JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 4, Number 3, 1985
Mary Ann Liebert, Inc., Publishers

3

Final Report on the Safety Assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate

The Sorbitan esters, including Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate, are used in cosmetic products as emulsifiers and stabilizers at concentrations normally under 5 percent. Toxicity was reported in subchronic and chronic studies at concentrations above that normally used in cosmetics. They are generally mild skin irritants but nonsensitizers in animals. They have the potential to induce cutaneous irritation in humans but not sensitization to normal skin.

Carcinogenic studies using Sorbitan Stearate and Laurate were negative. At concentrations of 10 percent or greater, Sorbitan Laurate is a tumor promoter in mouse skin. It is concluded that the latter is not relevant to the use of the Sorbitan esters at low concentrations in cosmetics and that the Sorbitan esters reviewed in the report are safe as cosmetic ingredients under present conditions of concentration and use.

INTRODUCTION

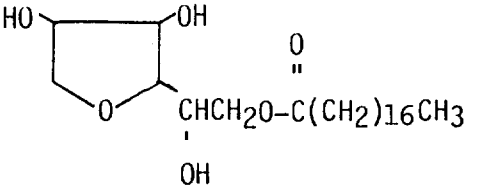
The Sorbitan fatty acid ester group includes the following ingredients: Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate. They are surfactants and are used primarily as emulsifiers, solubilizers, and stabilizers.[1-4]

CHEMICAL AND PHYSICAL PROPERTIES

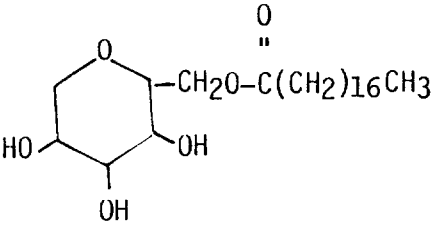
Structure

Sorbitan Stearate is the monoester of stearic acid and hexitol monoanhydride and dianhydride derived from sorbitol. It conforms to one of the following formulas:

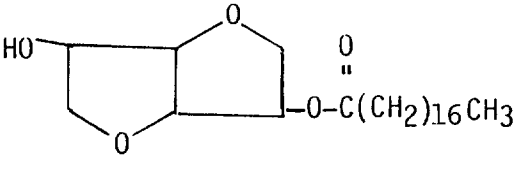
(a)



(b)



(c)

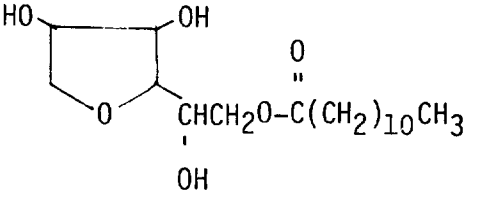


Sorbitan Stearate

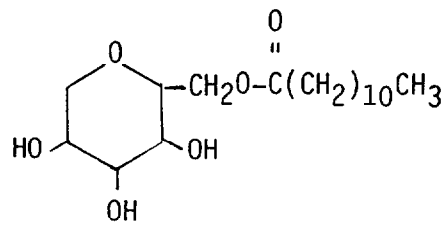
Synonyms include: Arlacel 60, Armotan MS, Copmul S, Emsorb 2505, Glycomul S, Hodag SMS, Liposorb S, Liposorb SC, Protachem SMS, Sorbitan Monostearate, Span 60.[2,4,5,7–9]

Sorbitan Laurate is the monoester of lauric acid and heixtol mono- and dianhydrides derived from sorbitol. Its structural formula is one of the following:

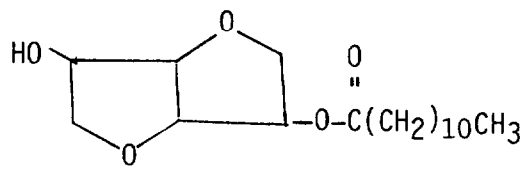
(a)



(b)



(c)

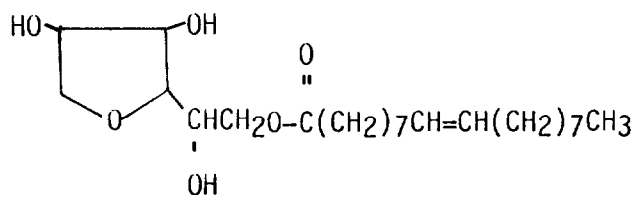


Sorbitan Laurate

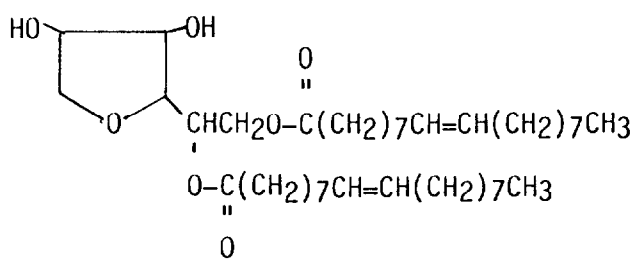
Other names include: Arlacel 20, Armotan ML, Emsorb 2515, Glycomul L, Glycomul LC, Liposorb L, Protachem SML, Sorbitan Monolaurate, Span 20.[2,4,5,7-9]

Sorbitan Sesquioleate is a mixed ester of oleic acid and hexitol anhydrides derived from sorbitol in a ratio of 1.5 moles of oleic acid to 1 mole of heixtol anhydrides. The structural formula is:

(a)



(b)



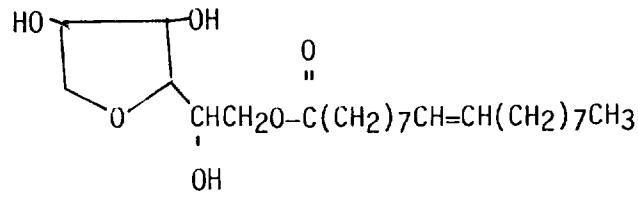
Sorbitan Sesquioleate

Other names include: Arlacel C, Arlacel 83, Emsorb 2502, Glycomul SOC, Hodag SSO, Liposorb SQO, Protachem SOC.[5,7,8]

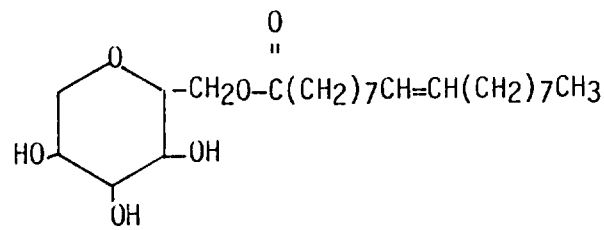
Sorbitan Oleate is the monoester of oleic acid and heixtol mono- and dianhy-

drides derived from sorbitol. It conforms to one of the following structural formulas:

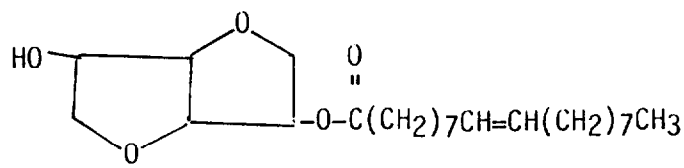
(a)



(b)



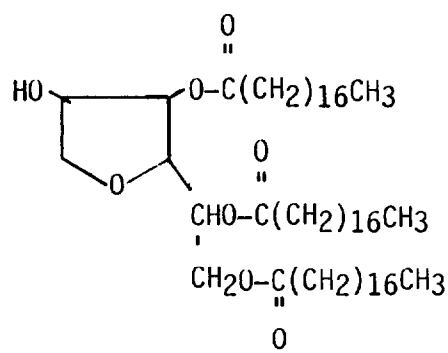
(c)



Sorbitan Oleate

Synonyms include: Arlacel 80, Armotan MO, Capmul O, Emsorb 2500, Glycomul 0, Liposorb O, Protachem SMO, Sorbitan Monooleate, Span 80.[1,2,5,7,8,13]

Sorbitan Tristearate is the triester of stearic acid and hexitol anhydrides derived from sorbitol. It has the structural formula:

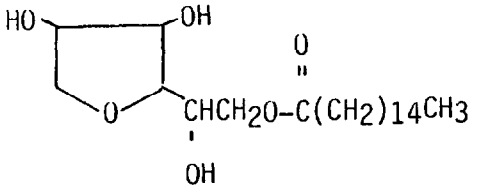


Sorbitan Tristearate

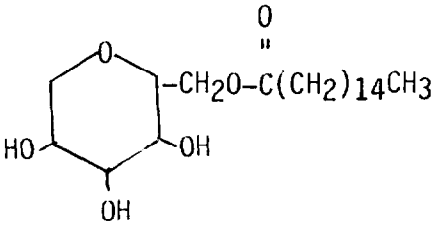
Other names include: Emsorb 2507, Glycomul TS, Liposorb TS, Protachem STS, Span 65.[2,5,7]

Sorbitan Palmitate is the monoester of palmitic acid and hexitol mono- and dianhydrides derived from sorbitol. The structural formulas may be:

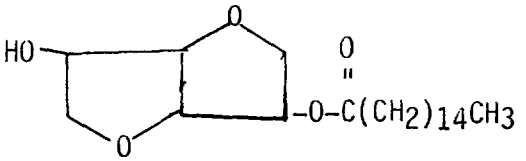
(a)



(b)



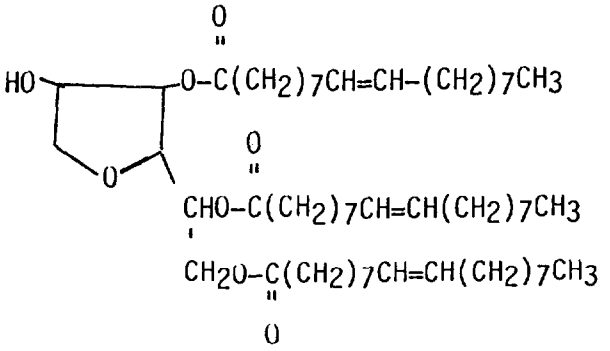
(c)



Sorbitan Palmitate

Synonyms include: Arlacel 40, Emsorb 2510, Glycomul P, Liposorb P, Protachem SMP, Sorbitan Monopalmitate, Span 40.[1,2,5,7,8]

Sorbitan Trioleate is the triester of oleic acid and hexitol anhydrides derived from sorbitol. Its structural formula is:



Sorbitan Trioleate

Other names include: Arlacel 85, Emsorb 2503, Glycomul TO, Liposorb TO, Protachem STO, Span 85.[5,7,8]

Properties

Generally, the Sorbitan fatty acid esters are solids or viscous liquids. They are insoluble or dispersable in water and soluble in organic solvents.[4,7,9] Specific properties of each Sorbitan ester are reported in Table 1.

Method of Manufacture

Each Sorbitan fatty acid ester is prepared by the reaction of sorbitol with the proper fatty acid at elevated temperatures. The methods of purification are proprietary.[6,10-12,14-16]

Reactivity

Undiluted Sorbitan fatty acid esters, as well as neutral, mildly alkaline, or mildly acidic solutions of Sorbitan esters are stable at room temperature. The compounds are stable within a pH range of 2 to 12. Hydrolysis occurs in the presence of water at high or low pH conditions.[1,6,10-12,14-16]

Analytical Methods

The Sorbitan fatty acid ester group can be identified through standard infrared spectroscopy.[7] Other standard assays specific for these types of compounds have been reported.[7,8,17] Thin-layer chromatography has been used for detection of this series of compounds.[18]

Impurities

The Sorbitan fatty acid esters may contain, as impurities, some residual free acid and alcohol. Minor impurities include arsenic (not more than 3 ppm), lead (not more than 10 ppm), and water.[8,17]

Ultraviolet Absorbance Spectra

UV absorbance spectra for Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Palmitate, and Sorbitan Trioleate were prepared using a Beckman 5240 double-beam recording instrument with 1 cm cells. All compounds were dissolved in absolute ethanol. At the highest concentration of Sorbitan Laurate (26,244 mg/liter), the maximum absorbance was at 230 nm and was down to 0.1 (maximum of 2.0) at a wavelength of 350 nm. Sorbitan Sesquioleate (8,397 mg/liter) had an absorbance of 1.98 (maximum of 2.0) at 245 nm and was 0.1 at 320 nm. Sorbitan Palmitate (27,982 mg/liter) had a maximum absorbance at 220 nm and was down to 0.1 at 350 nm. Sorbitan Trioleate (8,093 mg/liter) had maximum absorbance at 250 nm and was 0.1 at 320 nm. There was no absorbance in the UVA and UVB spectra for these compounds.[19,20]

USE

Purpose in Cosmetics

The Sorbitan fatty acid esters are lipophilic surfactants used to make emulsions. They also function as emulsion stabilizers and thickeners and as opacifiers in cosmetic creams and lotions.[1-3,6,10-12,14-16]

Noncosmetic Uses

The Sorbitan esters are added to foods and beverages as emulsifiers, stabilizers, rehydration aids, defoaming agents, and synthetic flavors.[2,4,21] Because they are emulsifiers, the Sorbitan esters are also used in drugs, textiles, and plastics.[2,22] See Table 2 for FDA regulations concerning Sorbitan esters.

Scope and Extent of Use in Cosmetics

These Sorbitan esters are added to a wide variety of cosmetics in concentrations of less than 0.1 to 25 percent. The majority of the products, however, contain concentrations of 0.1 to 5 percent as reported to the Food and Drug Administration (FDA) in 1981.

The cosmetic product formulation computer printout that is made available by the FDA is compiled through voluntary filing of such data in accordance with Title 21, part 720.4 of the Code of Federal Regulations.[23] 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 two- to ten-fold error in the assumed ingredient concentration.

See Table 3 for a listing of each ingredient, its frequency of use, and the concentration range in which it is found.[24]

Surfaces to Which Commonly Applied

Sorbitan fatty acid esters can be applied to all areas of the skin, hair, scalp, nails, and mucous membranes.[24]

Frequency of Application

The Sorbitan fatty acid esters are found in cosmetics that can be applied to the body as frequently as several times daily. These fatty acid esters are also ingredients of cosmetics used on a sporadic basis. Daily or occasional use may extend over many years.

Potential Interactions with Other Ingredients

The use of the Sorbitan esters as emulsifiers, stabilizers, and solubilizers of other cosmetic ingredients notwithstanding, no objectionable side reactions have been reported.

BIOLOGICAL PROPERTIES

Absorption, Metabolism, Deposition, and Excretion

The metabolism and deposition of Sorbitan Stearate were studied using nonfasted male rats. A single dose (dose range: 0.5 g/kg to 6.5 g/kg) of ^{14}C-labeled

TABLE 1. Properties of Sorbitan Fatty Acid Esters

Property	*S. Stearate*	*Reference*	*S. Laurate*	*Reference*	*S. Sesquioleate*	*Reference*
Normal state	Solid	1,7,8	Liquid	1,7,8	Liquid	7,8
Color	White to tan	1,7,8	Yellow	1,7,8	Yellow	7,8
Melting point (°C)	49–65	8				
Specific gravity (25°C)	0.98–1.03	1,2,6	1.0–1.06	1,2,6	0.95–1.00	2,7
Acid value	5–11.0	6–8	8 max	10	8.5–13.0	7,8,11
Saponification value	140–157	6–8	150–165	7,10	145–160	7,8,11
Hydroxyl value	230–260	6,7	330–360	7,10	182–215	7,11
Moisture content	1.5 percent max	7	1.0 percent max	7	1.0 percent max	7
Soluble in	Organic solvents Alcohols Carbontetrachloride Toluene	1,2,6	Isopropyl alcohol Mineral oil Methanol Ethanol Ethylene glycol Cottonseed oil	1,7,10	Alcohol Vegetable oils Mineral oil	7,11
Insoluble in	Water Mineral spirits Acetone	1,2,6	Water Propylene glycol	1,2,7,10	Water Propylene glycol	2,7,11

Property	*S. Oleate*	*Reference*	*S. Tristearate*	*Reference*
Normal state	Liquid	1,7,8	Solid	7
Color	Yellow to amber	1,7,8,13	Creamy white	7
Melting point (°C)			~54	2
Specific gravity (25°C)	~1.0	2,12	~1.0	2
Acid value	8 max	12	12–15	7,14

Saponification value	140–160	7,12	176–188	7,14
Hydroxyl value	193–215	7,12	66–80	7,14
Moisture content	1.0 percent max	7	1.0 percent max	7
Soluble in	Isopropyl alcohol Mineral oil Ethanol Vegetable oil	1,7,12,13	Isopropanol Ethanol Warm mineral oil Warm vegetable oil	7,14
Insoluble in	Water Propylene glycol	7,12 1,2,13	Water Propylene glycol	7,14 2

Property	*S. Palmitate*	*Reference*	*S. Trioleate*	*Reference*
Normal state	Solid	1,7,8	Liquid	7,8
Color	Creamy white	1,7,8	Yellow	7,8
Melting point (°C)	~54	2		
Specific gravity (25°C)	1.0–1.05	1,2		
Acid value	8 max	7,15	15 max	7,8,16
Saponification value	135–150	7,8,15	170–190	7,8,16
Hydroxyl value	275–305	7,15	55–75	7,16
Moisture content	2.0 percent max	7	1.0 percent max	7
Soluble in	Isopropanol Vegetable oils	7,15	Isopropanol Mineral oil Cottonseed oil Corn oil Methanol Ethanol	7,16
Insoluble in	Water Propylene glycol Ethanol	1,2,7,15	Water Propylene glycol	2,7,16

TABLE 2. FDA Regulation Status of Sorbitans Found Safe for Human Consumption

1982 21 CFR Part*	*Ingredient(s)*	*Category*	*Food/Product Type*	*Usage Limit*
172.515	S. Stearate	Direct food additive (DFA)	Synthetic flavoring	No limit set; to be used in minimum quantity required to produce intended effect
172.842	S. Stearate	DFA	Whipped edible oil topping	0.27 percent of final weight when used with polysorbate
			Cakes and cake mixes	0.61 percent when used alone; 0.66 percent when used with polysorbate
			Nonstandardized confectionary coating and standardized cacao products	1 percent
			Cake icings	0.7 percent by weight
			Milk or cream substitutes	0.4 percent total with or without polysorbate
			Mineral oil, petroleum wax, raw fruit or vegetable coating	No limit set; to be used in minimum quantity to produce intended effect
			Active dry yeast production	1 percent by weight
572.960	S. Stearate	N/A	Animal feed and drinking water	No limit set; may be used alone or in combination with polysorbate 60 as an emulsifier in mineral premixes and dietary supplements for animal feed
175.105	S. Stearate S. Oleate	Indirect food additive (IFA)	Adhesives	Either separated by functional barrier or subject to limits established for Good Manufacturing Practices (GMP)
175.320	S. Stearate S. Laurate S. Sesquioleate S. Oleate S. Tristearate S. Palmitate S. Trioleate	IFA	Resinous and polymeric coating	Coating applied as continuous film over one or both sides of a base film produced from one or more of the basic olefin polymers complying with 177.1520
178.3400	S. Stearate S. Laurate S. Oleate S. Palmitate	IFA	Emulsifiers and/or surface-action agents	No limit set; use amount reasonable required to accomplish intended technical effect

*CFR, Code of Federal Regulations.

TABLE 3. Product Formulation Data[24]

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations within Each Concentration Range (percent)				
			>10–25	>5–10	>1–5	>0.1–1	≤0.1
Sorbitan Stearate							
Baby lotions, oils, powders, and creams	56	1	–	–	–	1	–
Other bath preparations	132	2	–	–	–	2	–
Eyebrow pencil	145	4	–	–	–	4	–
Eyeliner	396	2	–	–	1	1	–
Eye shadow	2582	24	1	–	9	14	–
Eye lotion	13	1	–	–	1	–	–
Mascara	397	3	–	2	–	1	–
Other eye makeup preparations	230	5	–	–	5	–	–
Colognes and toilet waters	1120	1	–	–	–	1	–
Perfumes	657	1	–	–	–	1	–
Sachets	119	5	–	–	5	–	–
Other fragrance preparations	191	3	–	–	–	3	–
Hair rinses (noncoloring)	158	2	–	–	1	1	–
Tonics, dressings, and other hair grooming aids	290	2	–	–	2	–	–
Other hair preparations (noncoloring)	177	2	–	–	2	–	–
Other hair coloring preparations	49	1	–	–	1	–	–
Blushers (all types)	819	8	–	–	1	7	–
Makeup foundations	740	10	–	–	3	7	–
Lipstick	3319	1	–	–	–	–	1
Makeup bases	831	7	–	–	2	5	–
Deodorants (underarm)	239	5	–	–	–	5	–
Shaving cream (aerosol, brushless, and lather)	114	7	–	–	2	5	–
Other shaving preparation products	29	1	–	–	1	–	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	70	–	3	37	16	4
Face, body,and hand skin care preparations (excluding shaving preparations)	832	33	–	–	14	17	2
Moisturizing skin care preparations	747	66	–	5	48	13	–
Night skin care preparations	219	23	–	1	20	2	–
Paste masks (mud packs)	171	5	–	–	1	4	–

TABLE 3. (Continued)

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations within Each Concentration Range (percent)				
			>10–25	>5–10	>1–5	>0.1–1	≤0.1
Skin lighteners	44	1	–	–	–	1	–
Other skin care preparations	349	8	–	–	4	4	–
Suntan gels, creams, and liquids	164	3	–	–	3	–	–
Indoor tanning preparations	15	4	–	–	4	–	–
Other suntan preparations	28	3	–	–	1	2	–
1981 TOTALS		314	1	11	178	117	7
Sorbitan Laurate							
Baby shampoos	35	1	–	–	–	1	–
Eyeliner	396	2	–	–	–	2	–
Eye shadow	2582	1	–	–	1	–	–
Mascara	397	1	–	1	–	–	–
Wave sets	180	1	–	–	1	–	–
Other hair preparations (noncoloring)	177	1	–	–	1	–	–
Blushers (all types)	819	1	–	–	1	–	–
Lipstick	3319	49	–	–	23	26	–
Makeup bases	831	3	–	–	2	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	68	1	–	–	1	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	1	–	–	1	–	–
Moisturizing skin care preparations	747	3	–	–	–	3	–
Night skin care preparations	219	1	–	–	1	–	–
Paste masks (mud packs)	171	1	–	–	1	–	–
Indoor tanning preparations	15	1	–	–	1	–	–
1981 TOTALS		68	0	1	34	33	0

Sorbitan Sesquioleate							
Bath oils, tablets, and salts	237	1	–	–	–	1	–
Eyeliner	396	4	–	–	1	–	3
Eye shadow	2582	137	–	–	3	134	–
Eye makeup remover	81	2	–	1	1	–	–
Mascara	397	38	–	1	27	10	–
Other eye makeup preparations	230	10	–	–	2	8	–
Sachets	119	14	–	–	–	14	–
Hair conditioners	478	4	–	–	1	3	–
Hair rinses (noncoloring)	158	1	–	–	1	–	–
Tonics, dressings, and other hair grooming aids	290	9	–	–	7	1	1
Other hair preparations (noncoloring)	177	2	–	1	1	–	–
Blushers (all types)	819	35	–	–	11	23	1
Face powders	555	32	–	–	2	30	–
Makeup foundations	740	15	–	1	5	9	–
Lipstick	3319	5	–	–	4	1	–
Makeup bases	831	11	–	–	1	10	–
Rouges	211	9	–	–	2	7	–
Makeup fixatives	22	1	–	–	1	–	–
Other makeup preparations (not eye)	530	16	–	–	4	10	2
Deodorants (underarm)	239	1	–	–	–	1	–
Other personal cleanliness products	227	1	–	–	1	–	–
Shaving cream (aerosol, brushless, and lather)	114	2	–	–	2	–	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	34	–	1	22	10	1
Face, body, and hand skin care preparations (excluding shaving preparations)	832	13	–	–	8	5	–
Hormone skin care preparations	10	2	–	1	1	–	–
Moisturizing skin care preparations	747	33	–	2	11	20	–
Night skin care preparations	219	21	–	4	9	6	2
Paste masks (mud packs)	171	1	–	–	–	1	–
Wrinkle smoothers (removers)	38	1	–	1	–	–	–
Other skin care preparations	349	8	–	–	4	4	–
Suntan gels, creams, and liquids	164	5	–	–	2	3	–
1981 TOTALS		468	0	13	134	311	10

TABLE 3. (Continued)

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations within Each Concentration Range (percent)				
			>10–25	>5–10	>1–5	>0.1–1	≤0.1
Sorbitan Oleate							
Baby lotions, oils, powders, and creams	56	1	–	–	–	1	–
Eye shadow	2582	31	1	–	–	28	2
Other eye makeup preparations	230	1	–	–	–	1	–
Fragrance powders (dusting and talcum, excluding after-shave talc)	483	1	–	–	–	1	–
Hair conditioners	478	2	–	–	1	1	–
Tonics, dressings, and other hair grooming aids	290	1	–	–	–	1	–
Blushers (all types)	819	2	–	–	–	–	2
Makeup foundations	740	8	–	–	–	7	1
Lipstick	3319	1	–	–	–	–	1
Makeup bases	831	11	–	–	–	11	–
Rouges	211	2	–	–	–	1	1
Makeup fixatives	22	1	–	–	–	–	1
Cuticle softeners	32	1	–	–	–	1	–
Other manicuring preparations	50	2	–	–	1	1	–
Other personal cleanliness products	227	2	–	–	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	12	–	1	9	2	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	13	–	–	4	9	–
Moisturizing skin care preparations	747	17	–	–	10	6	1
Night skin care preparations	219	2	–	–	2	–	–
Skin fresheners	260	2	–	–	–	2	–
Other skin care preparations	349	1	–	–	–	–	1
Suntan gels, creams, and liquids	164	3	–	–	3	–	–
1981 TOTALS		117	1	1	30	75	10

Sorbitan Tristearate							
Eyeliner	396	2	–	–	–	2	–
Other fragrance preparations	191	2	–	–	2	–	–
Makeup foundations	740	1	–	–	–	–	1
Aftershave lotions	282	1	–	–	1	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	9	–	–	7	2	–
Moisturizing skin care preparations	747	4	–	–	1	3	–
Night skin care preparations	219	2	–	–	1	1	–
Other skin care preparations	349	2	–	–	–	2	–
Suntan gels, creams, and liquids	164	1	–	–	–	1	–
Other suntan preparations	28	1	–	–	–	1	–
1981 TOTALS		25	0	0	12	12	1
Sorbitan Palmitate							
Eye shadow	2582	1	–	–	–	1	–
Hair conditioners	478	2	–	–	1	1	–
Hair straighteners	64	1	–	–	1	–	–
Permanent waves	474	3	–	–	–	3	–
Hair rinses (noncoloring)	158	1	–	–	–	1	–
Tonics, dressings, and other hair grooming aids	290	2	–	–	2	–	–
Blushers (all types)	819	1	–	–	–	1	–
Makeup bases	831	1	–	–	1	–	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	17	–	–	16	1	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	4	–	–	4	–	–
Moisturizing skin care preparations	747	4	–	–	2	2	–
Night skin care preparations	219	1	–	–	1	–	–
Wrinkle smoothers (removers)	38	1	–	–	1	–	–
Other skin care preparations	349	1	–	–	–	1	–
Indoor tanning preparations	15	1	–	–	1	–	–
1981 TOTALS		41	0	0	30	11	0

TABLE 3. (Continued)

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations within Each Concentration Range (percent)				
			>10–25	>5–10	>1–5	>0.1–1	≤0.1
Sorbitan Trioleate							
Hair conditioners	478	1	–	–	1	–	–
Tonics, dressings, and other hair grooming aids	290	1	–	–	1	–	–
Face powders	555	1	–	–	–	1	–
Feminine hygiene deodorants	21	1	–	–	–	1	–
Other personal cleanliness products	227	4	–	–	–	1	3
Moisturizing skin care preparations	747	3	–	–	2	1	–
Night skin care preparations	219	3	–	–	–	3	–
Suntan gels, creams, and liquids	164	1	–	1	–	–	–
1981 TOTALS		15	0	1	4	7	3

Sorbitan Stearate as either a water emulsion or a solution in corn oil was administered orally to the rats. Some rats were given the emulsifier with the polyol moiety radiolabeled, whereas the others were given the compound with the label in the Stearate moiety. The animals were placed in individual metabolism chambers, and the expired CO_2 was collected at 6-hour intervals for 48 hours. Urine and feces were also collected. At the end of 48 hours, the animals were killed, and tissues and organs were taken from the carcasses for radioactivity determination. When fed as an oil solution, 14 to 24 percent of the polyol radioactivity and 7 to 33 percent of the stearate radioactivity were recovered from expired CO_2. The urine contained 16 to 66 percent of the polyol radioactivity and only 1 percent of the stearate radioactivity. The feeding of stearate-labeled compound in water resulted in a 69 to 72 percent excretion of the ester in the stool. When fed in oil, 33 to 37 percent was found in the feces. Between 6 and 54 percent of the polyol radioactivity in both oil and water was excreted. The combined tissues contained 5 to 7 percent of the administered ^{14}C 48 hours after the feeding, and crude fat extracts contained less than 0.1 percent. From the results, it was determined that approximately 90 percent of the Sorbitan Stearate in oil solution was hydrolyzed to stearic acid and anhydrides of sorbitol. When fed as a water emulsion, about 50 percent of the ester was hydrolyzed; the other 50 percent as ester was excreted as such in the feces.[25]

The accumulation and deposition of Sorbitan Stearate in body fat was studied using 9 adult rats. The animals were fed a diet containing 0.1 percent of this ester labeled with ^{14}C in the polyol moiety for 28 days. At termination of the study the animals were killed, and carcasses were frozen, dehydrated, and extracted for the Sorbitan ester with hot chloroform. The radioactivity of crude fat, fatty acids, glycerol, and residue was determined. A small portion (0.35 to 0.49 percent) of the radioactivity was in crude fat, 0.15 to 0.32 percent was in fatty acids, 0.01 to 0.07 percent was found in glycerol, and 0.04 to 0.09 was found in the residue. The polyol moiety of Sorbitan Stearate did not accumulate in body fat stores.[26]

Skin and Skin Cell Membrane Effects

Mezei et al.[27] studied the microscopic and metabolic changes in rabbit skin treated with nonionic surface-active agents. Sorbitans Laurate, Stearate, Oleate, and Trioleate were tested undiluted and in 60, 10, 5, and 1 percent concentrations in petrolatum or water. The compounds or solutions ($\sim$ 0.3 g) were applied daily to the clipped backs (8 test areas per rabbit) of New Zealand rabbits. After 10 and 30 days of application of the esters, skin sites were evaluated and skin biopsies 0.2 mm in thickness were taken from test sites. Oxygen consumption of skin was measured during the course of the 81-day experiment. The ester-treated skin had increased numbers of inflammatory cells in the dermis. Oxygen consumption of skin treated with the Sorbitan esters for 3 to 13 days was increased two-fold with Sorbitans Laurate and Stearate treatment and three-fold with Sorbitan Trioleate treatment. Skin taken after 30 to 81 days of treatment had two- to three-fold oxygen consumption increases with all the Sorbitan esters tested.[27]

The hypothesis that the site of action of surfactants is in the biological membranes was investigated by applying Sorbitan Trioleate to rabbit skin. The ester was applied daily in a 10 percent concentration to the clipped skin of the rabbits

for 4 or 10 days. The animals were then killed, and the skin was excised for the determination of surfactant-related changes. Treatment for 4 days with the ester resulted in a 27 to 58 percent increase in phosphorus content using DNA content as a reference standard. After 10 days of treatment, phosphorus content increased 18 to 35 percent. The probable reason for the increase in skin phosphorus (phospholipid) was suggested to be damage to the biological membranes. A higher concentration of phosphorus would be expected, in order to regenerate the original membrane structure or if there was lymphocytic infiltration due to inflammation, as mentioned in the previous study.[28]

Sorbitan Trioleate was used to study the effect of surfactants on the rate of water desorption from rabbit skin. A 10 percent solution of the ester was applied daily to depilitated skin for 4 days. Controls were treated with petrolatum. At termination of the study, the skin was excised and measured for water desorption on a microbalance. Treatment of skin with the Sorbitan ester increased the rate of water loss when compared to control water loss time, but there was no significant difference in water content of either control or treated skin after 30 minutes. This indicated that the deeper layers of treated skin lost water at a faster rate than control skin. The differences in water loss rates were interpreted by the investigators as being caused by permeability changes in cell membranes induced by the Sorbitan.[29]

ANIMAL TOXICOLOGY

Acute

Oral

Sorbitan Stearate was administered via stomach tube as a 30 percent suspension in 0.5 percent aqueous carboxymethylcellulose sodium to 10 male and 10 female rats. The single dose of the ingredient was 15.9 g/kg body weight. During the 14-day observation, no animals died.[22]

A single 15 g/kg dose of 100 percent Sorbitan Stearate was administered by stomach tube to each of 5 female albino rats. No deaths or abnormalities were observed during the 7 days of observation, and no lesions were found at necropsy. The LD_{50} was not reached, and the compound was considered nontoxic.[30]

The acute oral toxicity of a product containing 4 percent Sorbitan Stearate was tested using fasted Harlan Wistar rats. Each of 5 male and 5 female animals received the undiluted formulation as a 7 ml/kg dose by gavage. No deaths or signs of toxicity were observed during the 2-week study.[31]

Sorbitan Laurate (Span 20) was administered in a single oral dose of 20 g/kg to each of 10 male rats. No toxic effects were observed during a 2-day observation period.[32]

Sorbitan Laurate was administered orally to fasted rats. One group of 30 male rats received 25.1 to 39.8 g/kg. Two of 10 rats died after the administration of 39.8 g/kg, but none of 20 rats given the lower dosages died during the 14-day observation period. The LD_{50} was not reached for this group of rats. A group of 30 female rats was given similar doses of Sorbitan Laurate. The LD_{50} for this group was 33.6 g/kg body weight, with 95 percent confidence limits of 28.0 to 40.3 g/kg. A group of 60 male and female rats also received similar doses of the ingre-

dient. The LD_{50} was 41.25 g/kg, with 95 percent confidence limits of 35.3 to 48.3 g/kg.[22]

Ten male and ten female fasted rats received a single dose of 39.8 g/kg Sorbitan Sesquioleate as a 90 percent w/v concentration in corn oil. No deaths occurred during the 14-day observation period.[33]

A cleansing cream product containing 3.0 percent Sorbitan Sesquioleate was administered undiluted to two groups of 2 male and 2 female Charles River albino rats. The doses administered were 23.1 and 34.6 g/kg. No deaths, adverse effects on body weight, or gross alterations were noted; however, hypoactivity was noted among animals in both groups within 5 minutes after administration and subsided 6 to 22 hours later. Also, ruffled fur was observed in animals in the 34.6 g/kg group 6 to 22 hours after administration. This effect disappeared within 2 to 3 days, and no other signs of toxicity were noted. This product is practically nontoxic by oral administration.[34]

A dose of 39.8 g/kg Sorbitan Oleate, administered via stomach tube as a 90 percent w/v suspension in corn oil to 10 male and 10 female fasted rats, caused no deaths over the 14-day observation period.[22]

Sorbitan Oleate was administered orally to male rats. A 10 ml/kg dose of undiluted Sorbitan Oleate caused no deaths over a 6-day period. The livers and kidneys had no lesions.[22]

Ten male and ten female fasted rats were given a single oral dose of Sorbitan Tristearate as a 30 percent w/v suspension in 0.5 percent aqueous carboxymethylcellulose sodium. The dose of Sorbitan Tristearate was 15.9 g/kg body weight. No deaths or signs of toxicity were observed during the 14-day observation period, and this compound was classified as "relatively harmless."[22] Sorbitan Tristearate, administered orally to rats in a 10 g/kg dose, caused no deaths.[22]

A 30 percent suspension of Sorbitan Palmitate in 0.5 percent aqueous carboxymethylcellulose sodium was administered to 10 male and 10 female fasted rats via stomach tube. The dose of the ingredient was 15.9 g/kg; no deaths occurred during the 14-day observation period.[22]

No toxic signs were observed when Sorbitan Palmitate and water were used as the only food source for 10 male albino rats for 24 hours. The ingredient was offered ad libitum, and an average of 10 g/kg body weight of Sorbitan Palmitate was consumed.[22]

Five male and five female fasted Harlan Wistar rats were given a single oral 26 ml/kg dose of an undiluted lotion containing 4 percent Sorbitan Palmitate. No deaths or signs of toxicity were noted during the 7-day observation period.[35]

A 90 percent w/v suspension of Sorbitan Trioleate in corn oil was administered via stomach tube as a 39.8 g/kg dose to 10 male and 10 female fasted albino rats. During the 14-day observation, no deaths occurred, and the compound was considered "relatively harmless."[22]

Five male and five female fasted Harlan Wistar rats were given a single oral 5 ml/kg dose of a lotion containing 5 percent Sorbitan Trioleate. No deaths or toxic reactions occurred during the 7-day study.[36]

The acute oral toxicity data are summarized in Table 4.

Skin Irritation

Sorbitans Stearate, Laurate, Oleate, and Trioleate were applied at 1, 10, 60, and 100 percent concentrations to the clipped skin of New Zealand rabbits. An

TABLE 4. Acute Oral Toxicity

Ingredient	*Vehicle*	*Species and No. of Rats*	*Concentration (percent)*	*Ingredient Dose*	*Observation Period*	*Comments*	*Reference*
S. Stearate	0.5 percent aqueous CMC	10M, 10F	30	15.9 g/kg	14 days	No deaths	22
	None	5F	100	5 g/kg	7 days	No deaths or abnormalities; nontoxic	30
	Cream product	5M, 5F	4	0.28 ml/kg	14 days	No deaths or signs of toxicity	31
S. Laurate	None	10M	100	20 g/kg	2 days	No harmful effects	32
	None	30M	100	25.1–39.8 g/kg	14 days	2 of 10 rats died from 39.8 g/kg dose	22
	None	30F	100	25.1–39.8 g/kg	14 days	LD_{50} = 33.6 g/kg	22
	None	60 M,F	100	25.1–39.8 g/kg	14 days	LD_{50} = 41.25 g/kg	22
S. Sesquioleate	Corn oil	10M, 10F	90	39.8 g/kg	14 days	No deaths	33
	Cleansing cream	2M, 2F	3	0.69 g/kg	> 3 days	No deaths; nontoxic	34
	Cleansing cream	2M, 2F	3	1.04 g/kg	> 3 days	No deaths; nontoxic	34
S. Oleate	Corn oil	10M, 10F	90	39.8 g/kg	14 days	No deaths	22
	None	Male	100	10 ml/kg	6 days	No deaths; histologically normal livers and kidneys	22
S. Tristearate	0.5 percent aqueous CMC	10M, 10F	30	15.9 g/kg	14 days	No deaths or signs of toxicity	22
		F	–	10 g/kg	–	No deaths	22
S. Palmitate	0.5 percent aqueous CMC	10M, 10F	30	15.9 g/kg	14 days	No deaths	22
	None	10M	100	~ 10 g/kg	24 hours	Given as sole food source for 24 hours, no toxic symptoms	22
	Lotion product	5M, 5F	4	1.04 ml/kg	7 days	No deaths or toxic signs	35
S. Trioleate	Corn oil	10M, 10F	90	39.8 g	14 days	No deaths	22
	Lotion product	5M, 5F	5	0.025 ml/kg	7 days	No deaths or toxic reactions	36

untreated site served as the control, and dilutions of the esters were made in petrolatum. About 0.3 g of each substance was applied to the skin once daily for 10 or 30 days. The gross observations for Sorbitan esters after 3 days of application were as follows: Sorbitan Stearate in 60, 10, and 1 percent concentrations (not tested at 100 percent) produced no detectable changes. Sorbitan Laurate in 100 percent concentration caused intense erythema and edema; the 60 and 10 percent solutions produced edema and erythema, and the 1 percent concentration produced no visible change. Sorbitan Oleate caused erythema and edema when tested at 100 percent concentration but no visible changes at 60 and 10 percent concentrations (not tested at 1 percent). Sorbitan Trioleate caused erythema and edema at 100, 10, and 1 percent concentrations (not tested at 60 percent). The results for the Sorbitan esters after 10 days of application are as follows: Sorbitan Stearate caused edema and erythema from applications of 60, 10, and 1 percent. Sorbitan Laurate caused thickening at 100 and 60 percent concentrations; erythema and edema were observed at 10 and 1 percent concentrations. Sorbitan Oleate caused thickening at 100 percent and erythema and edema at 60 and 10 percent. Sorbitan Trioleate caused thickening at 100 percent and erythema and edema at 10 and 1 percent.[27]

In a Draize-type irritation test, Sorbitan Trioleate (100 percent), Sorbitan Palmitate (50 percent), and Sorbitans Stearate and Tristearate (both at 30 percent) were applied under occlusion to the clipped skin of rabbits for 24 hours. Test areas were scored at 24 and 72 hours. The Trioleate was mildly irritating to the rabbits' skin (Primary Irritation Index [PII], 1.5 out of a possible 8.0), whereas the Palmitate, Stearate, and Tristearate produced no irritation (PII, 0.0).[37]

The primary skin irritation potential of the ingredient Sorbitan Stearate was tested using the shaved back skin of 9 albino rabbits. The compound, diluted to 50 percent in corn oil, was applied in a single 0.1 ml application under occlusion. The dressing was removed after 24 hours of contact and the sites were graded for irritation after 2 and 24 hours on a scale of 0 (no effect) to 4 (deep red erythema, vesiculation, possible edema). Four animals had barely perceptible erythema and five had mild erythema. The compound was minimally irritating, with a calculated PII of 0.78.[38]

A cosmetic cream containing 4 percent Sorbitan Stearate was tested for skin irritation using 3 New Zealand rabbits. The fur was clipped from the back of each animal, and 0.5 ml was applied daily to the shaved areas for 4 consecutive days. During the 7-day observation period, slight erythema was observed 24 hours after the first application, well-defined erythema and slight edema developed in 2 to 4 days, and slight desquamation occurred after 4 to 7 days. The PII for this material was 1.5 (8.0 maximum). The product was mildly irritating.[31]

The primary irritation of a cleansing product containing 3.0 percent Sorbitan Sesquioleate was tested using 4 New Zealand rabbits. The back of each animal was clipped free of hair; one clipped area was abraded and one was left intact, and 0.5 ml of undiluted product or 0.5 g dried material moistened with 0.9 percent saline was applied to each site. Occlusive patches were placed over each area and left in place for 24 hours. Sites were graded 1 hour after patch removal and again 48 hours later, and scoring was according to the Draize criteria. Very slight erythema occurred in every animal in intact and abraded skin, but no edema was observed. The PII was 1.4, indicating the product has the potential for mild irritation.[39]

Sorbitan Oleate was tested for primary skin irritation using 9 albino rabbits. A 5 percent concentration of the ingredient in corn oil was applied under occlusion in 0.1 ml to the shaved skin of the back. The patches were left in place for 24 hours, and the sites were graded 2 and 24 hours after patch removal. The scoring was based on a scale of 0 (no effect) to 4 (severe erythema and vesiculation or edema). Four animals had no change and five had barely perceptible erythema. This material was classified as a minimal irritant with a PII of 0.28.[40]

A similar study using 9 albino rabbits was conducted with undiluted Sorbitan Oleate. Six animals had no irritation, one had barely perceptible erythema, and two had mild erythema. In a group of 9 control animals, the PII was 0.22. The test group PII was 0.28, which classified this material as a minimal irritant.[41]

A cosmetic product containing 4 percent Sorbitan Palmitate was applied to the shaved backs of 3 albino rabbits. Four daily 0.5 ml inunctions were made to one side, and the contralateral side of the back served as the control. The animals had mild to moderate erythema and edema throughout the test period, and mild desquamation was noted on Day 7. The mean irritation index was 2.4, indicating that this product is moderately irritating.[35]

A lotion containing 5 percent Sorbitan Trioleate was tested for acute skin irritation using the shaved backs of 3 albino rabbits. Four daily 0.5 ml applications of the lotion were made. Very slight erythema occurred after the first application, progressing to slight erythema and edema by the fourth application. The PII was 2.6 (8.0 max), and the compound was considered a moderate irritant.[36]

The acute skin irritation toxicity data are summarized in Table 5.

Dermal Toxicity

In order to determine its acute dermal toxicity, two groups of 2 male and 2 female albino rabbits received a 24-hour patch test of a cosmetic cleansing cream containing 3 percent Sorbitan Sesquioleate. One group received the undiluted product in a dose of 6.8 g/kg; the other, 10.2 g/kg. No deaths, abnormal behavior, adverse body weight changes, or gross alterations were noted during the 14-day observation period. At the end of the 24-hour contact period, definite red, well-defined erythema was observed at the contact site on each animal. The erythema subsided by Day 7[42] (Table 5).

Ocular

Draize ocular irritation tests were conducted using Sorbitans Stearate, Tristearate, and Palmitate at concentrations of 30 percent and Sorbitan Oleate at 100 percent concentration. A 0.1 ml volume of each substance was instilled into the right eye of each of 9 albino rabbits per substance. The eyes of 3 rabbits in each group were irrigated with 20 ml of water 2 seconds after instillation. Each eye was scored at 1, 24, 48, 72, and 96 hours and 7 days. Neither irrigated nor nonirrigated eyes had any irritation.[37]

Six New Zealand albino rabbits were used to evaluate the acute ocular irritation of a cosmetic product containing 4 percent Sorbitan Stearate. Each animal received 0.1 ml of cosmetic in one eye, and the other eye served as the control. Ocular reactions were scored after 1 hour and after 1, 2, 3, and 7 days. Slight conjunctival hyperemia developed in 5 animals 1 hour after treatment and cleared in 24 to 48 hours. No irritation to the cornea or iris was observed.[31]

Several studies were conducted on the effect of Sorbitan Laurate on the rab-

bit eye. A 30 percent concentration and two 100 percent concentrations of the ingredient were nonirritating.[22]

Sorbitan Sesquioleate (100 percent, and 30 percent in water) was instilled in 0.1 ml amounts into one eye of each of 9 albino rabbits. Six eyes were nonirrigated and three were irrigated with 20 ml of water after 2 seconds of exposure. Each eye was evaluated after 1, 2, 3, 48, 72, and 96 hours and 7 days. Scoring was based on the Draize scale of 0 (no irritation) to 110 (maximum irritation). All scores were recorded as zero, and the compound was not an eye irritant.[33]

A cleansing cream preparation containing 3.0 percent Sorbitan Sesquioleate was tested for ophthalmic irritation using New Zealand rabbits. Each of 5 animals received 0.1 ml of the product into one eye, and the other eye served as the control. A second group of 5 rabbits also received a 0.1 ml instillation, but 4 seconds after application the eye was flushed with 40 ml of water. Observations were made after 1, 24, 48, and 72 hours and 4 and 7 days, and the Draize scoring criteria were used. The average score for nonirrigated eyes at 1 hour was 7.8 and at 24 hours, 1.4 (110 maximum). Irritation had disappeared after 24 hours. The irrigated eyes had an average score of 8.0 at 1 hour and no irritation thereafter, indicating that this product is minimally to practically nonirritating.[43]

Sorbitan Oleate at 5 percent concentration in corn oil was tested for acute ocular irritation using rabbits. One eye of each of 6 albino rabbits received a single 0.1 ml instillation of the product, and observations for irritation were made until all eyes were negative or for a maximum of 7 days. This compound produced no irritation.[44]

A 40 percent concentration of Sorbitan Tristearate in water was instilled into the eyes of 9 albino rabbits. No irritation was seen during 7 days of observation.[22]

A cosmetic containing 4 percent Sorbitan Palmitate was tested for ocular irritation using 6 albino rabbits. An instillation of 0.1 ml of the product was made into one eye of each animal; observations were made for 7 days. Slight conjunctival redness was observed after 1 hour in all animals but had disappeared by 24 hours in 5 animals and by Day 3 in the remaining rabbit. The cornea and iris were clinically normal.[35]

An unidentified "lotion" containing 5 percent Sorbitan Trioleate was instilled into one eye of each of 6 albino rabbits. The contralateral eye served as the control, and no rinse was given. The 0.1 ml instillation caused slight conjunctival redness in 2 rabbits. The irritation had resolved within 48 hours.[36]

Acute ocular irritation results are summarized in Table 6.

Subchronic

Oral

Sorbitan Laurate (Span 20) was fed to chickens to determine its effect upon growth. Two groups of 24 chicks were fed either 0.1 or 1.0 percent Sorbitan Laurate for 10 weeks. A slight but inconsistent and statistically insignificant increase in growth occurred. Mortality, body weights, and necropsy findings were normal. In addition, three groups of 20 chicks were fed 0.1, 1.0, or 2.0 percent Sorbitan Laurate supplemented with penicillin in the diet for 10 weeks. There was an initial weight gain during the first 4 weeks, but this was not maintained during the next 6 weeks. Mortality, growth, and necropsy findings were all normal.[45]

TABLE 5. Acute Skin Irritation and Dermal Toxicity

Ingredient	Vehicle	Species and No. of Animals	Concentration (percent)	Ingredient Dose	PII*	Time: Contact	Time: Observation	Comments	Reference
				ACUTE SKIN IRRITATION					
S. Stearate	Petrolatum	New Zealand rabbits	60	~0.18 g	–	Up to 30 days	3 and 10 days	3 days: no visible change; 10 days: erythema, edema. Irritant	27
	Petrolatum		10	~0.03 g	–	Up to 30 days	3 and 10 days	3 days: no visible change; 10 days: erythema, edema. Irritant	27
	Petrolatum		1	~0.003 g	–	Up to 30 days	3 and 10 days	3 days: no visible change; 10 days: erythema, edema. Irritant	27
	Unknown	6 rabbits	30	0.15 g	0	24 hours	72 hours	No irritation. Nonirritant	37
	Corn oil	9 rabbits	50	0.5 ml	0.78	24 hours	2 and 24 hours	Barely perceptible to mild erythema. Minimal irritant	38
	Cream product	3 rabbits	4.0	0.02 ml	1.5	4–24 hour periods	7 days	Erythema, edema, slight desquamation. Mild irritant	31
S. Laurate	None	New Zealand rabbits	100	~0.3 g	–	Up to 30 days	3 and 10 days	3 days: intense erythema, edema; 10 days: thickening. Irritant	27
	Petrolatum		60	~0.18 g	–	Up to 30 days	3 and 10 days	3 days: erythema, edema; 10 days: thickening. Irritant	27
	Petrolatum		10	~0.03 g	–	Up to 30 days	3 and 10 days	3 days: erythema, edema; 10 days: erythema, edema. Irritant	27
	Petrolatum		1	~0.003 g	–	Up to 30 days	3 and 10 days	3 days: no visible change; 10 days: erythema, edema. Irritant	27
S. Sesquioleate	Skin cleansing product	4 rabbits	3.0	0.015 ml or 0.015 g	1.4	24 hours	72 hours	Slight erythema. Mild irritant	39

S. Oleate	None	New Zealand rabbits	100	~0.3 g	–	Up to 30 days	3 and 10 days	3 days: erythema, edema; 10 days: thickening. Irritant	27
	Petrolatum		60	~0.18 g	–	Up to 30 days	3 and 10 days	3 days: no visible change; 10 days: erythema, edema. Irritant	27
	Petrolatum		10	~0.03 g	–	Up to 30 days	3 and 10 days	3 days: no visible change; 10 days: erythema, edema. Irritant	27
	Corn oil	9 rabbits	5.0	0.005 ml	0.28	24 hours	2 and 24 hours	Barely perceptible. Minimal irritant	40
	None	9 rabbits	100	0.1 ml	0.28	24 hours	2 and 24 hours	Mild erythema. Minimal irritant	41
S. Tristearate	Unknown	6 rabbits	30	0.15 g	0	24 hours	72 hours	No irritation. Nonirritant	37
S. Palmitate	Unknown	6 rabbits	50	0.25 g	0	24 hours	72 hours	No irritation. Nonirritant	37
	Lotion product	3 rabbits	4.0	0.02 ml	2.4	4–24 hour periods	7 days	Moderate edema, erythema, desquamation. Moderate irritant	35
S. Trioleate	None	New Zealand rabbits	100	~0.3 g	–	Up to 30 days	3 and 10 days	3 days: erythema, edema; 10 days: thickening. Irritant	27
	Petrolatum		10	~0.03 g	–	Up to 30 days	3 and 10 days	3 days: erythema, edema; 10 days: erythema, edema. Irritant	27
	Petrolatum		1	~0.003 g	–	Up to 30 days	3 and 10 days	3 days: erythema, edema; 10 days: erythema, edema. Irritant	27
	None	6 rabbits	100	0.5 ml	1.5	24 hours	72 hours	Mild irritant	37
	Lotion product	3 rabbits	5.0	0.025 ml	2.6	4–24 hours	4 days	Erythema and edema. Moderate irritant	36
				DERMAL TOXICITY					
S. Sesqui-oleate	Cream product	2M, 2F rabbits	3.0	0.2 g/kg	–	24 hours	14 days	No deaths or abnormalities; definite erythema. Non-toxic; irritant	42
	Cream product	2M, 2F rabbits	3.0	0.3 g/kg	–	24 hours	14 days	No deaths or abnormalities; definite erythema. Non-toxic; irritant	42

*PII, Draize protocol Primary Irritation Index. Scores range from 0 (no irritation) to 8 (corrosive).

TABLE 6. Rabbit Ocular Irritation

Ingredient	*Vehicle*	*Species and No. of Rabbits*	*Concentration (percent)*	*Ingredient Dose (ml)*	*Observation Time*	*No. of Instillation*	*Wash Y/N*	*Comments*	*Reference*
S. Stearate	Water	6 albino	30	0.03	7 days	1	N	No irritation. Nonirritant.	37
		3 albino					Y	Washed after 2 seconds. No irritation. Nonirritant	
	Cream product*	6 New Zealand	4.0	0.004	7 days	1	N	Slight conjunctival irritation up to 48 hours. No iris or corneal irritation. Nonirritant	31
S. Laurate	Unknown	6	30	0.03	7 days	1	N	No irritation. Nonirritant	22
		3					Y		
S. Sesquioleate	None	6 albino	100	0.1	7 days	1	N	No irritation. Nonirritant	33
		3 albino					Y		
	Water	6 albino	30	0.03	7 days	1	N	No irritation. Nonirritant	33
		3 albino					Y		
	Cleansing lotion	5 albino	3.0	0.1	7 days	1	N	Slight irritation, clearing after 24 hours. Highest score was 18 out of 110. Mild irritant	43

		5 albino	3.0	0.1	7 days	1	Y	Slight irritation, clearing after 1 hour. Highest score was 11 out of 110. Mild irritant	43
S. Oleate	None	6 albino 3 albino	100	0.1	7 days	1	N Y	No irritation. Nonirritant Washed after 2 seconds. No irritation. Nonirritant	37
	Corn oil	6 albino	5.0	0.05	7 days	1	N	No irritation. Nonirritant	44
S. Tristearate	Water	6 albino 3 albino	30	0.03	7 days	1	N Y	No irritation. Nonirritant Washed after 2 seconds. No irritation. Nonirritant	37
	Water	6 3	40.0	0.04	7 days	1	N Y	No irritation. Nonirritant	22
S. Palmitate	Water	6 albino 3 albino	30	0.03	7 days	1	N Y	No irritation. Nonirritant Washed after 2 seconds. No irritation. Nonirritant	37
	Lotion product*	6 albino	4.0	0.04	7 days	1	N	Slight irritation, clearing by Day 3. Mild irritant	35
S. Trioleate	Lotion product*	6 albino	5.0	0.05	–	1	N	Slight irritation in 2 rabbits, clearing by 48 hours. Mild irritant	36

*Product type (cleanser, moisturizer, etc.) not available.

A study by ACI[32] reported that three groups of 12 rats fed diets containing 0, 1, or 4 percent Sorbitan Laurate for 6 weeks had slightly decreased growth rates. Total erythrocyte and leukocyte counts and tissues examined microscopically (liver, kidneys, intestines, pancreas, and urinary bladder) were normal. This same group reported that 2 rhesus monkeys, each given 2 g of Sorbitan Laurate per day for 6 weeks, had no changes from normal growth rate, blood parameters, or organ histological features.[32]

Groups of 15 male and 15 female Wistar rats were fed a diet containing 0 (control), 2.5, 5.0, or 10.0 percent Sorbitan Laurate for 90 days. Additional groups of 5 rats of each sex were fed 0, 5, or 10 percent Sorbitan Laurate for 2 or 6 weeks. No deaths or abnormal behavior occurred. Body weights, hemoglobin concentration,and packed cell volume values were decreased. Average weights of the brain, liver, and kidney were increased, but the average weights of the heart and gastrointestinal (GI) tract were decreased. Periportal vacuolization of hepatocytes and tubular nephrosis were also observed. In a paired feeding study, Sorbitan Laurate was fed to two groups of 10 rats at 0 or 10 percent concentrations for 13 weeks; body weights were decreased and average weights of the liver and kidney were increased.[46]

Ten male and ten female rats per group were fed Sorbitan Laurate at concentrations of 0 (control) 15, 20, and 25 percent for 23 weeks. Diarrhea, unkempt appearance, and severely retarded growth were observed in all test groups. Only 2 animals of the 25 percent group survived the 23-week test period. Findings at necropsy included pale and enlarged liver, enlarged common bile duct, and gangrene of the tail. Hepatic lesions included fatty changes, fibrosis, chronic inflammation, and necrosis. Other lesions were focal nephritis, increased numbers of foamy alveolar macrophages, and hyperplasia of cells of the bone marrow and spleen. All other organs examined were normal.[47]

Two groups of 36 hamsters were fed either 5 or 15 percent Sorbitan Laurate for 68 days. The hamsters fed the 5 percent Sorbitan Laurate diet had retarded growth rate, and mortality (4 deaths) was slightly greater than that of the control group (3 deaths). The hamsters of the 15 percent group developed diarrhea within 5 days, but this condition had disappeared by Day 26. Mortality was somewhat higher than in controls; 8 animals died in this group and 4 animals died in the paired-fed control group. Histopathologically, Sorbitan Laurate feeding produced GI mucosal hyperemia and edema and renal tubular epithelial degeneration.[48]

A 25 percent concentration of Sorbitan Laurate was incorporated into the diet of, and fed to, 14 Sprague-Dawley rats for 59 days. The animals lost weight and developed diarrhea and nasal hemorrhage. The tails of 3 rats became gangrenous. Only 1 rat completed the study, and at necropsy a fatty liver was found. In a second study, a diet containing 25 percent Sorbitan Laurate was fed to 14 male and 16 female rats for 70 days. Activity and appetite were decreased, and weight gains were reduced. Nasal bleeding and gangrene of the tail and hind legs were observed. Only 4 males and 7 females survived the study. The average weights of the brain, kidneys, heart, spleen, lungs, and liver were increased. Histopathologic alterations consisted of degenerative changes of the GI tract, kidneys, and liver.[49]

In a paired feeding study, two groups of 10 male rats were fed either 0 or 10 percent Sorbitan Laurate for 17 weeks. Body weights, packed cell volume, and

hemoglobin values were decreased in the test group. Kidney and liver weights were significantly increased. Sorbitan Oleate was fed to 15 male and 15 female Wistar rats in dietary concentrations of 0 (control), 2.5, 5, or 10 percent for 16 weeks. In addition, groups of 5 male and 5 female rats were fed diets containing 0, 5, or 10 percent ester for 2 or 6 weeks. The rats appeared clinically normal, but body weight gains were reduced. Average weights of the liver and kidneys were increased, as was the size of the livers. Fatty change of hepatocytes, degenerative changes of renal tubules, and reduced values of packed cell volume were recorded.[50]

See Table 7 for a summary of subchronic oral toxicity tests and results.

Dermal Toxicity

Sorbitan Stearate

A subchronic dermal toxicity study was conducted on a cosmetic product containing 2 percent Sorbitan Stearate. The compound was applied daily for 3 months to the clipped skin of the back of New Zealand albino rabbits. One group of 5 males and 5 females was treated with the cosmetic at a dose of 6.6 mg/cm^2 per 8.4 percent body surface area (BSA), and a second group was given a dose of 11 ml/cm^2 per 8.4 percent BSA. An untreated control group consisted of 7 males and 7 females. Observations were made with respect to physical appearance, skin changes, behavior, feed consumption, body weights, hematological values, clinical chemistry values, urinalysis parameters, organ weights, and gross and microscopic changes of organs and tissues. No treated rabbits died during the study, but 1 male and 1 female control died of septicemia. All surviving animals gained weight, and no treatment-related changes were found in respect to feed consumption, hematological values, clinical chemistry values, urinalysis parameters, or organ weights. In the skin, well-defined, moderate erythema, slight edema, and slight desquamation were observed, and inflammatory changes were present at the application sites. No evidence of systemic toxicity was observed. The skin irritation observed in this test does not indicate a potential hazard to humans.[51]

Sorbitan Sesquioleate

A hormone cream product containing 1.0 percent Sorbitan Sesquioleate was tested for subchronic dermal toxicity. The cosmetic was applied for 13 weeks to the clipped backs of five groups of 9 female New Zealand white rabbits at doses of 0 (control), 30, 300, 3000, and 3000 (cosmetic without hormone) mg/kg. Applications were made daily, 5 days per week, for a total of 65 treatments. The following parameters were observed: body weights (weekly), clinical observations for pharmacological effects (daily), and blood chemistry values (before the first application and then at Weeks 4, 7, and 13). Upon completion of the series of applications, all animals were killed for necropsy. Weights were taken of the brain, heart, liver, spleen, kidneys, adrenals, and uterus, and the adrenals, brain, ovaries, uterus, heart, large and small intestines, kidneys, liver, lungs, pancreas, skin, spleen, stomach, and bone marrow were examined microscopically. Body weights, physical appearance, behavior, and survival rates were unaffected by the product. One animal died and two were killed due to non-product-related diseases. All other animals were in good health, and either maintained or gained

TABLE 7. Subchronic Oral Toxicity

Ingredient	Species and No. of Animals	Concentration in Feed (percent)	Observation Period	Comments	Reference
Sorbitan Laurate	24 chickens	0.1	10 weeks	Normal with respect to mortality, growth, gross pathological changes	45
	24 chickens	1.0	10 weeks		
	20 chickens	0.1	10 weeks	Fed diet + S. Laurate + 2 g penicillin per ton of feed.	45
	20 chickens	1.0	10 weeks	Increased growth rate during the first 4 weeks;	
	20 chickens	2.0	10 weeks	growth not maintained during last 6 weeks; otherwise chicks were normal with respect to mortality, growth, gross and pathological changes	
	12M rats	0	6 weeks	Controls	32
	12M rats	1.0	6 weeks	Test animals grew at a slightly lower rate than controls. Red and white blood cell counts, livers, kidneys, intestines, pancreas, and bladders all comparable to controls	32
	12M rats	4.0	6 weeks		
	2 rhesus monkeys	2 g/day	6 weeks	Growth rate, terminal red and white blood cell counts, histological appearance of liver, kidneys, and spleens were all normal	32
	15M, 15F rats	0	90 days	Control	46
	15M, 15F rats	2.5	90 days	No deaths or untoward behavior. Body weights were lower than controls. Decreased hemoglobin and packed cell volumes. Increased brain, kidney, and liver weights and stomach weights. Decreased heart, GI tract, and testes. Periportal vacuolization of liver. Nephrosis of kidneys	46
	15M, 15F rats	5.0	90 days		
	15M, 15F rats	10.0	90 days		
	5M, 5F rats	0	2 or 6 weeks	Control	46
	5M, 5F rats	5	2 or 6 weeks	No deaths; no abnormal behavior. Decreased RBC count and body weights	46
	5M, 5F rats	10	2 or 6 weeks		
	10M rats	0	13 weeks	Control	46
	10M rats	10	13 weeks	Body weights lower. Liver, kidney, heart, and small intestine weight higher	46
	10M, 10F rats	0	23 weeks	Control	47
	10M, 10F rats	15	23 weeks	Diarrhea, unkempt appearance. Poor weight gain in all levels. Pale, enlarged liver; common bile duct	47
	10M, 10F rats	20	23 weeks		

	10M, 10F rats	25	23 weeks	enlargement; gangrene of tail at 25 percent level. Inflammation, necrosis, fatty deposits in liver at 25 percent. Focal nephritis; foamy alveolar macrophages; bone marrow and spleen hyperplastic. Other organs normal. 18 out of 20 rats died at 25 percent level	
	36 hamsters	5	68 days	Decreased growth rate. Less mortality than control group; 4 animals died	48
	36 hamsters	15	68 days	Mild diarrhea, depressed growth rate, slightly higher mortality than control; 8 died	48
	14 Sprague-Dawley rats	25	59 days	Weight loss. Diarrhea and nasal hemorrhage. Gangrenous tails in 3 rats. Only 1 rat survived study. Autopsy showed fatty liver	49
	14M rats	25	70 days	4/14 survived. Loss of appetite; gangrenous tails and hind legs. Nasal hemorrhage. Blood reduced hemoglobin. Fatty livers. Irritation of GI tract. Degeneration of kidney tubules. Focal hepatic necrosis	49
	16F rats	25	70 days	7/16 survived. Loss of appetite; gangrenous tails and hind legs. Nasal hemorrhage. Blood reduced hemoglobin. Fatty livers. Irritation of GI tract. Degeneration of kidney tubules. Focal hepatic necrosis	49
Sorbitan Oleate	15M, 15F Wistar rats	0	16 weeks	Control	50
	15M, 15F Wistar rats	2.5	16 weeks	No abnormalities; weight gain reduction	50
	15M, 15F Wistar rats	5	16 weeks	Males had lowered body weights	50
	15M, 15F Wistar rats	10	16 weeks	Lowered hemoglobin and packed cell volumes. Lowered heart, spleen, cecum, and stomach weights. Increased liver and kidney weights. Lowered body weights	50
	5M, 5F rats	0	2 or 6 weeks	Control	50
	5M, 5F rats	5	2 or 6 weeks	No abnormalities. Weight gain reduction	50
	5M, 5F rats	10	2 or 6 weeks	Lowered hemoglobin and packed cell volume. Lowered heart, spleen, cecum, and stomach weights	50
	10M rats	0	17 weeks	Control	50
	10M rats	10	17 weeks	Lowered weight gain; lowered hemoglobin and packed cell volume. Increased kidney and liver weight	50

weight during the study. The skin from the application sites had no irritation in the untreated control group, minimal irritation (slight irritation or slight desquamation) in the 30 mg/kg group, minimal or negligible irritation in the 300 mg/kg group, slight irritation beginning in the fifth test week in the 3000 mg/kg group, and slight irritation beginning in the fourth test week in the 3000 mg/kg group without the hormone. Hematological and urinalysis values and organs and tissues were normal. A dose-related increase in uterine weight was observed of rabbits topically exposed to 30, 300, and 3000 mg/kg for 13 weeks. A dose-related increase in splenic weight occurred in animals receiving 300 and 3000 mg/kg, and weight of the liver was decreased in animals given 30 and 3000 mg/kg. No other abnormal effects were noted; the investigators suggested that the effect on organ weight was caused by the estrogenic hormone rather than the Sorbitan Sesquioleate.[52]

Sorbitan Palmitate

The subchronic dermal toxicity of a product containing 4 percent Sorbitan Palmitate was studied using three groups of 4 male and 4 female albino rabbits. The backs of all animals were shaved, and the skin of 2 animals of each sex in each group was abraded. One group served as the untreated control, one group received an undiluted dose of 0.3 ml/kg per 75 cm^2 body surface area (BSA), and the third group received an undiluted dose of 0.9 ml/kg per 75 cm^2 BSA. Applications were made 5 days a week for 4 weeks, and the animals were necropsied 2 days following the last application. The following parameters were observed: feed consumption, behavior, appearance, weekly body weights, skin changes, hematological determinations, urinalysis, and necropsy findings. The organ weights were taken and body weight:organ weight ratios were calculated for the liver, kidneys, heart, spleen, thyroid, adrenals, testes, and ovaries. Histopathological examinations were performed on weighed organs as well as the thymus, urinary bladder, stomach, duodenum, jejunum, ileum, colon, straited muscle, and treated skin. No deaths occurred during this study. One control animal and one in the low-dose group became anorectic but recovered within a week. Body weights and feed consumption were normal. Animals treated with 0.3 ml/kg of the product developed mild to moderate skin erythema during the first 2 weeks of treatment. Mild to moderate edema and scaly desquamation developed during the second week. Two animals had severe erythema during the last week of treatment. Similar but more severe dermatitis developed in the high-dose group. Hematological analysis, urinalysis, and organ weight values were normal, and no compound-related abnormalities were found in the tissues examined. Under the conditions of this study, no systemic toxicity was produced by topical application of the product.[53]

Sorbitan Trioleate

A 93-day dermal toxicity study was performed to assess the toxicity of a product containing 5 percent Sorbitan Trioleate. The backs of 5 male and 5 female rabbits were clipped free of hair and applications of 0.36 ml/260 cm^2 per 3 kg rabbit were made daily for 93 consecutive days. A group of rabbits receiving applications of water served as the control. The rabbits were observed daily for changes in the skin and for alterations of behavior and physical appearance. Body weight was recorded weekly. Venous blood and urine samples were taken just before

the study started, after 48 treatments, and at termination. Other parameters evaluated included hematocrit and hemoglobin values, erythrocyte and total and differential leukocyte counts, pH and specific gravity of urine, and urinary glucose, protein, or occult blood. Upon necropsy on Day 94, the following tissues were examined: abdominal and thoracic viscera, kidneys, liver, spleen, thyroid, heart, adrenals, gonads, skin from application site, cecum, thymus, pancreas, salivary glands, lymph nodes, lungs, urinary bladder, gallbladder, stomach, duodenum, jejunum, ileum, colon, and straited muscle. The results of the study were as follows: 1 female treated rabbit became moribund and was killed on Day 57 and had empyema. All other animals survived the study and had no signs of toxicity except for skin irritation. In treated animals, very slight erythema developed after 1 week of treatment; irritation intensified to slight erythema with occasional slight edema. After 4 to 6 weeks of treatment, scaly desquamation occurred and persisted through the end of the study. The skin of water-treated animals was normal. Individual body weights and feed consumption were normal. Hematological, urinalysis, and organ weight values were all normal. No lesions that could be attributed to treatment were found at histological examination.[54]

See Table 8 for a summary of subchronic dermal toxicity tests and results.

Chronic Toxicity

Oral

The chronic oral toxicity of Sorbitan Stearate (Span 60) was evaluated in a 2-year study using Osborne-Mendel rats. Sorbitan Stearate was fed at concentrations of 0, 2, 5, 10, and 25 percent to groups of 24 rats, equally divided as to sex. Growth was significantly reduced in the 25 percent group but not in the other treatment groups. Survival rates were significantly decreased in the 10 and 25 percent groups. Hematologic values were normal. In rats of the 25 percent group, weights of liver and kidneys were increased, and the cecum and common bile duct were enlarged. This concentration of ester also caused hepatic cell vacuolation, which is indicative of fatty change. In this same study, 4 dogs were fed 5 percent Sorbitan Laurate in the diet for 20 months. There was no appreciable difference between tested and control dogs in food intake, body weight, longevity, or findings at necropsy.[47]

Sorbitan Stearate was tested for chronic oral toxicity using TO strain mice. Groups of 48 male and 48 female mice were fed 0, 0.5, 2.0, and 4.0 percent ester for 80 weeks. No toxic effects on condition, behavior, or mortality were observed in mice fed Sorbitan Stearate. Body weights were normal except for males of the 0.5 and 4.0 percent groups; these animals had reduced weight gain at Week 37 and reduced body weight at completion of the study. Abnormal hematological values occurred at Week 80 in both male and female mice fed 4 percent ester. The males had a higher total erythrocyte count, and females had a lower leukocyte count. Males in the 0.5 and 4.0 percent groups had decreased weights of the brain, kidneys, stomach, and spleen. Females in the 2 percent group had decreased stomach and increased brain weights. Females in the 4 percent group had increased weights of the kidneys and nephrosis.[55]

Sorbitan Stearate was fed at dietary concentrations of 0, 5, 10, and 20 percent to groups of 12 male and 20 female Wistar rats for 2 years. During the course of the study, observations were made of physical appearance, behavior, repro-

TABLE 8. Subchronic Dermal Toxicity

Ingredient	*Species and No. of Rabbits*	*Ingredient Concentration (percent)*	*Dose (entire product)*	*Time Applied*	*Comments*	*Reference*
S. Stearate	5M, 5F New Zealand	2.0	6.6 mg/cm²	Daily, 3 months	Moderate erythema; slight edema and desquamation. No systemic toxicity	51
	5M, 5F New Zealand	2.0	11 mg/cm²	Daily, 3 months	Moderate erythema; slight edema and desquamation. No systemic toxicity	51
S. Sesquioleate	45F New Zealand	1.0	0, 30, 300, or 3000 mg	13 weeks, 5 days per week	Minimal to slight skin irritation; no compound-related abnormalities	52
S. Palmitate	4M, 4F albino	4.0	Control (0)	4 weeks, 5 days per week	Normal	53
	4M, 4F albino	4.0	0.3 ml/kg	4 weeks, 5 days per week	Erythema began in first week of application, progressed to severe erythema at end of study. No systemic toxicity	
	4M, 4F albino	4.0	0.9 ml/kg	4 weeks, 5 days per week	Similar but more severe dermatitis. No systemic toxicity	
S. Trioleate	5M, 5F	5.0	0.36 ml/kg	93 days	Slight erythema, desquamation. No systemic toxicity	54

duction, and lactation through three successive generations, and gross and histologic evaluations were made at termination. Growth was normal, except for males in the 20 percent group. These animals had reduced weight gains.[56] Fertility and gestation parameters for the initial generation were similar for control and test groups. Infant deaths for the 10 and 20 percent ester groups were higher than for the control group. The author believed this was due to maternal neglect and reduced milk production. Reproduction and lactation data were also recorded for the F_1 and F_2 generations. The proportions of matings resulting in pregnancy were lower in the 20 percent dietary ester group, as was the proportion of nurselings surviving the lactation period.[57] No deviation from the normal range was found in hemoglobin values, leukocyte counts, blood sugar, or plasma cholesterol values. Urinalysis after 1 and 2 years had sporadic positive tests for the presence of albumin and reducing sugars.[58] No striking differences in number of deaths in any group were found up to 1½ years. However, during the last quarter of the study the number of deaths was greater for the 20 percent group. Lungs of both test and control animals were congested. In rats of the 10 and 20 percent ester groups, the livers were enlarged, but the incidence of hepatic necrosis was no greater in these groups than in lower dosed groups or controls. Also at the two higher dietary concentrations, the weights of the kidneys were increased, but no microscopic changes were observed. The stomach, GI tract, heart, spleen, pancreas, adrenals, thyroid, gonads, lymph nodes, bone marrow, and spinal cord had no compound-related lesions. The investigators concluded that chronic consumption of a few tenths of 1 percent of Sorbitan Stearate would pose no hazard to human health.[59]

Sorbitan Laurate (Span 20), at dietary concentrations of 0 or 5 percent, was fed to two groups of 50 and 30 male rats, respectively, for 2 years. No growth retardation or change in mortality was observed in the 5 percent Sorbitan Laurate group as compared to control rats. After 1 year, 40 percent of the rats from each group had died, and at termination of the study only 15 percent of both groups survived. No differences were found between the test and control groups in hemoglobin concentrations, red and white blood cell counts, or blood chemistry values. Upon necropsy, the heart, lungs, spleen, liver, kidneys, thyroids, and adrenals were of normal size. Also, there was no treatment-related gross or histopathological changes in the liver, kidneys, brain, spleen, GI tract, pancreas, thyroid, parathyroid, prostate, pituitary, salivary or adrenal glands, urinary bladder, heart, lungs, testes, striated muscles, or bone marrow.[32]

Two groups of 50 and 30 male rats were fed 0 and 5 percent Sorbitan Oleate, respectively, for 2 years. The ester had no adverse effects on growth rate, hemoglobin concentration, white and red blood cell counts, blood urea, blood glucose, serum cholesterol, or mortality. No gross and microscopic alterations were found in the heart, lungs, spleen, liver, kidneys, adrenals, thyroid, bone marrow, testes, striated muscle, prostate, GI tract, pancreas, urinary bladder, lymph nodes, brain, parathyroid, or pituitary glands.[32]

See Table 9 for a summary of chronic oral toxicity tests and results.

MUTAGENESIS AND CARCINOGENESIS

Mutagenesis

Sorbitan Stearate was tested for transformation on cryopreserved primary cultures of Syrian golden hamster embryo cells in vitro and for mutagenicity in

TABLE 9. Chronic Oral Toxicity

Ingredient	Species and No. of Animals	Concentration in Feed (percent)	Observation Period	Comments	Reference
Sorbitan Stearate	12M, 12F Osborne-Mendel rats	0	2 Years	Control	47
	12M, 12F Osborne-Mendel rats	2	2 years	No growth depression	47
	12M, 12F Osborne-Mendel rats	5	2 years	No growth depression	47
	12M, 12F Osborne-Mendel rats	10	2 years	No growth depression. Decreased survival rates	47
	24 Osborne-Mendel rats	25	2 years	Growth depression. Decreased survival rates. Increased weight in liver, kidneys; enlargement of cecum and common bile duct. Hepatic cell vacuolation	47
	4 dogs	5	20 months	Normal	47
	48M, 48F TO strain mice	0	80 weeks	Control	55
	48M, 48F TO strain mice	0.5	80 weeks	Males showed lowered body weight and decreased organ weights	55
	48M, 48F TO strain mice	2.0	80 weeks	Females had decreased stomach and increased brain weights	55
	4M, 48F TO strain mice	4.0	80 weeks	Males showed lowered body weight and a higher total erythrocyte count. Females showed lower leukocyte count. Males showed decreased organ weights; females showed increased kidney weights. Kidney nephrosis in males and females	55

	12M, 20F Wistar rats	0	2 years	Control	56–59
	12M, 20F Wistar rats	5	2 years	Normal weight gains. Normal blood chemistry. Sporadic positive tests for urine albumin and reducing sugar	56–59
	12M, 20F Wistar rats	10	2 years	Normal weight gains. Higher number of infant deaths. Sporadic positive tests for albumin and reducing sugars in urine. Normal blood chemistry	56–59
	12M, 20F Wistar rats	20	2 years	Decreased weight gains. Higher number of infant deaths. Lower proportion of both fecund matings and proportion of nurslings surviving lactation. Normal blood chemistry. Sporadic positive tests for urine albumin and reducing sugars. Mortality rate higher for this level than for lower levels only during the last quarter of the study. Increased kidney and liver weights. All other organs were normal	56–59
Sorbitan Laurate	50M rats	0	2 years	Control. 40 percent mortality after 1 year; 85 percent dead after 2 years	32
	30M rats	5	2 years	40 percent mortality after 1 year; 85 percent dead after 2 years. No growth retardation. Blood chemistry, organ weights, and gross microscopic evaluations of organs were normal	32
Sorbitan Oleate	50M rats	0	2 years	Control	32
	30M rats	5	2 years	No adverse effect on growth, hematology, clinical chemistry, or mortality. No gross or microscopic changes were seen in organs	32

Salmonella typhimurium. No transformations occurred in the embryo cells, and there was no mutagenic activity in the bacteria when tested with and without metabolic activation systems.[60]

Carcinogenesis

Both the carcinogenicity and the tumor-promoting activity of undiluted Sorbitan Laurate in skin were tested using groups of 50 male Swiss mice. The test area was a 2 × 2 cm area of the interscapular region that was clipped free of hair. In the carcinogenesis test, the 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 1 animal out of 50 developing one papilloma. Untreated control groups of 240 male and 240 female mice from the same colony were observed for their lifespan. One control female developed a papilloma, which regressed, whereas one male mouse developed a skin papilloma and one male mouse developed a squamous carcinoma. Two other groups of 100 males and 100 females were observed for over 100 weeks, and no skin tumors were observed. In the test of Sorbitan Laurate as a promoting agent, the first application of the ester was made 1 week after a single application of the tumor initiator (7,12-dimethylbenz(a)anthracene [DMBA], 1 percent in mineral oil, dose not given), and thereafter the ester was applied twice weekly for 75 weeks. Five of fifty mice developed a total of 8 tumors, 2 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.[61]

An extensive study was published by Setala[62] on the promoting and cocarcinogenic activity of a variety of nonionic-lipophilic-hydrophilic agents, including Sorbitans Laurate, Oleate, and Trioleate. A single dose of 150 μg of DMBA (0.3 percent in paraffin) was painted on the shaved backs of male mice (50 mice per group). Approximately 80 mg of the "promoting agent" was then painted on the test site 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 5 tumors in 4 animals, and no tumors were observed in animals receiving Sorbitan Trioleate after initiation with DMBA. Complete results are presented in Table 10. Sorbitans Oleate and Trioleate were inactive as tumor promotors, whereas Sorbitan Laurate was active on mouse skin as a tumor promotor.

This same study[62] investigated the cocarcinogenic activity of Sorbitans Laurate, Oleate, and Trioleate. Either 0.3 percent (150 μg), 0.03 percent (15 μg) or 0.003 percent (1.5 μg) DMBA dissolved in the various Sorbitans was applied to the shaved backs of mice (50 mice per group) 3 times a week. At the 0.3 percent 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 percent 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 percent carcinogen dose, the results

TABLE 10. Skin Tumor Promotion Following Single Application of DMBA[62]

"Promotor"	No. of Applications Per Day	Total No. of Tumors/Total No. of Tumor-Bearing Mice	No. of Malignant Tumors	No. of Animals Alive at 52 Weeks
S. Laurate	1	10/9	1	30
S. Laurate	2	33/21	0	29
S. Oleate	1	5/4	1	33
S. Trioleate	1	0/0	–	0*
None	–	0/0	–	8
Liquid paraffin	1	0/0	–	32
Liquid paraffin (no DMBA)	1	0/0	–	33
S. Laurate (no DMBA)	1	1/1	0	36
S. Laurate (no DMBA)	2	1/1	0	28
S. Oleate (no DMBA)	1	1/1	0	31
S. Trioleate (no DMBA)	1	1/1	0	28

*All animals were dead by Week 45.

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 percent DMBA.

Sorbitan Stearate was fed to groups of 48 male and 48 female TO strain mice in dietary levels of 0, 0.5, 2.0, or 4.0 percent for 80 weeks. Two of the parameters studied were tumor type and incidence. The numbers and types of neoplasms occurred either with comparable frequency in the test and control groups or were found more frequently in the controls.[55]

Gauden et al.[63] studied the inhibition by DNA repair by Sorbitan Oleate as evidence of its cocarcinogenic behavior. Experiments to demonstrate this effect involved studying the uptake of tritiated thymidine into the DNA of UV-radiated lymphocytes. The extent of uptake indicated the presence of a DNA repair capability in these cells. The ester added to the incubation mixtures at 0.01 percent concentration produced 50 percent inhibition of repair replication. The data indicated that Sorbitan Oleate was an inhibitor of DNA repair.

CLINICAL ASSESSMENT OF SAFETY

Effects of Ingestion

Steigmann et al.[64] studied the effect of acute and prolonged ingestion of Sorbitan Stearate on the gastrointestinal tract of humans. The acute phase dealt with 5 patients who received one 20 g dose of Sorbitan Stearate. Two of these individuals had increased gastric motility, and three had no change. One patient

had an increase in free gastric acidity, and all patients had normal gastric juices. In the prolonged ingestion tests, 9 patients received Sorbitan Stearate in 3 g doses twice daily for 28 days. No change was observed in gas pattern in 7 patients, more gas occurred in the eighth patient, and less in the ninth. There was no change in gallbladder function in 7 patients, better emptying time in the eighth, and less visualization in the last. Six patients had normal gastric emptying times, two had slower emptying times, and one had faster emptying time. Normal radiographic intestinal patterns were present in all patients.

Forty-two test subjects ingested 6 g of Sorbitan Stearate per day for 28 days to determine its pharmacological effect. During the course of the study and at its completion, no specific complaints were registered, and physical findings remained unchanged in all subjects. Eleven subjects had some albumin in urine at the end of the study. Four individuals had glycosuria when tested at the end of the study; however, 1 of these patients was diabetic, and another had an abnormal glucose tolerance test. No significant changes were found in hemoglobin values, hematocrit, erythrocyte count, or erythrocyte fragility. Blood chemical values were normal except for 1 patient who had slightly elevated total serum bilirubin. Approximately one third of the Sorbitan Stearate-fed patients had abnormal bromosulfophthalein retention. No other deleterious effects were seen.[65]

Skin Sensitization in Sensitive Individuals

Sorbitan Stearate combined with Sorbitan Oleate and Sorbitan Sesquioleate alone were tested for dermatological effects in patients suspected of having contact sensitivities to the esters. Sorbitans Stearate and Oleate were incorporated into petrolatum in concentrations of 5 percent each, to make the total ester concentration in the sample 10 percent. The concentration of Sorbitan Sesquioleate in petrolatum was 20 percent. The 20 percent Sorbitan Sesquioleate and the Sorbitan Stearate/Sorbitan Oleate mixture were applied to the backs of 486 panelists for 20 to 24 hours and evaluated for the first time about 30 minutes after sample removal. Both the combined esters and the Sorbitan Sesquiolate produced sensitization in 2 patients.[66]

These same substances, Sorbitan Stearate, Oleate, and Sesquioleate, were tested for dermatological effects in 1206 patients. Sorbitan Stearate and Sorbitan Oleate, each at test concentrations of 5 percent, were combined in petrolatum to make a total ester concentration of 10 percent; Sorbitan Sesquioleate was tested at a 20 percent concentration in petrolatum. All subjects were tested with both preparations. The substances were applied under occlusion for 24 hours, and the evaluations were made about 20 minutes after removal of the samples and again after 2 and 4 or 5 days. Six patients had allergic reactions to Sorbitan Sesquioleate, and five of these patients had a cross-sensitivity to the combined Sorbitan Stearate and Oleate. Sorbitan Sesquioleate caused severe eczema in 1 patient, and moderate allergic dermatitis in 2 other patients.[67]

Skin Sensitization and Irritation Tests

Sorbitan Stearate

Repeated Insult Patch Test (RIPT)

A cosmetic product containing 2 percent Sorbitan Stearate was used on 205 individuals in a modified Draize-Shelanski repeated insult patch test. Occlusive

patches impregnated with 0.1 g of the product were applied to the cleansed upper back or inner arm for a 6-week period. During the first 3 weeks, patches were applied each Monday, Wednesday, and Friday for 24 hours, after which the patches were removed and the sites scored. On Wednesday of the fourth week, a 48-hour induction patch was applied, followed by a 2-week nontreatment period. On Monday of the sixth week, two final 48-hour patches were applied, one to the original patch site and one to a previously unpatched site. The sites were scored 48 and 72 hours after application on a scale of 0 (no reaction) to 4+ (erythema, edema, possible ulceration). One subject developed a 2+ reaction (erythema and edema or induration) on the eighth and ninth treatment, and the tenth treatment was omitted; results of challenge testing were negative. Ten panelists had 1+ reactions (erythema), and two panelists had 2+ reactions during the induction phase, but these were considered irritant reactions and not clinically significant. Erythema was experienced by 10 panelists at one or more challenge patches. The investigators concluded that within the test population and procedure, the product was not a primary irritant or an allergic contact sensitizer.[68]

Another modified Draize-Shelanski repeated insult patch test was conducted as above on a cosmetic product containing 2 percent Sorbitan Stearate. Of the 108 men and women who completed the study, 1 person had erythema after the ninth induction patch. No other reactions occurred from the induction series. Three people had erythema after the first challenge patch. Within the parameters of population size and test procedure, this product was neither a primary irritant nor an allergic contact sensitizer.[69]

A similar test was conducted on a product containing 4 percent Sorbitan Stearate. A group of 107 women were given 10 repeated 48-hour patch tests, and a 48-hour challenge was performed 14 days later. No reactions occurred in any test panelist. The investigators concluded that the product was not a primary irritant and that its potential for sensitization was exceedingly low.[70]

21-Day Cumulative Irritancy Test

A cosmetic cream product containing 2 percent Sorbitan Stearate was tested for cumulative skin irritation. A 0.2 ml amount of the product was applied under occlusion to the skin of the back of 13 volunteers for 21 consecutive days (23 hours per day). Each site was graded 24 hours after application, and a new patch was applied immediately. This compound produced only mild irritation, and the total irritation score was 30.77 (630 maximum). The product was considered a "mild material."[71]

A similar test was conducted using a product containing 4 percent Sorbitan Stearate. Thirteen volunteers received 23-hour occlusive patches for 21 consecutive days. Each 0.2 ml application site was graded 24 hours after application, and a new patch was immediately replaced on each site. This product caused mild cumulative irritation, with a total score of 15.38 (630 maximum). This product was considered a "mild material."[72]

Phototoxicity Test

A cosmetic product containing 2 percent Sorbitan Stearate was tested for production of phototoxic reactions. The lower back area of 10 subjects was cleansed thoroughly, and two test sites were treated with approximately 5 $\mu l/cm^2$

of product. One treated site and an untreated site were exposed to the equivalent of 1 MED of UV light from a Krohmeyer Hot Quartz Spot Lamp (Emission spectrum: discontinuous bands with peaks at 254, 265, 297, 303, 313, and 365 nm). The sites were evaluated immediately and 24 and 48 hours after UV exposure; grading was according to the following scale: 0 (no reaction) to 4+ (intense erythema, edema, and blisters). No reactions occurred in any subject at either the UV exposed sites or the occluded sites. The product was not phototoxic.[73]

Photoallergy Test

The primary irritation and photosensitization potential of a cosmetic product containing 2 percent Sorbitan Stearate was tested using 27 individuals. The upper back area was cleansed, and 24-hour occlusive patches of the cosmetic were applied to each site. Twenty-four hours after application, the patches were removed, and one treated site and one untreated site were exposed for 30 seconds to light from a Krohmeyer Hot Quartz Spot Lamp (Emission spectrum: discontinuous bands with peaks at 254, 265, 297, 303, 313, and 365 nm). Evaluation of irritation was performed immediately after radiation. After 24 hours, the patches were reapplied, and the sequence of patching and radiation was repeated five times. Twelve days after the last induction, 24-hour challenge patches were applied, and one treated and one untreated site were radiated again for 30 seconds. These sites were scored after 24 and 48 hours on a scale of 0 (no reaction) to 4+ (intense erythema, edema and vesicles). One subject had two mild reactions at the unexposed patch during induction but none at challenge. All other subjects were unaffected, and the product was not a photoallergen.[74]

Sorbitan Laurate

A Schwartz Prophetic Patch Test using a 30 percent in distilled water or a 100 percent concentration of Sorbitan Laurate was conducted on 10 and 50 subjects, respectively. No irritant reactions were observed.[22]

Sorbitan Sesquioleate

Schwartz Prophetic Patch

Undiluted Sorbitan Sesquioleate was patch-tested on 50 human subjects. The material was applied under occlusion for 72 hours; the occlusion was then removed and the skin site evaluated. Seven days later, the material was reapplied under occlusion for 72 hours. The patch was removed, and the site was evaluated. Neither the first nor the second application produced irritation or sensitization in the subjects.[33]

A similar test, using 48-hour patches rather than 72-hour patches, was performed on 10 subjects using 30 percent Sorbitan Sesquioleate in water. No reactions occurred, and the product was neither a primary irritant nor a sensitizer.[33]

Repeated Insult Patch Test

A modified Draize repeated insult patch test was performed using a cosmetic product containing 1.0 percent Sorbitan Sesquioleate. The 109 panelists received nine 0.4 ml induction applications to their backs; the first induction patch was 48 hours in duration and subsequent patches were applied for 24 hours. After a 2-week nontreatment period, a challenge 48-hour patch was applied to previ-

ously untreated sites and scored at 20 minutes and 48 and 120 hours after patch removal. Two panelists had mild reactions 20 minutes after patch removal but no reactions thereafter. It was concluded that this product did not induce sensitization.[75]

A similar test was conducted using a hand cream containing 1.0 percent Sorbitan Sesquioleate. One subject out of 116 had mild erythema after inductions 5, 6, and 7 but had no reaction upon challenge. No other panelists had cutaneous reactions, and it was concluded that the product did not produce an allergic sensitization.[76]

A cleansing cream product containing 3 percent Sorbitan Sesquioleate was tested for human primary irritation and sensitization. The 51 panelists received seven 18-hour occlusive patches and one 24-hour patch of the undiluted product to the arm. After a 2-week nontreatment period, a 24-hour challenge patch was applied and scored 24, 48, and 72 hours postapplication. Severe erythema occurred in 1 person after induction patch 3 and in 1 person after induction patch 6. Moderate erythema occurred in 1 person after induction patches 3 and 5 and in 2 people after patches 6 and 7. Slight erythema occurred at a total of 56 sites during the seven inductions. The challenge patches produced slight erythema in 3 panelists after 24 and 48 hours and moderate erythema in 1 person after 48 hours. This compound was not considered to be a primary irritant or a sensitizer.[77]

A series of four 18-hour patches were applied to 25 panelists using a cleansing cream containing 3 percent Sorbitan Sesquioleate. Slight erythema occurred in 1 panelist after patch number 2 and in 5 panelists after patch numbers 3 and 4. This compound was not a primary irritant.[78]

A cleansing cream product containing 3 percent Sorbitan Sesquioleate was tested for human primary skin irritation and sensitization. Each of the 51 panelists received eight 6-hour patches and, after a 2-week nontreatment period, one 6-hour challenge patch. Severe erythema occurred in 1 person after the seventh and eighth inductions, and moderate erythema occurred in 5 people after the eighth induction. Slight erythema occurred in 23 people after induction patches 3 through 7. No reactions occurred after the challenge patches. This product was neither an irritant nor a sensitizer.[79]

Sorbitan Oleate

Repeated Insult Patch Test

Two products, each containing 1.75 percent Sorbitan Oleate, were used in a repeated insult patch test. A group of 53 individuals received a series of 12 daily 0.2 ml 24-hour applications to the upper arm. A series of four challenge applications was made on previously untreated sites. The test sites on one half of the group were abraded, whereas the other sites were not abraded. The contact area was evaluated after each patch was removed, and reactions were graded on a scale of 0 (no reaction) to 4+ (erythema, induration, vesiculation, ulceration). One cream caused irritation in 6 individuals after four or more induction applications. Irritation was minimal (1+) in 3 individuals, moderate (2+) in 2 people, and severe (4+) in 1. Abrading the skin did not increase the intensity or the incidence of irritation, and the product produced no sensitization reactions. The second product produced irritation in 7 panelists, 5 of whom reacted to the first

cream. Irritation appeared after six or more applications and ranged from minimal (1+) in 3 panelists to moderate (2+) in 3 individuals to severe (4+) in 1 person. Abrading the skin did not increase the severity or incidence of irritation, and no sensitization occurred.[80]

Twenty-three panelists enrolled in a repeated insult patch test of a product containing 2 percent Sorbitan Oleate. About 0.2 g of the product was applied under occlusion either to the inner aspect of the arm or on the back. After 24 hours, the patches were removed, the sites were graded, and another patch was applied until a series of 10 applications was completed. After a 10- to 14-day nontreatment period, a 24-hour challenge patch was applied, then the sites were graded immediately and 24 hours after patch removal. One subject had erythema (1+) and erythema and papules (2+) after induction numbers 2, 4, 5, and 7 and after the challenge patch. This product was not an irritant or a sensitizer.[81]

The Shelanski-Jordan repeated insult patch procedure was used to test the primary irritation and allergic sensitivity potential of a product containing 2 percent Sorbitan Oleate. The 210 panelists had no reactions to the induction patches, except for 1 individual who had erythema and papules after induction patches 9 and 10. At the first challenge application and at the 48-hour reading of the second challenge application, no reactions were observed. Erythema and papules were observed in 1 person 72 hours after the second challenge patch. It was concluded that the product was neither a strong irritant nor a strong contact sensitizer.[82]

Human Usage Test

Two cream products containing 1.75 percent Sorbitan Oleate were assayed for irritation in a 4-week usage test involving 53 individuals. The products were used on the hands and faces of the panelists. Twenty-five people used the first cream; of this group, 13 used the product twice daily, and 12 used it three times per day. The second group of 28 was divided into two subgroups; one subgroup (15 panelists) used the second product twice daily, and the other subgroup (13 panelists) used the product three times per day. None of the panelists using the second product experienced irritation. Three of the 25 people using the first product had mild irritation. One individual developed a rash on both arms, but these areas had not been exposed to the product. Patch tests of the product on this individual did not produce reactions, and it was concluded that the eruption was not related to the product. The second individual developed irritation around the eyes. This reaction was considered primary irritation and not sensitization. The third reactive individual had a maculopapular reaction on the elbows. The investigators concluded that the individual had some type of intolerance to the product, but the type of intolerance was not established.[80]

Maximization Test

A dry skin cream product containing 1.75 percent Sorbitan Oleate was assayed in a maximization test for its contact-sensitizing potential. The material was applied for five alternate 48-hour periods to a site on the volar forearm or back of 25 subjects. The site was pretreated for 24 hours with 2.5 percent aqueous sodium lauryl sulfate. After a 10-day nontreatment period, a 48-hour challenge patch was applied to a different site that had been pretreated for 1 hour with 5 to 10 percent sodium lauryl sulfate. Scorings were done immediately upon patch re-

moval and 24 hours later. No reactions were observed in any subject. The investigators concluded that this material was not a contact sensitizer in normal use.[83] A second dry-skin cream product, tested similarly, produced no contact sensitization in 25 adults. This second product was not a contact sensitizer in normal use.[84]

21-Day Cumulative Irritation Test

Four products containing Sorbitan Oleate were tested in 21-day cumulative irritancy tests. One product containing 1.75 percent Sorbitan Oleate was evaluated using 12 panelists. Very mild irritation occurred in the latter part of the test in 10 panelists. The irritation score for this product was 59.2 (maximum 630). The compound was slightly irritating.[85] A product containing 1.75 percent Sorbitan Oleate was tested on 10 panelists. Very mild, transient irritation was experienced by most panelists, and 1 person had more severe irritation. This compound had an irritation score of 60 (630 maximum). It was considered a "slightly irritating" product.[86] A cosmetic cream containing 20 percent Sorbitan Oleate was tested using 10 panelists. Two panelists had increasing irritation with subsequent applications toward the end of the study, and four others had mild, transient irritation. This compound had an irritation score of 59 (maximum 630), and it was classified as "slightly irritating."[87] A similar test on a second product containing 2.0 percent Sorbitan Oleate was conducted using 12 volunteers. This compound caused moderate irritation in 3 panelists toward the end of the application series. Very mild, transient irritation was experienced by 8 others. This compound had an irritation score of 99.0 (maximum 630), and the product was considered to be "probably mild in normal use."[88]

Phototoxicity Test

A product containing 2.0 percent Sorbitan Oleate was tested for phototoxicity using 16 panelists. An area on the inner surface of each forearm was tape-stripped to remove cornified epithelium, and 0.2 g of product was applied to it under occlusion for 24 hours. All patches were then removed, and application sites were graded according to a scale of 0 (no reaction) to 4+ (erythema, papules, edema, and vesicles). These sites were then treated for 5 minutes with the product, and one arm of each panelist was radiated, while the other served as the control. The sites were subjected to a UV light dose of 4400 $\mu W/cm^2$ (four GE, F40 black light bulbs in the UVA range with peak at 360 nm) for 15 minutes from a distance of 10 to 12 cm. Sites were scored immediately and 24 and 48 hours after irradiation. One week later, observations were made for tanning. After the UV exposure, 2 subjects had erythema, but no other reactions were observed. It was concluded that the product was not phototoxic.[81]

Photoallergy Test

A product containing 2 percent Sorbitan Oleate was tested for its photoallergic potential using 40 subjects. About 0.2 g of the product was applied under occlusion for 24 hours to the inner aspect of each forearm; the left forearm was the nonradiated control, and the right forearm was exposed for 15 minutes to a total UV dose of 4400 $\mu W/cm^2$ (four GE, F40 black light bulbs in the UVA range with peak at 360 nm) with the site 10 to 12 cm from the source. Sites were scored before and immediately after radiation. This procedure was repeated every Mon-

day, Wednesday, and Friday for a total of 10 applications. After a 10- to 14-day nontreatment period, a 24-hour challenge patch was applied to an untreated site. Upon patch removal, the site was scored, then radiated. After the UV exposure, the site was scored immediately and after 24 and 48 hours. The scoring scale ranged from 0 (no reaction) to 4+ (erythema, papules, edema, and vesicles). Five subjects had mild reactions (erythema, and erythema and papules) to the induction patches, and no reactions occurred after the challenge patches. The cream was not a significant irritant and was not a photoallergen.[81]

Sorbitan Tristearate

Prophetic Patch Test

A Schwartz prophetic patch test was conducted using a 40 percent aqueous solution of Sorbitan Tristearate and using the undiluted pure ingredient. The 40 percent solution produced no irritation in 10 panelists, and the undiluted pure ingredient produced no irritation in 201 people.[22]

Sorbitan Palmitate

Repeated Insult Patch Test

The Shelanski-Jordan repeated insult patch procedure was used for a product containing 4 percent Sorbitan Palmitate. A 206-member panel received patches on the cleansed upper back for 24 hours. Immediately after patch removal, the sites were graded and scored according to the following scale: 0 (no reaction) to 4+ (marked edema and vesicles). This procedure was repeated each Monday, Wednesday, and Friday for a period of 3½ weeks, for 10 insults. After a 10- to 14-day nontreatment period, a 48-hour challenge patch was applied and scored. Seven to ten days after this patch was removed, a second 48-hour challenge patch was applied, and the site was graded immediately and 24 hours after removal. One subject developed erythema after the seventh insult and one after the tenth insult. Also after the tenth patch, 1 person developed erythema, papules, and vesicles. The first challenge patch caused no irritation, but the second caused erythema in 3 panelists and erythema and papules in 1. The product was neither a primary irritant nor a sensitizer.[89]

21-Day Cumulative Irritation

Three products, each containing 4 percent Sorbitan Palmitate, were tested for skin irritation in a 21-day cumulative irritancy test. The first product was evaluated on 10 panelists. Three panelists developed minimal primary irritation toward the end of the patch series, and the product irritation score was 80 (maximum 630). The product was classified as "slightly irritating."[90] The second product was similarly tested on 15 panelists and had an irritation score of 70.7 (maximum 630). This product was classified as "slightly irritating."[91] The third product was evaluated on 9 panelists. Very mild irritation occurred in 3 panelists; the irritation score was 47.78 (maximum 630), and the product was classified as a "mild material."[92]

Sorbitan Trioleate

Repeated Insult Patch Test

A cosmetic product containing 5.0 percent Sorbitan Trioleate was tested for primary irritation and allergic sensitization by the Shelanski-Jordan repeated in-

sult procedure. Occlusive patches were applied to the upper back area of 210 men and women for 24 hours. After the 24-hour period, the patches were removed, and the sites were graded on a scale of 0 (no reaction) to 4+ (marked edema and vesicles). The patching procedure was repeated every Monday, Wednesday, and Friday for a total of 10 insults. After a 10- to 14-day nontreatment period, a 48-hour patch was applied and graded immediately upon removal. A second 48-hour patch was applied after 7 to 10 days. These sites were graded after patch removal and again 24 hours later. One individual had a 2+ reaction (erythema and papules) after the ninth and tenth patches. A similar reaction occurred in 1 panelist 24 hours after removal of the second challenge patch. No other reactions occurred. The product was neither a strong irritant nor a strong contact sensitizer.[93]

Predictive Patch and In-Use Test

A cosmetic moisturizer containing 5 percent Sorbitan Trioleate was used in a modified Schwartz-Peck procedure to determine its potential for irritation or allergic sensitization. A 4-week in-use test of this product was also conducted. The upper backs of 209 women were cleansed, and occlusive patches of the product were applied for 48 hours. Subjects reacting to the product were not included in the in-use test. The in-use portion of the test consisted of at least one daily application of the material for 4 weeks. Subjects were examined for reactions after 2 weeks. A second patch test was performed at the end of the in-use test. Of the 209 panelists in the initial patch test, 204 completed the entire series. One woman had blotching after the first patch, and another panelist reported a rash after the first in-use application. The author stated, however, that irritant reactions were not uncommon after the use of such products. No other reactions occurred. The product was not an irritant or sensitizer.[94]

21-Day Cumulative Irritation Test

A cream cosmetic product containing 5 percent Sorbitan Trioleate was tested for cumulative irritation in a 21-day patch test series. Eleven women received occlusive patches with 0.2 ml of the product 23 hours per day for 21 consecutive days. Test sites were scored 24 hours after application and new patches were applied immediately. Individual scores for each panelist were not reported; however, the cumulative score was 72 (maximum 630). This product was classified as slightly irritating.[95]

The above cited data are summarized in Table 11.

SUMMARY

Sorbitan fatty acid esters, including Sorbitans Stearate, Laurate, Sesquioleate, Oleate, Tristearate, Palmitate, and Trioleate, are waxy solids or viscous liquids soluble in organic solvents. They are manufactured by combining sorbital with the appropriate fatty acid at elevated temperatures, and they are stable at pHs ranging from 2 to 12. Hydrolysis of Sorbitan fatty acid esters can occur in the presence of water at excessively high or low pH. Impurities such as free acid and alcohol, arsenic (< 3 ppm), lead (< 10 ppm), and water may be found in Sorbitan fatty acid esters.

The Sorbitans are surfactants and are used in cosmetics primarily as emulsi-

TABLE 11. Clinical Assessment of Safety—Skin Tests

Ingredient	*Test*	*Ingredient Concentration (percent)*	*Product* Dose*	*No. of Subjects*	*Comments*	*Reference*
S. Stearate	Modified Draize-Shelanski (RIPT)	2	0.1 g	205	3-week induction; 3 challenge patches. 10 people had erythema and 2 had erythema and edema or induration during induction; 10 had erythema at challenge. Irritant; nonsensitizer	68
	Modified Draize-Shelanski (RIPT)	2	0.1 g	108	3-week induction; 3 challenge patches. 1 person had erythema during induction; 3 had erythema after challenge. Nonirritant; nonsensitizer	69
	RIPT	4	–	107	10 inductions; 1 challenge. No reactions. Nonirritant; nonsensitizer	70
	21-Day cumulative irritation	2	0.2 ml	13	Mild irritation; scored 30.77 out of 630. Product classified a "mild material." Mild irritant	71
	21-Day cumulative irritation	4	0.2 ml	13	Mild irritation; scored 15.38 out of 630. Classified a "mild material." Mild irritant	72
	Phototoxicity	2	~5 μl/cm²	10	No reactions. Nonphototoxic	73
	Photoallergy	2	–	27	5 inductions; 1 challenge. 1 mild reaction upon induction. No reaction at challenge. Nonphotosensitizer	74
S. Laurate	Schwartz prophetic patch	30 in distilled water	–	10	No irritation. Nonirritant; nonsensitizer	22
		100	–	50	No irritation. Nonirritant; nonsensitizer	22
S. Sesquioleate	Schwartz prophetic patch	100	–	50	2 72-hour patches. No reactions. Nonirritant; nonsensitizer	33
	Schwartz prophetic patch	30 in water	–	10	2 48-hour patches. No reactions. Nonirritant; nonsensitizer	33
	Modified Draize RIPT	1	0.4 ml (hormone cream)	109	2 mild reactions 20 minutes after challenge patch removal. Nonsensitizer	75
	RIPT	1	(Hand cream)	116	1 subject had a mild reaction during induction. No other reactions. Nonsensitizer	76

	RIPT	3.0	(Cleanser)	51	During 7 inductions, severe erythema at 2 sites, moderate erythema at 3, and slight erythema at 56 sites. During challenge, moderate erythema in 1, slight erythema in 3. Nonirritant; nonsensitizer	77
	RIPT	3.0	(Cleanser)	25	Slight erythema during induction at 10 sites. Mild irritant; nonsensitizer	78
	RIPT	3.0	(Cleanser)	51	During 7 inductions, severe erythema at 1 site, moderate at 5 sites, and slight at 23 sites. No reactions to challenge. Mild irritant; nonsensitizer	79
S. Oleate	RIPT	1.75	0.2 ml	53	12 24-hour patches to abraded and intact sites. Minimal irritation in 3 people, moderate in 2, and severe in 1. Abrasions did not affect the reactions. Minimal irritant; nonsensitizer	80
	RIPT	1.75	0.2 ml	53	12 24-hour patches to abraded and intact sites. Minimal in 3 people, moderate in 3, and severe in 1. Abrasions did not affect reactions. Minimal irritant; nonsensitizer	80
	RIPT	2.0	0.2 g	23	1 subject showed erythema and papules during induction and challenge. No other reactions. Nonirritant; nonsensitizer	81
	Shelanski-Jordan RIPT	2.0	–	210	2 subjects had erythema and papules, 1 at induction and 1 at second challenge; no other reactions. Mild irritant; nonsensitizer	82
	Usage test	1.75	–	25	3 people had mild irritation; 2 were product-related and 1 was not. Minimal irritant	80
		1.75	–	28	No reactions. Nonirritant	80
	Maximization test	1.75	(Moisturizer)	25	Sodium lauryl sulfate pretreated site; 5 inductions, 1 challenge. No reactions. Nonsensitizer	83
	Maximization test	1.75	(Moisturizer)	25	No reactions. Nonsensitizer	84
	21-Day cumulative irritation	1.75	0.3 ml (Moisturizer)	12	Very mild irritation in 10 panelists. Scored 59.2 out of 630. Classified "slightly irritating." Mild irritant	85
	21-Day cumulative irritation	1.75	0.4 ml (Moisturizer)	10	Very mild transient irritation. Scored 60 out of 630. Classified "slightly irritating." Mild irritant	86
	21-Day cumulative irritation	2.0	0.2 ml (Moisturizer)	10	Mild, transient irritation in 6 people. Scored 59 out of 630. "Slightly irritating." Mild irritant	87
	21-Day cumulative irritation	2.0	0.2 ml	12	Moderate irritation in 3 panelists; very mild irritation in 8 others. Scored 99.09 out of 630. Classified as "probably mild in normal use." Moderate irritant	88

TABLE 11. (Continued)

Ingredient	*Test*	*Ingredient Concentration (percent)*	*Product* Dose*	*No. of Subjects*	*Comments*	*Reference*
	Phototoxicity	2.0	0.2 g	16	2 subjects had slight erythema after UV exposure. No other reactions. Nonphototoxic	81
	Photoallergy	2.0	0.2 g	40	Induction patches caused erythema and papules in 5 people. No reactions to challenge. Mild irritant; nonphotoallergen	81
S. Tristearate	Schwartz prophetic patch	100	–	10	No irritation. Nonirritant; nonsensitizer	22
		40 in water	–	201	One reaction. Nonirritant; nonsensitizer	22
S. Palmitate	Shelanski-Jordan RIPT	4.0	–	206	10 inductions, 2 challenges. During induction, erythema in 2 people, erythema, papules, and vesicles in 1. Second challenge produced erythema in 3 and erythema and vesicles in 1. Nonirritant; nonsensitizer	89
	21-Day cumulative irritation	4.0	–	10	Minimal irritation in 3 panelists. Scored 80 out of 630; classified "slightly irritating." Mild irritant	90
	21-Day cumulative irritation	4.0	–	15	Scored 70.7 out of 630; classified as "slightly irritating." Mild irritant	91
	21-Day cumulative irritation	4.0	(Moisturizer)	9	Very mild irritation in 3 panelists. Scored 47.78 out of 630. Classified as a "mild material." Mild irritant	92
S. Trioleate	Shelanski-Jordan RIPT	5.0	–	210	1 person showed erythema and papules after induction; and 1 had erythema at the second challenge reading. Mild irritant; nonsensitizer	93
	Modified Schwartz-Peck predictive patch	5.0	(Moisturizer)	204	1 person reacted with blotching. No other reactions. Nonirritant; nonsensitizer	94
	In use	5.0	(Moisturizer)	204	4-week test; 1 person had a rash. No other reactions. Nonirritant; nonsensitizer	94
	21-Day cumulative irritation	5.0	0.2 ml	11	Scored 72 out of 630. Classified as "slightly irritating." Mild irritant	95

*Product type, if available, given in parentheses.

fiers, solubilizers, emulsion stabilizers, and thickeners. The majority of these cosmetics contain from 0.1 to 5 percent Sorbitan ester. These cosmetics are applied to all areas of the skin, hair, scalp, nails, and mucous membranes up to several times per day. The Sorbitan esters are also added to foods, beverages, drugs, textiles, and plastics.

Sorbitan Stearate is hydrolyzed to stearic acid and anhydrides of sorbitol when ingested. Approximately 90 percent of the Sorbitan Stearate is absorbed and hydrolyzed when fed to rats in oil solution, and 50 percent is absorbed and hydrolyzed when fed as a water emulsion. Sorbitan Stearate does not accumulate (< 0.5 percent) to any appreciable amount in the fat stores of the rat body.

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.

Carcinogenicity studies have been performed with Sorbitans Stearate and Laurate, and mutagenicity testing using *Salmonella typhimurium* strains has been done with Sorbitan Stearate. 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*. 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 promotor when painted on mice skin for 70 weeks. However, in another study, Sorbitan Laurate (Span 20) was a tumor promotor when applied twice daily to mice skin after initiation by DMBA. In the same study, Sorbitan Oleate and Sorbitan Trioleate were inactive as tumor promotors. In undiluted form, Sorbitan Laurate and Sorbitan Trioleate were active as cocarcinogens on mouse skin when applied with DMBA (0.003 percent).

Sorbitan Oleate at a concentration of 0.01 percent inhibited *in vitro* DNA repair.

The results of oral toxicity studies of Sorbitan fatty acid esters indicated that these Sorbitans in low concentration were relatively nontoxic via ingestion. The lowest rat LD50 in the 20 sorbitan ester studies reported was 31 g/kg for Sorbitan Stearate. 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 percent. When the feed concentration of Sorbitan Laurate was $\geq$ 10 percent, growth depression, decreased organ weights, diarrhea, unkempt appearance, hepatic and renal abnormalities, and GI tract irritation were generally observed. Subchronic feeding of Sorbitan Oleate to rats produced no abnormalities until the ester was at least 10 percent of the feed. At this concentration, the same types of abnormalities occurred as those observed in the Sorbitan Laurate fed animals. Chronic feeding studies have been conducted with Sorbitans Stearate, Laurate, and Oleate. At a 5 percent dietary concentration, Sorbitan Laurate or Sorbitan Oleate had no adverse effect on rats over a two-year period. Dogs fed 5 percent Sorbitan Stearate for 20 months had no compound related changes. A feed concentration of $\geq$ 10 percent 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. A 0.5 percent dietary concentration produced growth depression in male rats, and a 4 percent dietary concentration produced renal abnormalities as well.

Draize and Modified Draize ocular irritation studies using rabbits were performed with all of the Sorbitans in this report. One study using a high concentration of Sorbitan Stearate was negative for ocular irritation, and low concentrations in products caused slight conjunctival irritation. High concentrations of Sorbitan Sesquioleate produced no ocular irritation. One study with Sorbitan Laurate, and two studies each on Sorbitans Oleate, Tristearate and Palmitate were negative for ocular irritation in the rabbit.

Numerous skin irritation studies in animals indicate that the Sorbitans are minimal to mild irritants. Acute skin irritation tests with rabbits involving Sorbitan Stearate resulted in mild irritation. Sorbitan Laurate was mildly irritating to rabbit skin, causing dose-dependent erythema and edema. The rabbit dermal toxicity and irritation potential of Sorbitan Sesquioleate is minimal. Sorbitan Oleate was minimally irritating to rabbit skin. When solutions of Sorbitan Oleate were applied to rabbit skin, erythema and edema developed. Sorbitan Palmitate 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 was nonirritating when applied to the skin of rabbits. Sorbitan Trioleate was generally found to be a skin irritant in rabbits. Sorbitan Trioleate was applied to rabbit skin and produced erythema, edema, and thickening. No systemic toxicity was observed.

Three clinical assessments have evaluated the oral toxicity of Sorbitan Stearate. One acute dose of 20 g was administered to five subjects, two of whom had increased gastric motility. One subject had an increase in free gastric acidity, and all subjects had normal gastric juices. Nine patients were given 3 g Sorbitan Stearate twice daily for 28 days. Seven patients had normal gas patterns (determined radiographically), one had more, and one had less at the end of the observation period. Seven patients had no change in gall bladder function, the eighth had increased emptying time, and the ninth patient had fainter visualization. Normal radiographic intestinal patterns were observed for all nine patients. In an additional study, 42 subjects ingested 6 g Sorbitan Stearate daily for 28 days. Eleven subjects had albumin in their urine at the end of the study, and four had glycosuria; however, one of the four patients with glycosuria was diabetic, and another had an abnormal glucose tolerance test. No significant changes were found in hemoglobin content, hematocrit, red cell count or red cell fragility, and blood chemistry values were normal except in one patient who had slightly elevated total serum bilirubin.

The Sorbitans are also minimal to mild skin irritants in humans. Results from three RIPTs (involving a total of 420 subjects) indicated that Sorbitan Stearate is not a sensitizer. Products containing low concentrations 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-subject 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 percent Sorbitan Sesquioleate was a sensitizer; however, some subjects experienced mild irritation.

Several products containing 1.75 to 2.0 percent Sorbitan Oleate have been tested on human subjects. In four 21-Day Cumulative Irritation studies, the prod-

ucts tested were mildly irritating. In these 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. 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 percent 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 four-week usage test.

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 ultraviolet spectral analysis.

DISCUSSION

The Sorbitan esters, including Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate and Sorbitan Trioleate, are generally mild skin irritants but nonsensitizers in animals.

As a class, the Sorbitan esters have the potential to induce cutaneous irritation in humans, and they can cause sensitization in patients with damaged skin.

Sorbitan Stearate and Sorbitan Oleate do not appear to be human photosensitizers. Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Palmitate and Sorbitan Trioleate do not absorb radiation in the UVA and UVB spectra, which suggests that these compounds are not photosensitzers. No photosensitization data or UV spectra was available for Sorbitan Tristearate. However, it would be expected that Sorbitan Tristearate would react much the same as Sorbitan Stearate in photosensitization activity.

The Panel has reviewed the data concerning the tumor-promoting activity of the Sorbitan esters, and concludes that at concentrations of 10 percent or greater Sorbitan Laurate is a tumor promotor in mouse skin. However, the Panel agrees that this is not relevant to the use of the Sorbitan esters at low concentrations in cosmetics.

CONCLUSION

On the basis of the information presented herein, Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate are considered safe as cosmetic ingredients under present conditions of concentration and use.

ACKNOWLEDGMENT

Lorraine E. Cathers, Scientific Analyst and Writer, prepared the technical analysis used by the Expert Panel in developing this report.

REFERENCES

1. GREENBERG, L.A., and LESTER, D. (1954). *Handbook of Cosmetic Materials.* New York: Interscience.
2. HAWLEY, G.G. (ed.). (1971). *The Condensed Chemical Dictionary,* 8th ed. New York: Van Nostrand Reinhold Co.
3. BALSAM, M.S., and SAGARIN, E. (eds.). (1972). *Cosmetics: Science and Technology.* New York: Wiley Interscience.
4. GOSSELIN, R.E., HODGE, H.C., SMITH, R.P., and GLEASON, M.N. (1976). *Clinical Toxicology of Commercial Products,* 4th ed. Baltimore, MD: Williams & Wilkins.
5. ESTRIN, N.F., CROSLEY, P.A., and HAYNES, C. (eds.). (1982). *CTFA Cosmetic Ingredient Dictionary,* 3rd ed. Washington, DC: Cosmetic, Toiletry and Fragrance Association.
6. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION (CTFA). (November 18, 1981). Submission of data by CTFA. Cosmetic Ingredient Chemical Description of Sorbitan Stearate (2-9-56).*
7. CTFA. (1972). CTFA Standards (Part 3).
8. JAPAN COSMETIC INDUSTRY ASSOCIATION (JCIA). (1979). Japan, Yakuji Nippo, Ltd.
9. WINDHOLZ, M. (ed.). (1976). *The Merck Index,* 9th ed. Rahway, NJ: Merck & Co.
10. CTFA. (November 18, 1981). Submission of data by CTFA. Cosmetic ingredient chemical description of sorbitan laurate (2-9-53).*
11. CTFA. (November 18, 1981). Submission of data by CTFA. Cosmetic ingredient chemical description of sorbitan sesquioleate (2-9-52).*
12. CTFA. (November 18, 1981). Submission of data by CTFA. Cosmetic ingredient chemical description of sorbitan oleate (2-9-54).*
13. NATIONAL FORMULARY (NF). (1975). 14th ed. Washington, DC: American Pharmaceutical Association.
14. CTFA. (November 20, 1981). Submission of data by CTFA. Cosmetic ingredient chemical description of sorbitan tristearate (2-9-50).*
15. CTFA. (November 18, 1981). Submission of data by CTFA. Cosmetic ingredient chemical description of sorbitan palmitate (2-9-55).*
16. CTFA. (November 20, 1981). Submission of data by CTFA. Cosmetic ingredient chemical description of sorbitan trioleate (2-9-51).*
17. FOOD CHEMICALS CODEX. (1972). 2nd ed. Washington, DC: National Academy of Sciences.
18. GRZESICZAK, A. (1978). Search for methods of analyses of excipients used in suppository and ointment bases (separation, isolation, and identification). Farm. Pol. **34**(5), 291–6.
19. CTFA. (January 26, 1983). Submission of data by CTFA. Unpublished ultraviolet absorbance spectra for sorbitans laurate and palmitate.*
20. CTFA. (June 28, 1983). Submission of data by CTFA. Unpublished ultraviolet absorbance spectra for sorbitans sesquioleate and trioleate.*
21. FURIA, T.E. (1980). *Regulatory Status of Direct Food Additives.* Boca Raton, FL: CRC Press.
22. CTFA. (December 2, 1981: Date of Transmittal Letter). Unpublished human irritation studies and animal toxicology and irritation studies of Span 20 (sorbitan laurate), Span 40 (sorbitan palmitate), Span 60 (sorbitan stearate), Span 65 (sorbitan tristearate), Span 80 (sorbitan oleate), Span 85 (sorbitan trioleate) (2-9-6).*
23. CODE OF FEDERAL REGULATIONS, TITLE 21. (1982). Washington, DC: US Government Printing Office.
24. FOOD AND DRUG ADMINISTRATION (FDA). (December 22, 1981). Computer printout of voluntary submission of cosmetic ingredient data.
25. WICK, A.N., and JOSEPH, L. (1953). The metabolism of sorbitan monostearate. Food Res. **18,** 79.
26. WICK, A.N., and JOSEPH, L. (1953). Sorbitan monostearate metabolism. Lack of deposition upon chronic feeding. J. Agric. Food Chem. **1,** 398.

*Available upon request: Administrator, Cosmetic Ingredient Review, 1110 Vermont Ave., NW, Suite 810, Washington, DC 20005.

27. MEZEI, M., SAGER, R.W., STEWART, W.D., and DERUYTER, A.L. (1966). Dermatitic effect of nonionic surfactants. I. Gross, microscopic, and metabolic changes in rabbit skin treated with nonionic surface-active agents. J. Pharm. Sci. **55**(6), 584–90.
28. MEZEI, M., and SAGER, R.W. (1967). Dermatitic effect of nonionic surfactants. II. Changes in phospholipid and in deoxyribonucleic acid content of rabbit epidermis in vivo. J. Pharm. Sci. **56**(12), 1604–8.
29. MEZEI, M., and RYAN, K.J. (1972). Effect of surfactants on epidermal permeability in rabbits. J. Pharm. Sci. **61**(8), 1329–31.
30. CTFA. (December 15, 1976). Submission of data by CTFA. Unpublished acute oral toxicity test of 100 percent sorbitan stearate (2-9-40).*
31. CTFA. (January 2, 1980). Submission of data by CTFA. Unpublished acute oral, dermal, and ocular toxicity of a product containing 4 percent sorbitan stearate (2-9-34).*
32. ATLAS CHEMICAL INDUSTRIES (ACI). (1970). Toxicology report on Span 20 and Span 80 (1950). Summaries of toxicological data. Lifespan feeding studies on Sorbitan Monolaurate and Sorbitan Mono-oleate. Food Cosmet. Toxicol. **8,** 339.
33. CTFA. (August 1972). Submission of data by CTFA. Unpublished human patch test and animal toxicology and irritation test of sorbitan sesquioleate (2-9-7).*
34. CTFA. (November 4, 1968). Submission of data by CTFA. Unpublished acute oral toxicity test of a product containing 3 percent sorbitan sesquioleate (2-9-12).*
35. CTFA. (July 31, 1978). Submission of data by CTFA. Unpublished acute oral, dermal, and ocular testing of a product containing 4 percent sorbitan palmitate (2-9-26).*
36. CTFA. (October 8, 1975). Submission of data by CTFA. Unpublished acute oral, dermal, and ocular testing of a product containing 5 percent sorbitan trioleate (2-9-19).*
37. TREON, J.F. (1963). Physiological properties of selected nonionic surfactants. Proc. Sci. Sect. Toilet Goods Assoc. **40,** 40.
38. CTFA. (December 15, 1976). Submission of data by CTFA. Unpublished primary rabbit skin irritation test of 50 percent sorbitan stearate (2-9-42).*
39. CTFA. (October 1968). Submission of data by CTFA. Unpublished primary dermal irritation in rabbits of a product containing 3 percent sorbitan sesquioleate (2-9-13).*
40. CTFA. (August 17, 1977). Submission of data by CTFA. Unpublished primary rabbit skin irritation of 5 percent sorbitan oleate (2-9-44).*
41. CTFA. (February 24, 1978). Submission of data by CTFA. Unpublished primary rabbit skin irritation of sorbitan oleate (2-9-45).*
42. CTFA. (November 4, 1968). Submission of data by CTFA. Unpublished acute dermal toxicity test in rabbits of a product containing 3 percent sorbitan sesquioleate (2-9-11).*
43. CTFA. (October 1968). Submission of data by CTFA. Unpublished ophthalmic irritation in rabbits of a product containing 3 percent sorbitan sesquioleate (2-9-14).*
44. CTFA. (August 17, 1977). Submission of data by CTFA. Unpublished ocular irritation test in rabbits of 5 percent sorbitan oleate (2-9-43).*
45. RINGROSE, A.T., and WALLER, F.F. (1959). High level feeding of surface-active agents to chicks. Toxicol. Appl. Pharmacol. **1,** 548.
46. CATER, B.R., BUTTERWORTH, K.R., GAUNT, I.F., HOOSON, J., GRASSO, P., and GANGOLLI, S.D. (1978). Short-term toxicity study of sorbitan monolaurate (Span 20) in rats. Food Cosmet. Toxicol. **16**(6), 519–26.
47. FITZHUGH, O.G., SCHOUBOE, P.J., and NELSON, A.A. (1960). Oral toxicities of lauric acid and certain lauric acid derivatives. Toxicol. Appl. Pharmacol. **2,** 59.
48. HARRIS, R.S., SHERMAN, H., and JETTER, W.W. (1951). Nutritional and pathological effects of sorbitan monolaurate, polyoxyethylene sorbitan monolaurate and polyoxyethylene monolaurate when fed to hamsters. Arch. Biochem. Biophys. **34,** 259.
49. HARRIS, R.S., SHERMAN, H., and JETTER, W.W. (1951). Nutritional and pathological effects of sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, polyoxyethylene monolaurate and polyoxyethylene monostearate when fed to rats. Arch. Biochem. Biophys. **34,** 249.
50. INGRAM, A.J., BUTTERWORTH, K.R., GAUNT, I.F., GRASSO, P., and GANGOLLI, S.D. (1978). Short-term toxicity study of sorbitan mono-oleate (Span 80) in rats. Food Cosmet. Toxicol. **16**(6), 535–42.
51. CTFA. (October 1980). Submission of data by CTFA. Unpublished subchronic dermal toxicity study in rabbits of a product containing 2 percent sorbitan stearate (2-9-33).*
52. CTFA. (March 19, 1976). Submission of data by CTFA. Unpublished subacute dermal toxicity study in rabbits of a product containing 1.0 percent sorbitan sesquioleate (2-9-47).*

53. CTFA. (May 7, 1979). Submission of data by CTFA. Unpublished subchronic dermal toxicity study in rabbits of a product containing 4 percent sorbitan palmitate (2-9-27).*
54. CTFA. (April 1976). Submission of data by CTFA. Unpublished subacute dermal toxicity study in rabbits of a product containing 5 percent sorbitan trioleate (2-9-20).*
55. HENDY, R.J., BUTTERWORTH, K.R., GAUNT, I.F., KISS, I.S., and GRASSO, P. (1978). Long-term toxicity study of sorbitan monostearate (Span 60) in mice. Food Cosmet. Toxicol. **16**(6), 527–34.
56. OSER, B.L., and OSER, M. (1956). Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. I. General plan and procedures: growth and food utilizatiion. J. Nutr. **60,** 367.
57. OSER, B.L., and OSER, M. (1956). Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. 2. Reproduction and lactation. J. Nutr. **60,** 489–505.
58. OSER, B.L., and OSER, M. (1957). Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. III. Clinical and metabolic observations. J. Nutr. **61,** 149.
59. OSER, B.L., and OSER, M. (1957). Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. IV. Mortality and post-mortem pathology: general conclusions. J. Nutr. **61,** 235.
60. INOUE, K., SUNAKAWA, T., and TAKAYAMA, S. (1980). Studies of in vitro cell transformation and mutagenicity by surfactants and other compounds. Food Cosmet. Toxicol. **18**(3), 289–96.
61. SAFFIOTTI, U., and SHUBIK, P. (1963). Studies on promoting action in skin carcinogenesis. Natl. Cancer. Inst. Monogr. **10,** 489–507.
62. SETALA, H. (1956). Tumor promoting and co-carcinogenic effects of some non-ionic lipophilic-hydrophilic (surface active) agents: an experimental study on skin tumors in mice. Acta Pathol. Microbiol. Scand. [Suppl. 115].
63. GAUDIN, D., GREGG, R.S, and YIELDING, K. (1971). DNA repair inhibition: a possible mechanism of action of co-carcinogens. Biochem. Biophys. Res. Commun. **45,** 630–6.
64. STEIGMANN, F., GOLDBERT, E.M., and SCHOOLMAN, H.M. (1953). The effect of emulsifying agents (Tween 60 and Span 20) on the gastrointestinal tract. Am. J. Dig. Dis.
65. WALDSTEIN, SHELDON S., SCHOOLMAN, HAROLD M., and POPPER, H. (July 1954). The effect of feeding large amounts of emulsifiers polyoxyethylene (20) sorbitan monostearate (Tween 60) and sorbitan monostearate (Span 60) to humans. Am. J. Dig. Dis. 181–5.
66. HANNUKSELA, M., KOUSA, M., and PIRILA, V. (1976). Allergy to ingredients of vehicles. Contact Dermatitis **2,** 105–10.
67. HANNUKSELA, M., KOUSA, M., and PIRILA, V. (1976). Contact sensitivity to emulsifiers. Contact Dermatitis **2**(4), 201–4.
68. CTFA. (April 1980). Submission of data by CTFA. Unpublished human repeated insult patch test of a product containing 2 percent sorbitan stearate (2-9-37).*
69. CTFA. (April 1979). Submission of data by CTFA. Unpublished human repeated insult patch test of a product containing 2 percent sorbitan stearate (2-9-32).*
70. CTFA. (July 30, 1973). Submission of data by CTFA. Unpublished human skin irritation of a product containing 4 percent sorbitan stearate (2-9-36).*
71. HILL TOP RESEARCH (HTR). (April 20, 1981). Submission of data by CTFA. Unpublished human cumulative skin irritation test of a product containing 2 percent sorbitan stearate (2-9-31).*
72. HTR. (April 20, 1981). Submission of data by CTFA. Unpublished human cumulative skin irritation test of a product containing 4 percent sorbitan stearate (2-9-35).*
73. LEO WINTER ASSOCIATES (LWA). (December 1979). Submission of data by CTFA. Unpublished human phototoxicity testing of a product containing 2 percent sorbitan stearate (2-9-39).*
74. LWA. (December 1979). Submission of data by CTFA. Unpublished human photo-contact allergenicity of a product containing 2 percent sorbitan stearate (2-9-38).*
75. HTR. (January 26, 1976). Submission of data by CTFA. Unpublished repeated insult patch test of a product containing 1.0 percent sorbitan sesquioleate (2-9-46).*
76. CTFA. (December 12, 1977). Submission of data by CTFA. Unpublished allergic contact sensitization test of a product containing 1.0 percent sorbitan sesquioleate (2-9-48).*
77. CTFA. (April 1976). Submission of data by CTFA. Unpublished human primary irritation/sensitization test of a product containing 3 percent sorbitan sesquioleate (2-9-8).*
78. CTFA. (September 27, 1976). Submission of data by CTFA. Unpublished human primary irritation test of a product containing 3 percent sorbitan sesquioleate (2-9-9).*
79. CTFA. (October 1976). Submission of data by CTFA. Unpublished human primary irritation/sensitization test of a product containing 3 percent sorbitan sesquioleate (2-9-10).*
80. PRODUCT INVESTIGATIONS (PI). (March 30, 1978). Submission of data by CTFA. Unpublished human dermal irritation test of a product containing 1.75 percent sorbitan oleate (2-9-4).*

81. FOOD AND DRUG RESEARCH LABORATORIES (FDRL). (December 1979). Submission of data by CTFA. Unpublished photoallergy, phototoxicity, and repeated insult patch tests of a product containing 2 percent sorbitan oleate (2-9-23).*
82. LWA. (March 1979). Submission of data by CTFA. Unpublished human repeated insult patch test of a product containing 2 percent sorbitan oleate (2-9-22).*
83. IVY RESEARCH LABORATORIES (IRL). (January 5, 1977). Submission of data by CTFA. Unpublished maximization test of a product containing 1.75 percent sorbitan oleate (2-9-49).*
84. IRL. (November 15, 1976). Submission of data by CTFA. Unpublished maximization test of a product containing sorbitan oleate (2-9-3).*
85. HTR. (November 19, 1976). Submission of data by CTFA. Unpublished human cumulative irritation test of a product containing 1.75 percent sorbitan oleate (2-9-2).*
86. HTR. (March 1, 1977). Submission of data by CTFA. Unpublished human cumulative irritation test of a product containing 1.75 percent sorbitan oleate (2-9-1).*
87. HTR. (April 18, 1979). Submission of data by CTFA. Unpublished human cumulative irritation test of a product containing 2 percent sorbitan oleate (2-9-21).*
88. HTR. (May 27, 1981). Submission of data by CTFA. Unpublished human cumulative skin irritation test of a product containing 2 percent sorbitan oleate (2-9-24).*
89. LWA. (August 1, 1977). Submission of data by CTFA. Unpublished repeated insult patch test of a product containing 4 percent sorbitan palmitate (2-9-30).*
90. HTR. (October 6, 1978). Submission of data by CTFA. Unpublished cumulative irritation test of a product containing 4 percent sorbitan palmitate (2-9-25).*
91. HTR. (October 6, 1977). Submission of data by CTFA. Unpublished cumulative irritation test of a product containing 4 percent sorbitan palmitate (2-9-29).*
92. HTR. (October 17, 1979). Submission of data by CTFA. Unpublished human cumulative skin irritation test of a product containing 4 percent sorbitan palmitate (2-9-28).*
93. LWA. (September 1978). Submission of data by CTFA. Unpublished repeated insult patch test of a product containing 5 percent sorbitan trioleate (2-9-15).*
94. LWA. (March 1975). Submission of data by CTFA. Unpublished predictive patch test and in-use test of a product containing 5 percent sorbitan trioleate (2-9-18).*
95. HTR. (October 6, 1978). Submission of data by CTFA. Unpublished cumulative irritation test of a product containing 5 percent sorbitan trioleate (2-9-16).*