentrations ranging from <1% to 13%, no primary or cumulative irritation or sensitization was reported. A few subjects (<5% of the approximate 4000 subjects tested) reacted to a few, isolated induction patches. Slight, if any, reactions were observed after challenge patching at original or adjacent sites on the upper backs or forearms of some subjects (~<2%). Intensity of observed reactions to the formulations was not directly related to the concentrations of the fatty acid ingredients. Cosmetic product formulations containing 1% to 13% Oleic, Palmitic, or Stearic Acid produced no photosensitization in human subjects. Slight reactions to a few induction patches were observed (Elder 1987).

In clinical studies, 100 subjects had no signs of irritation after a 24-hour single-insult skin patch with undiluted Isostearic Acid, and product formulations containing up to 4% Isostearic Acid produced, at most, minimal irritation when similarly tested using 221 subjects. In another study, 35% Isostearic Acid in mineral oil was neither an irritant nor a sensitizer in 168 subjects. A subset population of 25 individuals from this study group, when tested in a similar manner but exposed to UVA and UVB, gave no indication that Isostearic Acid was a photosensitizer. Isostearic Acid at 10% in mineral oil was neither irritating nor sensitizing for 103 subjects. Product formulations containing 2.5% to 2.85% Isostearic Acid produced no evidence of contact sensitization when tested in repeated insult patch tests on 333 subjects (Elder 1983).

Comedogenicity

A product containing 5% Sorbitan Isostearate was tested to determine its comedogenicity potential in 20 human subjects. Reactions that scored a value of one or greater, and were statistically different from the negative control, were considered positive for comedogenicity. Data from the global assessment of the test and the control values were compared statistically to determine biological significance ($p \leq .05$). No significant clinical irritation was observed during the study period. Reactions ranging from +0.5 to +1.0 were observed occasionally in 9 of the 20 subjects. Comparison of the test sites and untreated control sites through statistical analysis for the formation of microcomedone yielded a p value of greater than .05. It was concluded that this product did not elicit evidence of comedogenicity (CTFA 1998a).

Photosensitization

Photosensitization assessments on products containing Sorbitan Stearate or Sorbitan Oleate classified both products as nonphototoxic and nonphotoallergenic. Sorbitans Laurate, Sesquioleate, Palmitate, and Trioleate did not absorb radiation in the UVA and UVB range in UV spectral analysis (Elder 1985).

Ocular Irritation

No data were available on the ocular irritancy in humans of the Sorbitan Fatty Acid Esters.

No treatment-related ocular irritation was observed in female subjects, some of whom were contact lens wearers, involved in two 3-week exaggerated use studies of mascara formulations containing 2% and 3% Oleic Acid. These formulations were used in combination with other eye area cosmetics (Elder 1987).

Case Reports

A 63-year-old woman had palpable purpura over the legs and thighs and areas of necrosis. In a skin biopsy, the changes included superficial and deep perivenular infiltrate of neutrophils and lymphocytes, fibrin deposition, and extravasation of erythrocytes. The lesions improved after treatment with oral corticosteroids. Over the next year, she developed eczema of her legs and forearms, as well as a further episode of cutaneous vasculitis. The condition improved after treatment with topical and oral corticosteroids, but worsened after treatment was discontinued and after a wet dressing containing Sorbitan Sesquioleate

was applied. The patient was patch tested with the Portuguese Contact Dermatitis Research Group (GPEDC) standard, medicament, and fragrance series; Sorbitans Oleate and Sesquioleate (5% and 20%, respectively, in petrolatum) produced (++) and (+++) reactions. When fragrances without the Sorbitan Fatty Acid Esters were tested, the results were negative (Pereira, Cunha, and Das 1997).

A 23-year-old woman had hand dermatitis of 3 months duration and intense itching and burning of her hands followed within 2 hours of a topical application of a corticosteroid ointment. Low-grade erythema was observed on her fingers; the working diagnosis was contact urticaria syndrome, possibly immunologic in type, from a component of the ointment. Upon open testing, the patient developed an extensive wheal and flare to the application of 30 μl of 1% Sorbitan Sesquioleate in ethanol, but no reactions were observed after testing with the ethanol control and other components of the ointment (Hardy and Maibach 1995).

Mallon and Powell (1994) treated five patients that had chronic venous leg ulcers with a series of emulsifiers including Sorbitans Sesquioleate and Oleate (2% in petrolatum), PEG-20 Sorbitan Palmitate (10% in petrolatum), and PEG-20 Sorbitan Oleate (2% in petrolatum). All five patients had strong positive reactions to Sorbitan Sesquioleate on days 1 and 4 of the study. One patient had a positive reaction to a topical medication containing Sorbitan Sesquioleate, and two patients had positive reactions to Sorbitan Oleate.

SUMMARY

The Sorbitan Fatty Acid Esters are mono-, di-, and tri-esters of fatty acids and sorbitol-derived hexitol anhydrides. These ingredients function as surfactants in cosmetic formulations. In 1998, these ingredients were used in 759 product formulations. They were used at concentrations up to 25% in 1984, and recent industry data reported use concentrations up to 7.5%.

This safety assessment is an addendum to the Final Report on Sorbitan Laurate, Sorbitan Oleate, Sorbitan Palmitate, Sorbitan Sesquioleate, Sorbitan Stearate, Sorbitan Trioleate, and Sorbitan Tristearate. This review also includes Sorbitan Caprylate, Sorbitan Cocoate, Sorbitan Diisostearate, Sorbitan Dioleate, Sorbitan Distearate, Sorbitan Isostearate, Sorbitan Olivate, Sorbitan Sesquiisostearate, Sorbitan Sesquistearate, and Sorbitan Triisostearate. Few data were found on the safety of the latter group of ingredients, therefore, data on the previous Sorbitan Fatty Acid Esters, Sorbitol, Fatty Acids, and Coconut Acid have been added as a further basis for the assessment of safety.

When ingested by rats, Sorbitan Stearate was hydrolyzed to Stearic Acid and anhydrides of Sorbitol and did not accumulate in the fat stores of the body. Fatty Acids were absorbed, metabolized, and transported in animals and humans.

The Sorbitan Fatty Acid Esters were relatively nontoxic via ingestion, and the lowest acute oral LD_{50} reported was 31 g/kg (Sorbitan Stearate). The no-effect dose of Sorbitan Stearate was 7.5 g/kg/day using rats fed the ingredient for 2 years. The acute oral LD_{50} of Sorbitan Sesquiisostearate was 25 ml/kg in a study using female ddY mice.

The Sorbitan Fatty Acid Esters (concentrations up to 100%) were generally minimal to mild skin irritants in various animal studies. Sorbitan Isostearate, however, was a moderate irritant in one study using rabbits and intradermal injections of the ingredient caused mild to severe irritation in a study using guinea pigs. Concentrations up to 100% Sorbitan Isostearate had low sensitization potential in guinea pigs. Sorbitan Isostearate and Sorbitan Sesquiisostearate (10%) were non- to weak irritants to the intact and abraded skin of rabbits. The same concentrations caused weak cumulative irritation in a study using guinea pigs. In other studies, the ingredient did not produce significant irritation, sensitization, or comedone formation. The Fatty Acids typically caused only slight irritation, depending on the concentration, but 5% Stearic Acid produced moderate reactions in a study using rats. The Fatty Acids caused only slight sensitization and were not photosensitizing. In a rabbit external ear study, a formulation containing 2.5% Isostearic Acid was irritating and comedogenic.

The Sorbitan Fatty Acid Esters and Fatty Acids were generally not ocular irritants. In one study, Sorbitan Isostearate (10%) was nonirritating to the eyes of rabbits, whereas the same concentration of Sorbitan Sesquiisostearate was minimally irritating.

Fatty acids are normal components of diet for which no data are available concerning reproductive or developmental toxicity. Sorbitol (2.5% to 10%) had no adverse effects on the reproduction of CD rats during a multigeneration feeding study. Hydrogenated starch hydrolysates (~7% Sorbitol) were not reproductive toxins at doses of 3000 to 7000 mg/kg/day for 2 years.

Sorbitan Stearate did not transform hamster ovary cells and was nonmutagenic in *Salmonella*. Sorbitan Oleate inhibited in vitro DNA repair in one study. An unspecified Sorbitan Fatty Acid Ester had equivocal results in an Ames test and chromosome aberration assay using Chinese hamster fibroblasts. In a feeding study using rats, the ester altered PK activity in the liver, suggesting that the compound weakly enhanced hepatocarcinogenicity. The Fatty Acids were generally nonmutagenic. Oleic and Lauric Acids inhibited mutagenicity in one assay, but induced mitotic aneuploidy in another. Sorbitol was nonclastogenic and did not appear to cause sex-linked recessive lethal mutations. It did, however, indirectly increase the frequency of chromosome aberrations in hamster ovary cells. Sorbitol and other sugars reduced the mutagenicity of cigarette smoke condensates in *Salmonella* (with metabolic activation).

The Sorbitan Fatty Acid Esters had no antitumor activity against Ehrlich ascites tumors in mice. Sorbitan Stearate was neither a mouse skin carcinogen or tumor promoter. Sorbitans Laurate and Trioleate were cocarcinogens in one mouse skin study, but the latter ester and Sorbitan Oleate were not tumor promoters in another. The Fatty Acids and Sorbitol were noncarcinogenic.

In clinical studies, the Sorbitan Fatty Acid Esters were generally minimal to mild skin irritants in humans and were

nonsensitizing. In other studies, however, concentrations of 1% to 20% Sorbitan Sesquioleate increased the incidence of irritation or sensitization reactions produced in 709 patients with suspected contact dermatitis. Cross-sensitization was reported after 1206 patients with eczema were treated with 5% to 20% Sorbitans Stearate, Oleate, and Sesquioleate, and two Polysorbates. Sorbitan Isostearate and Sorbitan Sesquiisostearate (10%) were nonirritating in a 24-hour occlusive patch test using 56 subjects.

Formulations containing Sorbitan Stearate and Sorbitan Oleate were nonphototoxic and nonphotoallergenic; Sorbitans Laurate, Sesquioleate, Palmitate, and Trioleate did not absorb radiation in the UVA or UVB range.

The fatty acid moieties of these fatty acid esters, tested alone, were nonirritating during primary and cumulative irritation studies, and did not produce sensitization reactions in RIPTs. Oleic Acid was not a clinical ocular irritant.

DISCUSSION

Considering the available data on the Sorbitan fatty acid esters covered by this report, previous and new data on other Sorbitan fatty acid esters, and data on fatty acids, the Expert Panel concluded that the Sorbitan Fatty Acid Esters were safe as used in cosmetic formulations, which is expected to be up to 20%.

The Expert Panel did not choose a 10% concentration limit based on the predictive, single-insult human patch test study because single-insult patch testing was considered an inappropriate source for establishing such concentrations. An RIPT at 2.5% was negative, but in provocative testing with atopic patients at concentrations of 20%, little sensitization was seen.

The Expert Panel considered the finding that treatment of normal, human lymphocytes with 0.01% Sorbitan Oleate reduces DNA repair following UV irradiation, and the researchers' hypothesis that this effect may be a mechanism in cocarcinogenesis. The Panel carefully considered the data on the cocarcinogenesis of the Sorbitan Esters, noting the high exposure levels used, the high frequency of exposure, and the lack of a dose-response, and concluded that the positive response in these studies does not constitute a risk in cosmetic formulations.

CONCLUSION

The CIR Expert Panel concludes that Sorbitan Fatty Acid Esters are safe for use as cosmetic ingredients under the present practices of use.

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