Article

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Safety Assessment of Sorbitan Esters as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) assessed the safety of 20 sorbitan esters; this report included sorbitan esters that were reviewed in 1985 and 2002, as well as 3 previously unreviewed sorbitan esters (sorbitan undecylenate, sorbitan sesquicaprylate, and sorbitan palmate). Most of the sorbitan esters are reported to function in cosmetics as surfactant-emulsifying agents. The Panel reviewed the data from previous sorbitan ester reports, as well as additional data included in this report, to determine the safety of these ingredients. The Panel concluded that the sorbitan esters included in this safety assessment are safe in cosmetics in the present practices of use and concentration.

Keywords

safety, cosmetics, sorbitan esters

Introduction

In 1985, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of 7 sorbitan esters; based on the data presented in that assessment, the panel concluded that sorbitan stearate, sorbitan laurate, sorbitan sesquioleate, sorbitan oleate, sorbitan tristearate, sorbitan palmitate, and sorbitan trioleate were safe as cosmetic ingredients under [then] present conditions of concentration and use.[1] In 2002, the Panel considered the safety of an additional 10 sorbitan fatty acid esters and, based on new data as well as data from the 1985 review, concluded that the sorbitan fatty acid esters were safe for use in cosmetic ingredients under the [then] present practices of use.[2]

The Panel also determined that the data from those safety assessments, together with the new data presented on the sorbitan esters, support the safety of 3 additional esters that had not yet been reviewed (indicated below by bolded text), and the Panel reopened the safety assessment to add these esters. The ingredients included in this rereview are:

Fatty sorbitan monoesters
Sorbitan caprylate (2002)
Sorbitan undecylenate
Sorbitan laurate (1985)
Sorbitan palmitate (1985)
Sorbitan isostearate (2002)
Sorbitan oleate (1985)
Sorbitan stearate (1985)

Fatty sorbitan sesquiesters
Sorbitan sesquicaprylate
Sorbitan sesquiisostearate (2002)
Sorbitan sesquioleate (1985)
Sorbitan sesquistearate (2002)

Fatty sorbitan diesters
Sorbitan diisostearate (2002)
Sorbitan dioleate (2002)
Sorbitan distearate (2002)

Fatty sorbitan triesters
Sorbitan triisostearate (2002)
Sorbitan trioleate (1985)
Sorbitan tristearate (1985)

Mixed-chain sorbitan esters
Sorbitan cocoate (2002)
Sorbitan olivate (2002)
Sorbitan palmate

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All 20 of these ingredients share an identical sorbitan structural core and only vary by the fatty acid substituents. Most of the sorbitan esters are reported to function as a surfactant-emulsifying agent in cosmetic ingredients[3] (Table 1).

Much of the new data included in this safety assessment were found on the European Chemicals Agency (ECHA) web site.[4] The ECHA web site provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

Chemistry

Definition and Structure

The sorbitan esters are mono-, di-, and triesters, and mixtures thereof, of fatty acids and 1,4-sorbitan. Generally, these ingredients can be depicted using a 5-membered ring shown as the tetrahydrofuran form (Figure 1). However, some of the 6-membered ring, tetrahydropyran, may also be present.

The ingredients in this safety assessment are the reaction products of fatty acids, ranging from 8 carbons in length (ie, sorbitan caprylate) to 18 (eg, sorbitan stearate), with hexitol anhydrides derived from sorbitol (eg, sorbitan tristearate; Figure 2). "Sorbitan" is a generic name for anhydrides (ie, cyclic ether tetrahydric alcohols) derived from sorbitol by the removal of 1 molecule of water with concomitant cyclization.

Chemical and Physical Properties

Sorbitan esters are waxy solids or viscous liquids soluble in inorganic solvents (Table 2).[1] Sorbitan esters are stable at pH ranging from 2 to 12. Hydrolysis of sorbitan fatty acid esters can occur in the presence of water at excessively high or low pH. Sorbitol, the compound from which the hexitol anhydrides of the sorbitan esters are derived, is a crystalline, hexahydric alcohol.[5]

Methods of Manufacture

Sorbitan esters are manufactured by combining sorbitol with the appropriate fatty acid at elevated temperatures.[1]

Composition and Impurities

Impurities such as free acid or alcohol, arsenic (3 ppm), lead (10 ppm), and water may be found in sorbitan fatty acid esters.[1] Pyranyl isomers of these sorbitan esters may be present.

Use

Cosmetic

Most of the sorbitan esters are reported to function in cosmetics as surfactant-emulsifying agents (Table 1).[3] In aqueous (aq.) formulations, the emulsifying agent function is a result of the classic surfactant structural combination of a polar head group (the sorbitan core) and apolar fatty chain(s).

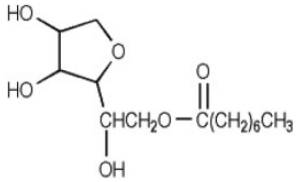
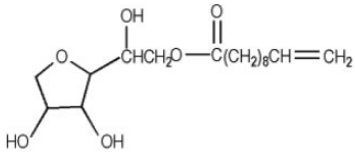
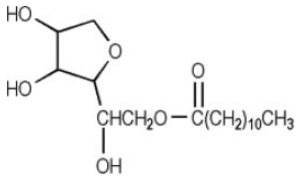
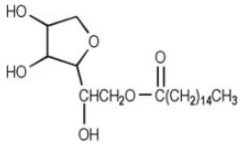
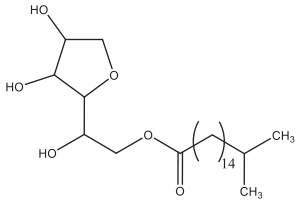
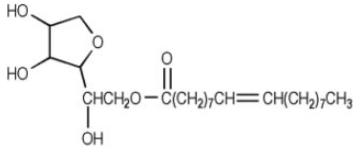
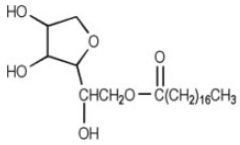
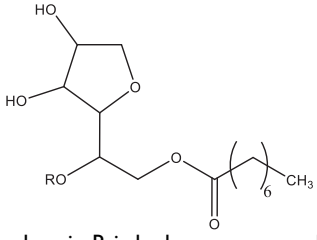
The US Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetic formulations as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). The VCRP data obtained from the FDA in 2014[6] and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council)[7] indicate that 13 of the 20 sorbitan esters named in this safety assessment are currently used in cosmetic formulations. Sorbitan stearate has the most reported uses, 968, followed by sorbitan isostearate, 401 reported uses, and several of the sorbitan esters have a few hundred uses (Table 3). The results of the concentration of use survey indicate that the sorbitan esters are used at less than 10% in cosmetic formulations; sorbitan triisostearate has the highest reported use concentration, 9.1% in rouges. Use concentration data were reported for sorbitan caprylate, but no uses were received in the VCRP; it should be presumed that there is at least one use in every category for which a concentration is reported. The ingredients not in use according to the VCRP and industry survey are listed in Table 4.

Both historical and current use data are provided in Table 3. Concentration of use data were provided in the 1985 report, but these data were not available for the 2002 assessment; however, the 2002 assessment stated that the expected concentration of use was up to 20% in cosmetics. Additionally, it should be noted that frequency of use data for the 7 sorbitan esters included in the 1985 report were updated in the 2002 report; the updated information is included in Table 3. Although the frequency of use of these ingredients has increased, the concentration of use has not.

The sorbitan esters have many uses in the eye area; the highest concentration of use reported for eye products is 7.7% sorbitan olivate in mascara.[7] Some sorbitan esters are reported to be used in baby products (eg, 0.99% sorbitan stearate in baby lotions, oils, and creams), in products applied to the mucous membranes, or in products that could possibly be ingested (eg, 5.3% sorbitan palmitate in lipsticks).

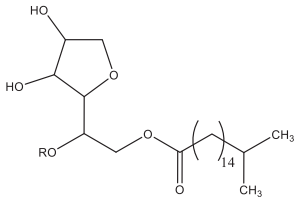
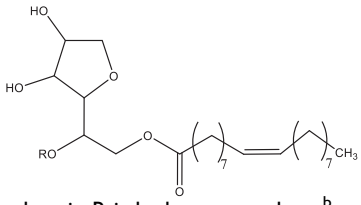
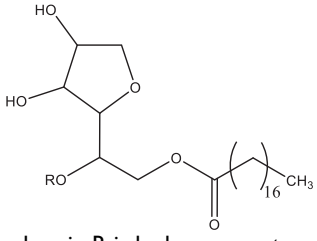
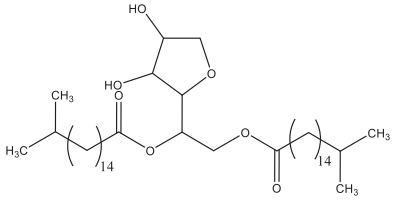
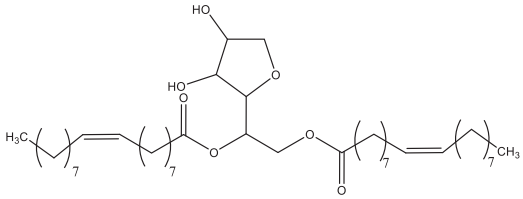
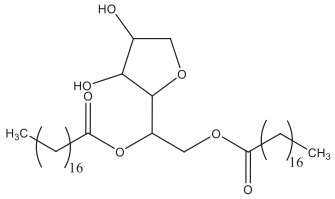
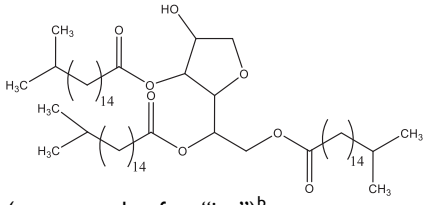
Additionally, some of the sorbitan esters are used in cosmetic sprays and could possibly be inhaled; for example, sorbitan isostearate is reported to be used at 2.3% in pump hair sprays. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared to pump sprays.[8,9] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[10,11] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[10] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. All of the sorbitan

Table 1. Definition, Structure, and Function.

Ingredient (CAS No.)	Definition[3,a]	Structure[3,b]	Function(s)[3]
Fatty sorbitan monoesters			
Sorbitan caprylate [95508-00-2]	The monoester of caprylic acid and hexitol anhydrides derived from sorbitol		Surfactant-emulsifying agent
Sorbitan undecylenate (93963-92-9)	The monoester of undecylenic acid and the hexitol anhydrides derived from sorbitol		Surfactant-emulsifying agent
Sorbitan laurate (1337-30-0; 1338-39-2; 5959-89-7)	The monoester of lauric acid and hexitol anhydrides derived from sorbitol		Surfactant-emulsifying agent
Sorbitan palmitate (26266-57-9; 5050-91-9)	The monoester of palmitic acid and hexitol anhydrides derived from sorbitol		Surfactant-emulsifying agent
Sorbitan isostearate (54392-26-6; 71902-01-7)	The monoester of isostearic acid and hexitol anhydrides derived from sorbitol	 (one example of an "iso")	Surfactant-emulsifying agent
Sorbitan oleate (1338-43-8; 37318-79-9)	The monoester of oleic acid and hexitol anhydrides derived from sorbitol		Fragrance ingredient; surfactant-emulsifying agent
Sorbitan stearate (1338-41-6; 5093-91-4; 56451-84-4)	The monoester of stearic acid and hexitol anhydrides derived from sorbitol		Fragrance ingredient; surfactant-emulsifying agent
Fatty sorbitan sesquiesters			
Sorbitan sesquicaprylate (91844-53-0)	A mixture of mono- and diesters of caprylic acid and hexitol anhydrides derived from sorbitol	 wherein R is hydrogen or caprylate[b]	Skin-conditioning agent—misc.; surfactant-solubilizing agent; viscosity-increasing agent—aq.

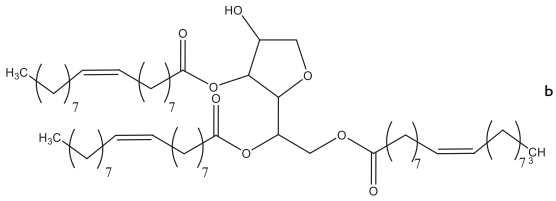
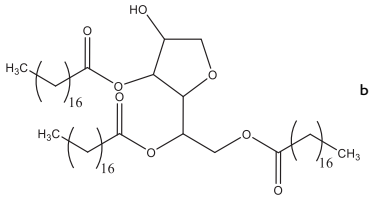
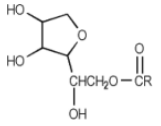
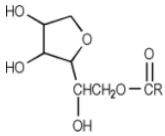
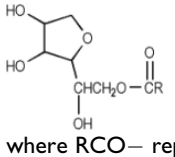
(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[3,a]	Structure[3,b]	Function(s)[3]
Sorbitan sesquiisostearate (71812-38-9)	A mixture of mono- and diesters of isostearic acid and hexitol anhydrides derived from sorbitol	 wherein R is hydrogen or isostearate (one example of an "iso")[b]	Surfactant-emulsifying agent
Sorbitan sesquioleate (8007-43-0)	A mixture of mono- and diesters of oleic acid and hexitol anhydrides derived from sorbitol	 wherein R is hydrogen or oleate[b]	Surfactant-emulsifying agent
Sorbitan sesquistearate (51938-44-4)	A mixture of mono and diesters of stearic acid and hexitol anhydrides derived from sorbitol	 wherein R is hydrogen or stearate[b]	Surfactant-emulsifying agent
Fatty sorbitan diesters			
Sorbitan diisostearate (68238-87-9)	The diester of isostearic acid and hexitol anhydrides derived from sorbitol		Surfactant-emulsifying agent
Sorbitan dioleate (29116-98-1)	The diester of oleic acid and hexitol anhydrides derived from sorbitol		Surfactant-emulsifying agent
Sorbitan distearate (36521-89-8)	The diester of stearic acid and the hexitol anhydrides derived from sorbitol		Surfactant-emulsifying agent
Fatty sorbitan triesters			
Sorbitan triisostearate (54392-27-7)	The triester of isostearic acid and hexitol anhydrides derived from sorbitol	 (one example of an "iso")[b]	Surfactant-emulsifying agent

(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[3,a]	Structure[3,b]	Function(s)[3]
Sorbitan trioleate (26266-58-0)	The triester of oleic acid and hexitol anhydrides derived from sorbitol	 b	Surfactant-emulsifying agent
Sorbitan tristearate (26658-19-5)	The triester of stearic acid and hexitol anhydrides derived from sorbitol	 b	Surfactant-emulsifying agent
Mixed chain length sorbitan monoesters			
Sorbitan cocoate (68154-36-9)	The monoester of coconut acid and hexitol anhydrides derived from sorbitol: *The fatty acid residues from coconut acid are primarily comprised of caprylate, caprate, laurate, myristate, palmitate, stearate, and oleate*	 where RCO− represents the fatty acid radical derived from coconut acid (ranging in chain length from 8 to 18 carbons[a])	Surfactant-emulsifying agent
Sorbitan olivate (223706-40-9)	The monoester of the fatty acids derived from olive oil and hexitol anhydrides derived from sorbitol: *The fatty acid residues from olive oil are primarily comprised of palmitate, palmitoleate stearate, oleate, linoleate, and linolenate*	 where RCO− represents the fatty acid radical derived from olive oil (ranging in chain length from 16 to 18 carbons[a])	Surfactant-emulsifying agent
Sorbitan palmate [37318-29-9]	The monoester of palm acid and hexitol anhydrides derived from sorbitol: *The fatty acid residues from palm acid are primarily comprised of myristate, palmitate, stearate, oleate, and linoleate*	 where RCO− represents the fatty acid radical derived from elaeis guineensis (palm) oil (ranging in chain length from 14 to 18 carbons[a])	Emulsion stabilizer; skin conditioning agent—emollient

Abbreviations: aq., aqueous; misc., miscellaneous.
[a]Information in italics was provided by the Cosmetic Ingredient Review (CIR) Chemist.
[b]These structures were provided by the CIR Chemist.

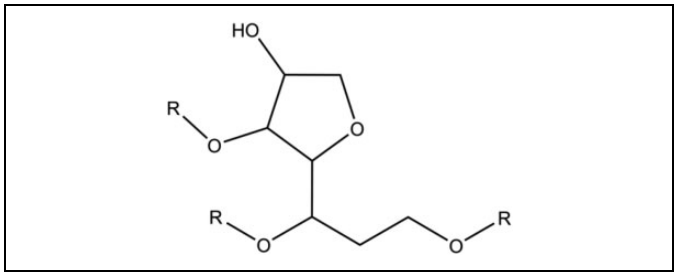


Figure 1. Sorbitan esters, wherein R represents either a fatty acid residue or hydrogen.

esters named in this report are listed in the European Union inventory of cosmetic ingredients.[12]

Noncosmetic

As described in the 1985 safety assessment, sorbitan esters are direct and indirect food additives.[1] Additionally, several sorbitan esters are inactive ingredients in drugs.[13] These ingredients are used in drugs that are administered via most possible routes, including topical, transdermal, inhalation oral, and/or across mucous membranes (Table 5). The greatest maximum potency concentration used in topically administered drugs is 8% sorbitan stearate and in orally administered drugs is 15% sorbitan oleate. Additionally, sorbitan oleate, sorbitan stearate, and sorbitan tristearate are diluents in color additive mixtures for drug use exempt from certification (ingested drugs) (21CFR73.1001).

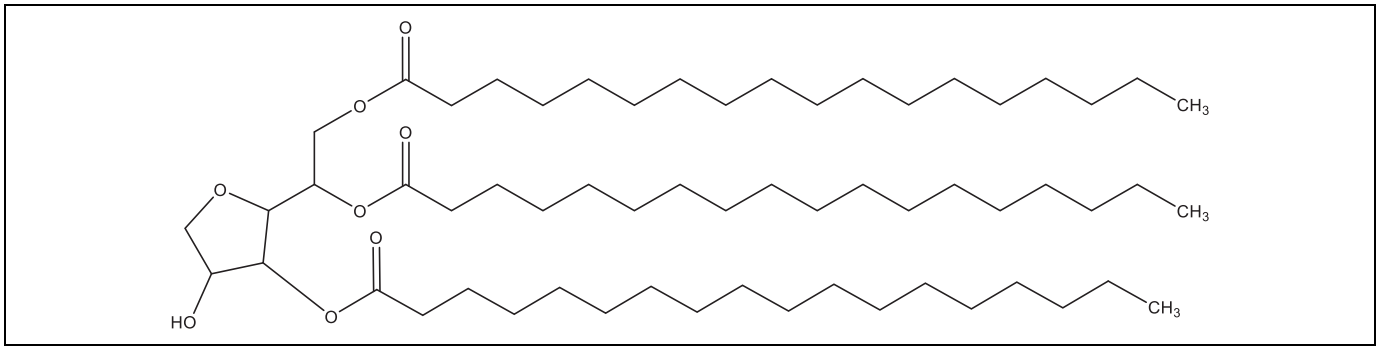


Figure 2. Sorbitan tristearate.

Table 2. Physical and Chemical Properties.

Property	Description	Reference
Sorbitan laurate		
Physical characteristics	Amber-colored oily viscous liquid, light cream to tan beads or flakes, or a hard waxy solid with a slight odor	41
Molecular weight	346.46 Da	5
Solubility	Soluble in mineral oil, cottonseed oil, methanol, ethanol, isopropyl alcohol, ethylene glycol; insoluble in water and propylene glycol; dispersible in hot and cold water	5,41
Sorbitan palmitate		
Physical characteristics	Light cream to tan beads or flakes, or a hard waxy solid with a slight odor	42
Congealing range	45°C-47°C	42
Solubility	Soluble at temperatures above its melting point in ethanol, methanol, ether, ethyl acetate, aniline, toluene, dioxane, petroleum ether, and carbon tetrachloride; insoluble in cold water; dispersible in warm water	42
Sorbitan oleate		
Physical characteristics	Amber-colored oily viscous liquid, light cream to tan beads or flakes, or a hard waxy solid with a slight odor	43
Molecular weight	428.61 Da	5
Solubility	Soluble in ethanol and isopropyl alcohol; miscible with mineral and vegetable oils; insoluble in water and propylene glycol; soluble at temperatures above its melting point in ethanol, ether, ethyl acetate, aniline, toluene, dioxane, petroleum ether, and carbon tetrachloride; insoluble in cold water; dispersible in warm water	5,43
Sorbitan stearate		
Physical characteristics	Light cream to tan beads or flakes or a hard waxy solid with a slight characteristic odor	44
Molecular weight	430.63 Da	5
Melting point	49°C-65°C	5
Congealing range	50°C-52°C	44
Solubility	Soluble at temperatures above its melting point in toluene, dioxane, carbon tetrachloride, ether, methanol, ethanol, and aniline; soluble with haze at temperatures above 50°C in mineral oil and ethyl acetate; insoluble in cold water; dispersible in warm water	44
Sorbitan tristearate		
Physical characteristics	Light cream to tan beads or flakes or a hard waxy solid	45
Congealing range	47°C-50°C	45
Solubility	Slightly soluble in toluene, ether, carbon tetrachloride, and ethyl acetate; dispersible in petroleum ether, mineral oil, vegetable oils, acetone, and dioxane; insoluble in water, methanol, and ethanol	45

Sorbitan sesquioleate is used as an emulsifier in fragrance mix I, a mixture used in patch testing.[14] Sorbitan laurate and sorbitan palmitate are used as emulsifiers in niosomes (nonionic surfactant-based vesicles).[15,16] Niosomes are microscopic vesicles composed of nonionic surface active agent bilayers, and the intended use of these vesicles is as a drug delivery system.

Toxicokinetics

Sorbitan stearate is hydrolyzed to stearic acid and anhydrides of sorbitol when ingested.[1] Approximately 90% of the sorbitan stearate is absorbed and hydrolyzed when fed to rats in oil solution, and 50% is absorbed and hydrolyzed when given as a water emulsion. Sorbitan stearate does not accumulate (<0.5%) 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.

Toxicological Studies

The results of oral toxicity studies of sorbitan fatty acid esters indicated that these sorbitans in low concentration were

Table 3. Current and Historical Frequency and Concentration of Use According to Duration and Exposure.

	# of uses		Max conc. of use (%)		# of uses		Max conc. of use (%)	
	Sorbitan caprylate				Sorbitan laurate			
	2014[6]	1998[2]	2014[7]	1999[2]	2014[6]	1998[2]	2014[7]	1981[1]
Totals[a]	NR	NR	1-1.5	NA	118	93	0.00003-3	0.1-10
Duration of use								
Leave-on	NR	NR	1-1.5	NA	106	81	0.00003-3	0.1-10
Rinse-off	NR	NR	1	NA	11	12	0.0009-3	0.1-5
Diluted for (bath) use	NR	NR	NR	NA	1	NR	0.02	NR
Exposure type								
Eye area	NR	NR	1.5	NA	17	9	0.00003-0.3	0.1-10
Incidental ingestion	NR	NR	NR	NA	1	15	NR	0.1-5
Incidental inhalation—spray	NR	NR	NR	NA	1; 26[b]; 33[c]	5; 13[b]; 7[c]	NR	0.1-5[b]; 1-5[c]
Incidental inhalation—powder	NR	NR	1-1.5[d]	NA	2; 33[c]	7[c]	0.03-1[d]	1-5[c]
Dermal contact	NR	NR	1-1.5	NA	105	74	0.00003-3	0.1-10
Deodorant (underarm)	NR	NR	NR	NA	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NA	3	2	NR	0.1-5
Hair—coloring	NR	NR	NR	NA	NR	NR	0.0009	NR
Nail	NR	NR	NR	NA	NR	NR	0.000075	NR
Mucous membrane	NR	NR	NR	NA	3	15	0.02	0.1-5
Baby products	NR	NR	NR	NA	1	NR	NR	0.1-1
	Sorbitan palmitate				Sorbitan isostearate			
	2014[6]	1998[2]	2014[7]	1981[1]	2014[6]	1998[2]	2014[7]	1999[2]
Totals[a]	109	39	0.00003-5.5	0.1-5	401	37	0.00038-6.5	NA
Duration of use								
Leave-on	92	26	0.00003-5.5	0.1-5	382	36	0.00038-6.5	NA
Rinse-off	17	12	1.8	0.1-5	19	1	0.003-1	NA
Diluted for (bath) use	NR	1	NR	NR	NR	NR	NR	NA
Exposure type								
Eye area	22	10	0.00003-5.5	0.1-1	49	16	0.00038-4	NA
Incidental ingestion	3	3	2.3-5.3	NR	119	NR	0.0005-2.2	NA
Incidental inhalation—spray	32[b]; 29[c,e]	1; 6[b]; 1[c]	NR	0.1-5[b]; 1-5[c]	78[b]; 45[c]	1[b]; 1[c]	Pump: 2.3; aerosol: 1.4; 0.03-3; 0.09-3[b]	NA
Incidental inhalation—powder	29[c,e]	1[c]	0.03-1.5[d]	1-5[c]	4; 1[d]; 45[c]	1[c]	0.001-1; 0.001-2.6[d]	NA
Dermal contact	103	34	0.00003-5.5	0.1-5	255	36	0.00038-6.5	NA
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NA
Hair—noncoloring	3	2	NR	0.1-5	9	1	0.09-2.3	NA
Hair—coloring	NR	NR	NR	NR	8	NR	NR	NA
Nail	NR	NR	0.000075	NR	NR	NR	NR	NA
Mucous membrane	3	4	1.8-5.3	NR	120	1	0.0005-2.2	NA
Baby products	NR	NR	NR	NR	1	3	NR	NA

(continued)

relatively nontoxic via ingestion.[1] The lowest rat lethal dose, 50% (LD_{50}) 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%. When the feed concentration of sorbitan laurate was ≥10%, growth depression, decreased organ weights, diarrhea, unkempt appearance, hepatic and renal abnormalities, and gastrointestinal tract irritation were generally observed. Subchronic feeding of sorbitan oleate to rats produced no abnormalities until the ester was at least 10% 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 3 sorbitans. At a 5% dietary concentration, sorbitan laurate and sorbitan oleate had no adverse effect on rats over a 2-year period. Dogs fed 5% sorbitan stearate for 20 months had no compound-related

Table 3. (continued)

	# of uses		Max conc. of use (%)		# of uses		Max conc. of use (%)	
	Sorbitan oleate				Sorbitan stearate			
	2014[6]	1998[2]	2014[7]	1981[1]	2014[6]	1998[2]	2014[7]	1981[1]
Totals[a]	311	68	0.0025-7	≤0.1-25	968	308	0.00000072-5	≤0.1-25
Duration of use								
Leave-on	205	59	0.0025-3	≤0.1-25	738	266	0.00000072-5	≤0.1-25
Rinse-off	106	9	0.013-7	0.1-10	230	42	0.0013-3.5	≤0.1-10
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	0.1-1
Exposure type								
Eye area	12	5	0.0081-0.08	≤0.1-25	109	41	0.001-3.2	0.1-25
Incidental ingestion	2	1	0.8	≤0.1	5	NR	NR	≤0.1
Incidental inhalation—spray	131[b]; 34[c]	4; 23[b]; 4[c]	Aerosol: 0.018; pump: 0.02; 0.05-3[b]	0.1-1[b]; 0.1-5[c]	3; 305[b]; 217[c,e]	9; 78[b]; 78[c,e]	0.00000072 -1.7; pump: 0.4; 0.0002-2.4[b]	0.1-5; 0.1-10[b]; ≤0.1-5[c]
Incidental inhalation—powder	1; 34[c]	4[c]	0.0025-2.7[d]	0.1 -1; 0.1-5[c]	15; 6[d]; 217[c,e]	78[c,e]	0.001-2.1; 0.013-4[d]	≤0.1-5[c]
Dermal contact	200	59	0.0025-7	≤0.1-25	756	284	0.00000072-5	≤0.1-25
Deodorant (underarm)	NR	NR	0.06 (not spray)	NR	9[b]	5[b]	0.5 (not spray)	0.1-1[b]
Hair—noncoloring	20	5	0.01-3	0.1-5	19	9	0.0002-3	0.1-5
Hair—coloring	87	NR	NR	NR	160	NR	0.0013-1.5	1-5
Nail	2	3	NR	0.1-5	1	3	1-1.5	NR
Mucous membrane	3	1	0.8	≤0.1-1	9	NR	NR	≤0.1-1
Baby products	NR	NR	NR	0.1-1	6	5	0.8-0.99	0.1-1
	Sorbitan sesquiisostearate				Sorbitan sesquioleate			
	2014[6]	1998[2]	2014[7]	1999[2]	2014[6]	1998[2]	2014[7]	1981[1]
Totals[a]	340	16	0.005-3	NA	323	170	0.005-8	≤0.1-10
Duration of use								
Leave-on	339	16	0.005-3	NA	305	157	0.005-8	≤0.1-10
Rinse-off	1	NR	1	NA	17	12	0.35	≤0.1-10
Diluted for (bath) use	NR	NR	NR	NA	1	1	NR	0.1-1
Exposure type								
Eye area	240	6	0.005-3	NA	91	42	0.01-5	0.1-10
Incidental ingestion	2	NR	3	NA	18	16	0.0051-3	0.1-5
Incidental inhalation—spray	6[c]	NR	NR	NA	24[b]; 17[c]	32[b]; 9[c]	8[b]	≤0.1-10[b]; 0.1-5[c]
Incidental inhalation—powder	13; 6[c]	3	2; 2-3[d]	NA	31; 17[c]	10; 2[d]; 9[c]	0.016-1; 0.25-2[d]	0.1-5; 0.1-5[c]
Dermal contact	338	16	0.005-3	NA	267	130	0.005-5	≤0.1-10
Deodorant (underarm)	NR	NR	3 (not spray)	NA	NR	NR	0.009-2 (not spray); aerosol: 0.0064	0.1-1[b]
Hair—noncoloring	NR	NR	NR	NA	6	2	8	≤0.1-10
Hair—coloring	NR	NR	1	NA	NR	NR	NR	NR
Nail	NR	NR	NR	NA	1	2	NR	NR
Mucous membrane	2	NR	3	NA	22	17	0.0051-3	0.1-5
Baby products	NR	NR	NR	NA	5	2	4	NR

(continued)

changes. A feed concentration of ≥10% sorbitan stearate was required to produce depressed growth and hepatic and renal abnormalities. Mice appeared more sensitive to toxic effects of sorbitan stearate than rats. A 0.5% dietary concentration produced growth depression in male rats, and a 4% dietary concentration produced renal abnormalities as well.

Subchronic dermal studies of 2% sorbitan palmitate and 4% sorbitan palmitate were negative for any systemic toxicity. No systemic toxicity was observed with dermal application of 5% sorbitan trioleate for 93 days.

Three clinical assessments have evaluated the oral toxicity of sorbitan stearate. One acute dose of 20 g was administered to 5 subjects, 2 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

Table 3. (continued)

	# of uses		Max conc. of use (%)		# of uses		Max conc. of use (%)	
	Sorbitan triisostearate				Sorbitan trioleate			
	2014[6]	1998[2]	2014[7]	1999[2]	2014[6]	1998[2]	2014[7]	1981[1]
Totals[a]	4	NR	0.24-9.1	NA	36	20	0.00001-5	≤0.1-10
Duration of use								
Leave-on	3	NR	0.24-9.1	NA	16	18	0.00001-2.5	0.1-10
Rinse-off	1	NR	NR	NA	16	2	1-5	≤0.1-5
Diluted for (bath) use	NR	NR	NR	NA	4	NR	NR	NR
Exposure type								
Eye area	1	NR	NR	NA	4	1	0.00001-2.5	NR
Incidental ingestion	2	NR	0.24-2	NA	NR	NR	0.3	NR
Incidental inhalation—spray	NR	NR	NR	NA	NR	3[b]; 1[c]	NR	0.1-5[b]; 0.1-1[c]
Incidental inhalation—powder	NR	NR	NR	NA	NR	1; 1[c]	0.3; 0.5-2.5[d]	0.1-1; 0.1-1[c]
Dermal contact	2	NR	4.2-9.1	NA	30	19	0.00001-5	≤0.1-10
Deodorant (underarm)	NR	NR	NR	NA	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NA	6	1	NR	1-5
Hair—coloring	NR	NR	NR	NA	NR	NR	NR	NR
Nail	NR	NR	NR	NA	NR	NR	0.000025	NR
Mucous membrane	2	NR	0.24-2	NA	4	NR	0.3	≤0.1-1
Baby products	NR	NR	NR	NA	NR	NR	NR	NR
	Sorbitan tristearate				Sorbitan olivate			
	2014[6]	1999[2]	2014[7]	1981[1]	2014[6]	1998[2]	2014[7]	1999[2]
Totals[a]	100	8	0.13-2.6	≤0.1-5	214	NR	0.004-7.7	NA
Duration of use								
Leave-on	99	6	0.13-2.6	≤0.1-5	179	NR	0.004-7.7	NA
Rinse-off	1	2	0.13	NR	35	NR	0.7-0.88	NA
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NA
Exposure type								
Eye area	36	NR	0.4-2.6	0.1-1	36	NR	0.014-7.7	NA
Incidental ingestion	2	NR	0.7-1	NR	10	NR	0.018-1	NA
Incidental inhalation—spray	17[b]; 38[c]	3[b]; 1[c]	NR	1-5; 0.1-5[b]	41[b]; 61[c]	NR	1.6-4[b]	NA
Incidental inhalation—powder	38[c]	1[c]	0.5-2[a]	NR	1; 61[c]	NR	0.015-1.9[d]	NA
Dermal contact	88	8	0.13-2.6	≤0.1-5	192	NR	0.004-7	NA
Deodorant (underarm)	NR	NR	NR	NR	3[b]	NR	NR	NA
Hair—noncoloring	NR	NR	NR	NR	3	NR	1.6-4	NA
Hair—coloring	NR	NR	NR	NR	NR	NR	NR	NA
Nail	1	NR	NR	NR	NR	NR	NR	NA
Mucous membrane	2	NR	0.13-1	NR	18	NR	0.018-1	NA
Baby products	NR	NR	NR	NR	3	NR	NR	NA

(continued)

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 9 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 4 had glycosuria; however, 1 of the 4 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; other blood chemistry values were normal except in 1 patient who had slightly elevated total serum bilirubin.

The no-effect dose of sorbitan stearate was 7.5 g/kg/d using rats fed the ingredient for 2 years.[2] The acute oral LD_{50} of sorbitan sesquiisostearate was 25 mL/kg in a study using female ddY mice.

Table 3. (continued)

	# of uses	Max conc. of use (%)	# of uses	Max conc. of use (%)
	Sorbitan palmate			
	2014[6]	2014[7]		
Totals[a]	NR	0.45-0.75		
Duration of use				
Leave-on	NR	0.45-0.75		
Rinse-off	NR	NR		
Diluted for (bath) use	NR	NR		
Exposure type				
Eye area	NR	0.75		
Incidental ingestion	NR	NR		
Incidental inhalation—spray	NR	NR		
Incidental inhalation—powder	NR	0.45-0.75[a]		
Dermal contact	NR	0.45-0.75		
Deodorant (underarm)	NR	NR		
Hair—noncoloring	NR	NR		
Hair—Coloring	NR	NR		
Nail	NR	NR		
Mucous membrane	NR	NR		
Baby products	NR	NR		

Abbreviations: NA, at the time of the original safety assessment, concentration of use data were not reported by the Food and Drug Administration; NR, no reported use.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[b]Includes products that can be sprays, but it is not known whether the reported uses are sprays.
[c]Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation.
[d]Includes products that can be powders, but it is not known whether the reported uses are powders.
[e]Has reported use as a foot powder/spray.

Table 4. Ingredients Not Reported to Be Used.

Sorbitan undecylenate
Sorbitan sesquicaprylate
Sorbitan sesquistearate
Sorbitan diisostearate
Sorbitan dioleate
Sorbitan distearate
Sorbitan cocoate

Single-Dose (Acute) Toxicity

The original safety assessments of the sorbitan esters included data that indicated that this group of ingredients was relatively nontoxic upon ingestion of a single dose. Additional oral studies in mice and rats on sorbitan laurate, sorbitan palmitate, sorbitan isostearate, sorbitan stearate, sorbitan sesquioleate, and sorbitan tristearate support those findings (Table 6).[17-22] In 4-hour inhalation exposure studies, sorbitan laurate and sorbitan trioleate had an lethal concentration 50% (LC_{50}) in rats that was $\geq$5 mg/L.[17,23]

Repeated Dose Toxicity

Oral. Male rats (number not specified) were fed a diet containing 5% sorbitan palmitate for 2 years.[18] The no-observable adverse effect level (NOAEL) was 5%. Thirty male rats were fed a diet with 5% sorbitan stearate, equivalent to 5,000 mg/kg body weight (bw)/d, for 2 years.[20] No effects on clinical signs, mortality, bw, feed consumption, hematology, clinical chemistry, gross or microscopic lesions, or pathology were reported. Sorbitan tristearate, 5% (equivalent to 5,000 mg/kg bw/day), was also administered in the diet to a group of 30 male rats for 2 years.[22] No effects on clinical signs or mortality, bw or weight gains, or gross or microscopic lesions were reported.

Reproductive and Developmental Toxicity

Fatty acids are normal components of diet for which (at the time of this report) no data were available concerning reproductive or developmental toxicity.[2] Sorbitol (2.5% to 10%) had no adverse effects on the reproduction of CD rats during a multigenerational feeding study. Hydrogenated starch hydrolysates ($\sim$7% sorbitol) were not reproductive toxins at doses of 3,000 to 7,000 mg/kg/d for 2 years.

Gravid female Wistar rats, 20 per group, were dosed once daily by gavage with 0, 500, or 1,000 mg/kg bw/d sorbitan stearate on days 0 to 20 of gestation, and the animals were killed.[20] The NOAEL for maternal toxicity and for teratogenicity was 1,000 mg/kg bw/d. No test article–related embryotoxic results were reported.

Table 5. Inactive Ingredient in Drugs.

Ingredient	Route	Dosage form(s)	Maximum potency (per route)[13]
Sorbitan laurate	Topical	Gel; aerosol; emulsion, aerosol foam	4.74% (aerosol)
	Oral	Suspension; syrup; tablet; granule	0.05% (suspension); 83.9 mg (tablet)
	Ophthalmic	Ointment	Ns
Sorbitan palmitate	Topical	Lotion; cream emulsion; patch	2% (cream emulsion); 10.5 mg (patch)
	Intramuscular	Injection	NS
Sorbitan isostearate	Topical	Lotion	NS
Sorbitan oleate	Topical	Cream; lotion; emulsion; ointment	7% (lotion)
	Transdermal	Controlled release film	NS
	Oral	Solution; suspension; tablet; capsule	15% (solution); 153.9 mg
	Rectal	Suppository	22 mg
Sorbitan stearate	Topical	Lotion; ointment; cream emulsion; suspension; solution	8% (cream emulsion)
	Oral	Suspension	1.25%
	Vaginal	Augmented cream; cream emulsion; tablet	5% (cream emulsion)
Sorbitan sesquioleate	Topical	Ointment	2%
	Rectal	Ointment	2%
Sorbitan trioleate	Oral	Syrup; tablet; capsule; powder (for suspension)	0.03% (powder for suspension)
	Inhalation	Metered aerosol	0.0694%
	Nasal	Metered aerosol	0.0175%
Sorbitan tristearate	Topical	Augmented cream	0.5%

Abbreviation: NS, not specified.

Table 6. Acute Toxicity Studies.

Ingredient	Animals	No./group	Vehicle	Concentration/dose/protocol	LD_{50} or LC_{50}/results	Reference
Oral						
Sorbitan laurate	Wistar rats	2/sex		2 g/kg by gavage	>2 g/kg	17
Sorbitan laurate	Rats	10/sex	None	16 g/kg by gavage	>16 g/kg	17,a
Sorbitan palmitate	NMRI mice	5 males	Corn oil	5 g/kg by gavage	>5 g/kg	18
Sorbitan palmitate	Rats	10/sex	Vegetable oil	16 g/kg of an 80% solution by gavage	>16 g/kg	18,a
Sorbitan isostearate	CFY rats	5/sex	Neat	16.5 g/kg by gavage	>16.5 g/kg	19
Sorbitan stearate	Wistar rats	2/sex	Peanut oil	2 g/kg by gavage	>2 g/kg	20
Sorbitan stearate	Rats	10/sex	CMC	30%; 17.8 g/kg by gavage	>17.8 g/kg	20,a
Sorbitan stearate	Wistar Rats	10/sex	Water	90%; 16 g/kg by gavage (high application dose administered in 2 portions)	>16 g/kg	20,a
Sorbitan stearate	Male rats	Not specified	Neat	31 g/kg by gavage	>31 g/kg	20
Sorbitan sesquioleate	Mice	10 males	Not specified	31.6 g/kg; route not specified	>31.6 g/kg	21,a
Sorbitan sesquioleate	Wistar rats	2/sex	Peanut oil	5 g/kg by gavage	>5 g/kg	21
Sorbitan sesquioleate	Rats	5/sex	Not specified	31.6 g/kg; route not specified	>31.6 g/kg	21,a
Sorbitan tristearate	Wistar rats	5/sex	CMC	100 g/L, 2 g/kg bw vehicle by gavage	>2 g/kg bw	22
Inhalation						
Sorbitan laurate	Wistar rats	3/sex	Air	5 mg/l; 4-hour nose-only exposure; 40% particles were <4 μm; MMAD/GSD: 4.6 and 4.7 μm/2.0 and 2.1 μm	>5 mg/L	17
Sorbitan trioleate	Wistar rats	3/sex	Air	5.27 mg/l; 4-hour nose-only exposure; particle size distribution: 73.8% inhalable fraction (<4 μm); MMAD/GSD: 2.14 μm/2.68 μm	>5.27 mg/L	23

Abbreviations: bw, body weight; CMC, carboxymethylcellulose; GSD, geometric standard deviation; MMAD, mean mass aerodynamic diameter.
[a]Study disregarded by European Chemicals Agency applicant because only a short abstract was available (reason may have included no data on analytical purity of test substance, no gross pa thology performed, no necropsy).

Groups of 12 male and 12 female Sprague Dawley rats were dosed by gavage once daily with 0, 40, 200, or 1,000 mg/kg bw/d sorbitan stearate in water.[20] The females were dosed 2 weeks prior to mating until day 4 of lactation; the males were dosed for 42 days. No signs of toxicity; no effects on mortality, bw, or bw gains; and no gross or microscopic lesions were observed. Effects on feed consumption, hematology, and clinical chemistry were not examined.

Genotoxicity

Sorbitan stearate was not mutagenic in bacteria with or without metabolic activation systems.[1] Sorbitan stearate did not

transform primary Syrian golden hamster embryo cells in vitro. Sorbitan oleate at a concentration of 0.01% inhibited in vitro DNA repair.

An unspecified sorbitan fatty acid ester had equivocal results in an Ames test and chromosome aberration assay using Chinese hamster fibroblasts.[2] In a feeding study using rats, the ester altered pharmacokinetic activity in the liver.

Sorbitan laurate, sorbitan palmitate, sorbitan stearate, sorbitan sesquicaprylate, sorbitan sesquioleate, and sorbitan trioleate were not mutagenic in the Ames test, with or without metabolic activation (Table 7).[17,18,20,21,23,24] Sorbitan laurate was not genotoxic to peripheral human lymphocytes in a chromosomal aberration assay,[17] but the results of a chromosomal aberration assay in Chinese hamster cells with sorbitan stearate were ambiguous.[20]

Carcinogenicity

Mice fed ≤4% sorbitan stearate for 80 weeks had no difference in tumor type and incidence when compared to control animals.[1] Sorbitan laurate was inactive as a carcinogen or tumor promoter when painted on mice skin for 70 weeks. However, in another study, sorbitan laurate was a tumor promoter when applied twice daily to mice skin after initiation by 7,12 dimethylbenz[a]anthracene (DMBA). In the same study, sorbitan oleate and sorbitan trioleate were inactive as tumor promoters. In undiluted form, sorbitan laurate and sorbitan trioleate were active as cocarcinogens on mouse skin when applied with DMBA (0.003%).

The sorbitan fatty acid esters had no antitumor activity against Ehrlich ascites tumors in mice. Sorbitan stearate was neither a mouse skin carcinogen nor tumor promoter. Sorbitan laurate and sorbitan trioleate were co-carcinogens in one mouse skin study, but the latter ester and sorbitan oleate were not tumor promoters in another.

Irritation and Sensitization

Dermal

Nonhuman. Numerous skin irritation studies in animals indicate that the sorbitans are minimal to mild irritants.[1] Skin irritation tests in which up to 60% sorbitan stearate in petrolatum and up to 100% sorbitan laurate, sorbitan oleate, and sorbitan trioleate were applied for 30 days produced no visible changes at 3 days but erythema and edema after 10 days. A formulation containing 4% sorbitan stearate applied for 7 days resulted in mild irritation. The dermal irritation in rabbits of a formulation containing 3% sorbitan sesquioleate was minimal. Undiluted sorbitan oleate was minimally irritating to rabbit skin when applied for 24 hours. Sorbitan palmitate, 50%, was not irritating to rabbit skin when applied for 24 hours. Sorbitan tristearate, 30%, was nonirritating when applied to the skin of rabbits for 24 hours.

Sorbitan isostearate, however, was a moderate irritant in one study using rabbits; intradermal injections of the ingredient caused mild to severe irritation in a study using guinea pigs.[2] Concentrations up to 100% sorbitan isostearate had low sensitization potential in guinea pigs. Sorbitan isostearate and sorbitan sesquiisostearate (10%) were non- to weak irritants to the intact and abraded skin of rabbits. The same concentrations caused weak cumulative irritation in a study using guinea pigs. In other studies, the ingredient did not produce significant irritation, sensitization, or comedone formation.

In studies published since the original assessments, several of the sorbitan esters were considered not irritating to rabbit skin (Table 8). Sorbitan palmitate, sorbitan isostearate, and sorbitan stearate were applied at concentrations of up to 100% using 24-hour occlusive patches.[18-20] Sorbitan sesquioleate was applied for 24 hours using a semiocclusive patch,[21] 40% aq. sorbitan tristearate was applied using a 24-hour occlusive patch,[22] and undiluted sorbitan sesquicaprylate and sorbitan trioleate were applied with a 4-hour semiocclusive patch.[23,24] Sorbitan sesquicaprylate was not a sensitizer in a guinea pig maximization test (GPMT); intradermal induction was conducted at a concentration of 5%, and topical induction and challenge were performed at 100%.[24] In a GPMT of sorbitan trioleate, intradermal induction (2%), topical induction (100%), and challenge (50% and 100%) resulted in slight to moderate erythema and slight edema were observed in test and control animals[23]; at re-challenge (25 and 50%), slight erythema was observed in 2 test animals.

Human. The sorbitans are minimal to mild skin irritants in humans.[1] Results from 3 human repeated insult patch tests (HRIPTs; involving a total of 420 patients) indicated that sorbitan stearate at up to 4% is not a sensitizer. Products containing 2% to 4% of sorbitan stearate were mild irritants in 21-day cumulative irritation studies. A Schwartz prophetic patch test with 30% sorbitan laurate produced no irritation. Human skin tests for sensitivity to sorbitan sesquioleate were negative; 2 Schwartz prophetic patch tests with undiluted sorbitan sesquioleate produced no reactions; and in 5 HRIPTs, products containing 1% to 3% sorbitan sesquioleate were not sensitizers, but some patients did experience mild irritation. Several products containing 1.75% to 2.0% sorbitan oleate have been tested on humans. In four, 21-day cumulative irritation studies, the products tested were mildly irritating; in these tests using entire product formulations, the specific ingredient(s) causing irritation was not determined. Formulations containing up to 2% sorbitan oleate were nonsensitizers in several HRIPTs. No irritation was observed in a maximization test with a formulation containing 1.75% sorbitan oleate, but in a product usage test, a cream containing 1.75% sorbitan oleate produced mild irritation in 2 of 53 individuals. A Schwartz prophetic patch test with undiluted sorbitan tristearate produced no irritation in 201 patients. Formulations containing 4% sorbitan palmitate were found to be slightly irritating in humans in 21-day cumulative irritation tests (34 patients total). In a Shelanski/Jordan RIPT (206 patients), a skin care product containing 4% sorbitan palmitate was nonirritating and nonsensitizing. Several products containing 5%

Table 7. Genotoxicity Studies.

Test article	Concentration/ vehicle	Procedure	Test system	Results	Reference
In vitro					
Sorbitan laurate	0.1-333 μg/mL (without) 10-350 μg/mL (with) in DMSO	Mammalian cell gene mutation assay, with and without metabolic activation; with valid positive controls	Mouse lymphoma L5178Y cells	Negative	17
Sorbitan laurate	33-500 μg/mL in DMSO	Chromosomal aberration assay (OECD guideline 473), with and without metabolic activation; with valid positive controls	Peripheral human lymphocytes	Negative	17
Sorbitan palmitate	Not specified	Ames test, with and without metabolic activation; no data were available on the use of valid positive controls	*Salmonella typhimurium* TA98, TA100	Negative	18
Sorbitan stearate	3-5,000 μg/plate in DMSO	Ames test, with and without metabolic activation; valid controls were used	*S typhimurium* TA1535, TA1537, TA98, TA100, TA102	Negative	20
Sorbitan stearate	8-5,000 μg/plate in DMSO	Ames test, with and without metabolic activation; valid controls were used	*S typhimurium* TA1535, TA1537, TA1538, TA98, TA100	Negative	20
Sorbitan stearate	313-5,000 μg/plate in DMSO	Ames test, with and without metabolic activation; valid controls were used	*S typhimurium* TA1535, TA1537, TA98, TA100, *Escherichia coli* wp2 uvrA	Negative	20
Sorbitan stearate	0.13-0.5 mg/mL (without) 1.1-4.3 mg/mL (with) in CMC sodium solution	Chromosomal aberration assay, with and without metabolic activation; with positive controls, *submitter disregarded the study for relevant methodological deficiencies (analytical purity of test substance not specified, limited documentation, cyclophosphamide was used as positive control both with and without metabolic activation, and did not induce a stat. sig. increase in the total number of aberrant cells in the presence of metabolic activation system)*	Chinese hamster cells	Results were considered ambiguous; stat. sig. increase in cells with aberrations with 0.13 mg/mL without and with all doses with activation, but no sig. increases with positive controls	20,a
Sorbitan sesquicaprylate	Not specified	Ames test, with and without metabolic activation; no data were available on the use of valid positive controls. *Submitter disregarded study because only a short abstract was available*	*S typhimurium* TA98, TA100	Negative	24,a
Sorbitan sesquicaprylate	3-5,000 μg/plate in DMSO	Ames test, with and without metabolic activation; valid controls were used	*S typhimurium* TA1535, TA1537, TA98, TA100, TA102	Negative	24
Sorbitan sesquioleate	Not specified	Ames test, with and without metabolic activation	*S typhimurium* TA98, TA100	Negative	21
Sorbitan sesquioleate	8-5,000 μg/plate in DMSO	Ames test, with and without metabolic activation; valid controls were used	*S typhimurium* TA1535, TA1537, TA1538, TA98, TA100	Negative	21
Sorbitan trioleate	Not specified	Ames test, with and without metabolic activation	*S typhimurium* TA98, TA100	Negative	23

Abbreviations: CMC, carboxymethylcellulose; DMSO, dimethyl sulfoxide; stat. sig., statistically significant.
[a]Study disregarded by European Chemicals Agency applicant.

Table 8. Dermal Irritation and Sensitization.

Test article	Concentration/dose	Test population	Procedure	Results	Reference
Nonhuman					
Sorbitan palmitate	Neat	6 male NZW rabbits	24-hour occlusive application to shaved and abraded skin; the test sites were scored at 24 and 72 hours	Not irritating	18
Sorbitan isostearate	Neat; 0.5 mL	6 albino rabbits	24-hour occlusive application to shaved and abraded skin; the test sites were scored at 24 and 72 hours	Erythema score—1.78/4; edema score—0.94/4. Neither erythema nor edema was fully reversible after 72 hours	19
Sorbitan stearate	10 in peanut oil, 25% in peanut oil	10 male hairless mice, 5 male hairless mice	2 open applications/day for 10 days. *Disregarded because only a short abstract was available (limited documentation, repeated application, up to 25% test substance evaluated, test substance purity not specified)*	No adverse effects reported	20,a
Sorbitan stearate	Neat, 0.5 g	6 NZW rabbits	4-hour semiocclusive patches to shaved and abraded skin	Not irritating Erythema score—0.3/4, fully reversible after 72 hours Edema score—0/4	20
Sorbitan stearate	0.5 mL	NZW rabbits, 3/sex	24-hour occlusive patch to intact and abraded skin	Not irritating Erythema score—0.7/4, fully reversible after 72 hours in 4/6 animals; edema score—0/4	20
Sorbitan sesquicaprylate	Neat; 0.5 mL	NZW rabbits, 1 male and 2 females	4-hour semiocclusive application to clipped skin; test sites scored at 1, 24, 48, and 72 hours after patch removal	Classified as not irritating Erythema and edema scores—0/4	24
Sorbitan sesquicaprylate	Intradermal induction: 5% topical induction: 100%; challenge: 100%; vehicle: peanut oil	10 guinea pigs	GPMT induction: intradermal, 3 pairs of 0.1 mL injection, with 1:1 FCA/saline, test article, and FCA/vehicle; topical induction, 48-hour patch 7 days after intradermal induction; challenge: after 14 days, 24-hour patch	Not a sensitizer. No reactions were observed during induction or challenge	24
Sorbitan sesquioleate	Neat; 0.5 mL	6 male NZW rabbits	24-hour semiocclusive application to shaved and abraded skin; the test sites were scored at 24 and 72 hours	Classified as not irritating Erythema score—1.89/4; edema score—0.78/4 Neither erythema or edema were fully reversible after 72 hours	21
Sorbitan trioleate	Neat, 0.5 mL	2 NZW rabbits	4-hour semiocclusive application to clipped skin; test sites scored at 1, 24, 48, and 72 hours after patch removal	Classified as not irritating Erythema and edema scores—0/4	23

(continued)

sorbitan trioleate were tested on humans; these products were slightly irritating in 21-day cumulative irritation tests, Shelanski/Jordan HRIPT, modified Schwartz-Peck predictive patch tests, and in a 4-week usage test.

Photosensitization assessments on products containing 2% sorbitan stearate or 2% sorbitan oleate classified both products as nonphototoxic and nonphotoallergenic. Sorbitan laurate, sorbitan sesquioleate, sorbitan palmitate, and sorbitan trioleate did not absorb radiation in the UV-A and UV-B range in UV spectral analysis.

In clinical studies, the sorbitan fatty acid esters were generally minimal to mild skin irritants in humans, and 20% sorbitan sesquioleate increased the incidence of irritation or sensitization reactions produced in 709 patients with suspected contact dermatitis.[2] Cross-sensitization was reported after 1,206 patients with eczema were treated with 5% to 20% sorbitans

Table 8. (continued)

Test article	Concentration/dose	Test population	Procedure	Results	Reference
Sorbitan trioleate	Induction: intradermal, 2% in olive oil; topical, 100% in liquid paraffin; challenge: 50% and 100% in liquid paraffin; rechallenge: 25% and 50% in liquid paraffin	10 male Dunkin-Hartley guinea pigs	GPMT induction: intradermal, 3 pairs of 0.1 mL injection, with 1:1 FCA/saline, test article, and 50% FCA/4% test article; topical induction, two 48-hour patches; challenge: on day 20, 24-hour patches; rechallenge: on day 28, 24-hour patches	Induction: No signs of irritation during induction; challenge: slight to moderate erythema that decreased in occurrence with time, but was still present at in some animals at 72 hours, and slight edema at 24 hours only was reported for both control and test groups; rechallenge: slight erythema was observed in test animals at 24 hours (25%, 1 animal; 50%, 2 animals) and at 48 hours (50%, 1 animal); no reactions were observed in the negative controls	23
Sorbitan tristearate	40% aq.; 0.5 mL	6 NZW rabbits	24-hour occlusive application to shaved and abraded skin; the test sites were scored at 24 and 72 hours	Not irritating Erythema and edema scores—0/4	22
Human					
Sorbitan palmitate	30% in water	1 male; 9 females	Occlusive patch applied for 5 days	Not an irritant	18
Sorbitan palmitate	50% in water	50 subjects (gender not specified)	72-hour occlusive application using a 1 sq. in cotton pad	Not an irritant	18
Sorbitan stearate	30% in olive oil; 0.1 g	25 subjects	HRIPT; 6 patches over 15 days with Finn chambers	Not an irritant	20
Sorbitan stearate	30% aq.	10 subjects	Patch test; 5-day initial application, 48-hour challenge performed after a 10-day nontreatment period	Not a sensitizer	20
Sorbitan stearate	30% aq.	50 subjects	3-day initial occlusive patch, 3-day challenge performed after a 7-day nontreatment period	Not an irritant or sensitizer	20
Sorbitan sesquioleate	30% aq.	10 subjects	Occlusive patch test; 5-day initial application, 48-hour challenge after a 10-day non-treatment period	Not an irritant or sensitizer	21
Sorbitan trioleate	30% aq.	10 subjects	Patch test; 5-day initial application, 48-hour challenge performed after a 10-day nontreatment period	Not a sensitizer	23
Sorbitan trioleate	30% aq.	50 subjects	3-day initial occlusive patch, 3-day challenge performed after a 7-day nontreatment period	Not an irritant or sensitizer	23

Abbreviations: aq., aqueous; GPMT, guinea pig maximization test; NACDG, North American Contact Dermatitis Group; NZW, New Zealand white; ROAT, repeated open application test; TRUE, thin-layer rapid use epicutaneous.
[a]Study disregarded by European Chemicals Agency applicant.

stearate, oleate, and sesquioleate, as well as 2 polysorbates. Sorbitan isostearate and sorbitan sesquiisostearate (10%) were nonirritating in a 24-hour occlusive patch test using 56 patients.

In clinical testing published since the original assessments, 30% sorbitan palmitate, 30% sorbitan stearate, 30% sorbitan sesquioleate, and 30% sorbitan trioleate were not irritants or sensitizers when applied for up to 5 days, followed by a challenge application after 7 to 10 days (Table 8).[18,20,21,23] Sorbitan palmitate, 50%, also was not an irritant after a 72-hour occlusive application.[18]

Sorbitan sesquioleate is an emulsifier at a concentration of 5% in fragrance mix I, a mixture used as part of a patch test series.[14] Some researchers have stated that evidence has suggested that sensitization to sorbitan sesquioleate has been

increasing, and the researchers have hypothesized that the increase may be due to an increased use of sorbitan sesquioleate as an emulsifier in corticosteroids.[14,25] Therefore, several researchers have postulated that a positive allergic reaction to a test mixture actually could be due to the emulsifier and reiterated the importance of patch testing the individual components of the mixture, in addition to the test mixture itself, to properly identify the contact allergen.[14,25-29]

Case reports. Several case studies of patients with diseased skin have been described (Table 9). Positive reactions to sorbitan laurate (0.4% incidence),[30] sorbitan oleate (0.6% incidence with 5%; up to 2.7% incidence with 20%),[14,30-33] sorbitan stearate (2.3% incidence with 5%),[32] and sorbitan sesquioleate (up to 9.8% incidence with 20%) were observed in provocative tests in patients with contact allergy and contact dermatitis.[14,31-34]

Case reports of contact dermatitis to sorbitan laurate, sorbitan oleate, and sorbitan sesquioleate have been described. For example, reactions to 2%[35] or 5% aq. sorbitan laurate[36] used as an emulsifier in a hydrocortisone cream have been reported; 3 of 23 patients with chronic leg ulcers had an allergic reaction to 20% sorbitan oleate in petrolatum[37]; 3 patients with recalcitrant wounds from sensitization to a nonadhering dressing had positive reactions to sorbitan sesquioleate, a component of the dressing[38]; and 6 pediatric patients with recalcitrant dermatitis had positive reactions to 20% sorbitan sesquioleate in petrolatum.[39]

Effect on nonimmunologic immediate contact reactions. A 10 × 20 cm^2 area of skin on the backs of 6 male and 6 female subjects was treated with 0.5 mL of sorbitan sesquioleate in petrolatum (20:80) 3 times per day for 2 days; a contralateral site was treated in a similar manner with petrolatum only.[40] On day 3, 10 μL of 31, 62, 125, 250, or 500 mM benzoic acid in petrolatum only or petrolatum containing 20% sorbitan sesquioleate was applied without occlusion to the pretreated areas on the back of each subject. Each site was scored visually for irritation 40 minutes after application of the benzoic acid. Additionally, cutaneous blood flow to the test sites was measured using laser Doppler flowmetry (LDF). When assessed with LDF, reactions to 125 or 250 mM benzoic acid in petrolatum only were stronger on the sites that were pretreated with sorbitan sesquioleate when compared to the areas pretreated with petrolatum only; these differences were not apparent using visual observation. No differences were observed with the lower concentrations of benzoic acid. However, a weaker reaction was observed, visually and with LDF, when 31 or 62 mM benzoic acid in petrolatum containing sorbitan sesquioleate was applied to skin pretreated with sorbitan sesquioleate and petrolatum alone, when compared to application of benzoic acid in petrolatum alone.

Ocular Irritation

Draize and modified Draize ocular irritation studies using rabbits were performed with all of the sorbitans in the original report.[1] One study of 30% sorbitan stearate was negative for ocular irritation, and a cream product containing 4% sodium stearate caused slight conjunctival irritation. Undiluted sorbitan sesquioleate produced no ocular irritation. A study with 30% sorbitan laurate and studies with up to undiluted sorbitan oleate, 40% sorbitan tristearate, and 30% sorbitan palmitate were negative for ocular irritation in the rabbit.

The sorbitan fatty acid esters were generally not ocular irritants.[2] In one study, sorbitan isostearate (10%) was nonirritating to the eyes of rabbits, whereas the same concentration of sorbitan sesquiisostearate was minimally irritating. In studies published since the original assessments, undiluted sorbitan stearate, sorbitan sesquicaprylate, sorbitan sesquioleate, and sorbitan trioleate were classified as not irritating to rabbit eyes following a single instillation without rinsing (Table 10).[20,21,23,24]

Summary

In 1985, the Panel reviewed the safety of the cosmetic use of 7 sorbitan esters, and in 2002, the Panel reviewed the safety of another 10 sorbitan esters; in both instances, the Panel concluded that the sorbitan fatty acid esters were safe as used in cosmetic ingredients. An additional 3 sorbitan esters have been identified and are reviewed in this assessment; all 20 of these esters share an identical sorbitan structural core and only vary by fatty acid substituents. Most of the sorbitan esters are reported to function as a surfactant-emulsifying agent in cosmetic ingredient

The VCRP data obtained from the FDA, and data received in response to surveys of the maximum reported use concentration by category that were conducted by the Council, indicate that 13 of the 20 sorbitan esters included in this safety assessment are used in cosmetic formulations. Sorbitan stearate has the most reported uses, 968, followed by sorbitan isostearate, 401 reported uses; several of the sorbitan esters have a few hundred uses. The sorbitan esters are used at less than 10% in cosmetic formulations; sorbitan triisostearate has the highest reported use concentration, 9.1% in rouges. The frequency of use of these ingredients has increased since the original safety assessments, but the concentration of use has not.

Sorbitan laurate, sorbitan palmitate, sorbitan isostearate, sorbitan stearate, sorbitan sesquioleate, and sorbitan tristearate were relatively nontoxic in mice and rats following a single oral exposure. In single-exposure inhalation studies, the LC_{50} in rats was $\geq$5 mg/L for sorbitan laurate and sorbitan trioleate. Administration of a diet containing 5% sorbitan palmitate, 5% sorbitan stearate, or 5% sorbitan tristearate to rats for 2 years did not result in any adverse effects. In oral reproductive toxicity studies in rats, the NOAEL for sorbitan stearate was 1,000 mg/kg bw/d, the highest dose administered.

Sorbitan laurate, sorbitan palmitate, sorbitan stearate, sorbitan sesquicaprylate, sorbitan sesquioleate, and sorbitan trioleate were not mutagenic in the Ames test, with or without metabolic activation. Sorbitan laurate was not genotoxic to peripheral human lymphocytes in a chromosomal aberration assay; the results of a chromosomal aberration assay in Chinese hamster cells with sorbitan stearate were ambiguous.

Table 9. Case Studies of Patients With Diseased Skin.

Test article	Concentration/ dose	Test population	Procedure	Results	Reference
Sorbitan laurate	Not specified, but assumed neat	475 patients with contact allergy	European retrospective survey of allergic contact reactions to cosmetics	2 patients had a positive reaction (0.4%)	30
Sorbitan oleate	Not specified, but assumed neat	475 patients with contact allergy	European retrospective survey of allergic contact reactions to cosmetics	2 patients had a positive reaction (0.4%)	30
Sorbitan oleate	5% (vehicle not specified)	945 patients with contact dermatitis	Occlusive patches using Finn chambers were applied for 48 hours; reactions were evaluated at 48-72 hours and 96-168 hours	6 patients reacted positively (0.6%); 3 reactions were identified as macular erythema, 3 reactions were weak, 1 was strong	33
Sorbitan oleate and sorbitan sesquioleate	Sorbitan oleate: 20% in petrolatum; sorbitan sesquioleate: 5% pet	112 patients with dermatitis	48-hour occlusive application using Finn chambers; test sites were scored at 48 and 72 hours; a modified NACDG standard series, a cosmetic series (which included the sorbitan esters), and a fragrance series were tested	1 subject (0.9%) reacted to sorbitan oleate only; 10 subjects (8.9%) reacted to sorbitan sesquioleate only; 2 subjects (1.8%) reacted to both at 72 hours, all but one reaction to the sesquioleate were +; the other reaction was +++	14
Sorbitan oleate and sorbitan sesquioleate	Sorbitan oleate: 20% in petrolatum; sorbitan sesquioleate: 5% pet	591 patients with contact dermatitis	Sites were scored at 48 and 72 hours; a modified NACDG standard and a cosmetic series were tested, but specific information on the testing protocol was not provided	1 subject (0.17%) reacted to sorbitan oleate only; 19 subjects (3.2%) reacted to sorbitan sesquioleate only; 4 subjects (0.68%) reacted to both at 72 hours, all but 2 reactions were +; 2 subjects had a ++ reaction to sorbitan oleate	31
Sorbitan oleate and sorbitan stearate	5% (each) in petrolatum	86 patients with dermatoses	Patch test; 24-hour occlusive application using Finn chambers	+,++ reaction in 2 subjects (2.3%)	32
		2 patients with positive reactions	ROAT; 0.1 mL applied 2×/day for 7 days to a 5 cm^2 area of the forearm	Positive reaction in both	
Sorbitan sesquioleate	20% in petrolatum	86 patients with dermatoses	Patch test; 24-hour occlusive application using Finn chambers	Equivocal reaction—2 subjects (2.3%); questionable reaction—2 subjects (2.3%); positive (++,+++) reaction—5 subjects (5.8%)	32
		9 patients with positive reactions	ROAT; 0.1 mL applied 2×/day for 7 days to a 5 cm^2 area of the forearm	?,+ reactors—1 negative and 3 positive reactions; ++,+++ reactors—all positive	
Sorbitan sesquioleate	20% in petrolatum	4,469 patients with eczematous dermatitis	24-hour occlusive application using Finn chambers; test sites were scored at 72 or 96 hours	25 patients had an allergic response, + or stronger (0.6%)	34
Sorbitan sesquioleate	20% (vehicle not specified)	870 patients with contact dermatitis	TRUE test; occlusive patches using Finn chambers were applied for 48 hours; reactions were evaluated at 48-72 hours and 96-168 hours	9 patients reacted positively (0.7%); 6 reactions were identified as macular erythema, 2 reactions were weak, 1 was strong	33

Several of the sorbitan esters were considered not irritating to rabbit skin; sorbitan palmitate, sorbitan isostearate, and sorbitan stearate were applied at concentrations of up to 100% using 24-hour occlusive patches, sorbitan sesquioleate was applied for 24 hours using a semiocclusive patch, 40% aq. sorbitan tristearate was applied under a 24-hour occlusive patch, and undiluted sorbitan sesquicaprylate and sorbitan trioleate were applied with a 4-hour semiocclusive patch. Sorbitan sesquicaprylate was not a sensitizer in a GPMT; intradermal induction was conducted at a concentration of 5%, and topical induction and challenge were performed at 100%. In a GPMT of sorbitan trioleate, concentration of 2% were used for intradermal induction, 100% for topical induction, 50% and 100% at challenge, and 25% and 50% at rechallenge. Slight to moderate erythema and slight edema were observed in test and control animals; at rechallenge, slight erythema was observed in only 2 test animals.

Table 10. Ocular Irritation Studies.

Test article	Concentration/ dose	Animals	Method	Results	Reference
Alternative studies					
Sorbitan sesquicaprylate	Neat; 200 μL	Chicken eggs	In vitro; test substance was applied to the chorioallantoic membrane	Slightly irritating; score of 3.83/21	24
Nonhuman studies					
Sorbitan stearate	10% in peanut oil; 0.1 mL	6 male NZW rabbits	Single instillation; eyes were not rinsed. *Disregarded because only a short abstract was available (limited data; no scores available for assessment, no data on test substance purity)*	Not irritating	20,a
Sorbitan stearate	0.1 g	6 female NZW rabbits	Single instillation; eyes were not rinsed. *Disregarded because of limited documentation (no data on test substance purity)*	Not irritating	20,a
Sorbitan stearate	Neat, 0.1 mL	NZW rabbits, 3 males and 3 females	Single instillation; eyes were not rinsed	Not irritating	20
Sorbitan stearate	neat, 0.1 mL	6 female Vienna white rabbits	Single instillation; eyes were not rinsed	Not irritating	20
Sorbitan stearate	Neat, 0.1 g	NZW rabbits, 5 males and 1 female	Single instillation; eyes were not rinsed	Not irritating	20
Sorbitan stearate	Neat, 0.1 g	NZW rabbits, 4 males and 5 females	Single instillation; eyes were not rinsed for 6/9 animals	Not irritating	20
Sorbitan sesquicaprylate	Neat, 0.1 mL	NZW rabbits, 1 male and 2 females	Single instillation; eyes were not rinsed	Not irritating. All animals had a slight ocular reaction 1 and 24 hours after instillation; no irritation was observed day 7	24
Sorbitan sesquioleate	10% in peanut oil; 0.1 mL	6 male NZW rabbits	Single instillation; eyes were not rinsed. *Disregarded because "does not meet important criteria of today standard methods" (only tested at a concentration of 10%)*	No signs of irritation	21,a
Sorbitan sesquioleate	30% in distilled water; 0.1 mL	9 male NZW rabbits	Single instillation; eyes were not rinsed for 6/9 animals. *Disregarded because "does not meet important criteria of today standard methods" (only tested at a concentration of 30%)*	No signs of irritation	21,a
Sorbitan trioleate	30% in distilled water; 0.1 mL	9 male NZW rabbits	Single instillation; eyes were not rinsed for 6/9 animals. *Disregarded because "does not meet important criteria of today standard methods" (only tested at a concentration of 30%)*	No signs of irritation	23,a
Sorbitan trioleate	Neat, 0.1 mL	2 NZW rabbits	Single instillation; eyes were not rinsed	Not irritating	23

[a]Study disregarded by European Chemicals Agency applicant.

In clinical testing, sorbitan palmitate, sorbitan stearate, sorbitan sesquioleate, and sorbitan trioleate, all tested at 30%, were not irritants or sensitizers when applied for up to 5 days, followed by a challenge application after 7 to 10 days. Sorbitan palmitate, 50%, was also not an irritant after a 72-hour occlusive application. Case studies were performed in patients with diseased skin; reactions were observed in patients with contact allergy and contact dermatitis with sorbitan laurate (0.4% incidence), sorbitan oleate (0.6% incidence with 5%; up to 2.7% incidence with 20%), sorbitan stearate (2.3% incidence with 5%), and sorbitan sesquioleate (up to 9.8% incidence with 20%). Undiluted sorbitan stearate, sorbitan sesquicaprylate, sorbitan sesquioleate, and sorbitan trioleate were classified as not irritating to rabbit eyes following a single instillation without rinsing.

Discussion

In 1985, the Panel determined that 7 sorbitan esters were safe as used in cosmetic ingredients. In 2002, the Panel reviewed the safety of 10 additional sorbitan esters and issued an addendum to the 1985 report, concluding that the sorbitan fatty acid esters

were safe as used in cosmetic ingredients. The Panel reaffirmed the safe as used conclusions of the 1985 and 2002 safety assessments. The Panel also determined that the data from those safety assessments, together with the new data presented on the sorbitan esters, support the safety of 3 additional esters that had not yet been reviewed, and the Panel reopened the safety assessment to add these esters.

Some of the components of the sorbitan esters are botanical ingredients. The Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

The Panel stated that some of the sorbitan esters are used in products that could be incidentally inhaled, for example, sorbitan isostearate is reported to be used at 2.3% in pump hair sprays. Because single-dose, 4-hour inhalation studies of sorbitan laurate and sorbitan trioleate reported LC_{50} values > 5 mg/L, and because sorbitan trioleate has been reported to be used as an inactive ingredient in drugs at a maximum concentration of 0.0694% in a nasal aerosol product, the Panel was not concerned with the use of these ingredients in formulations that might be inhaled. The Panel also noted that in aerosol products, 95% to 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Conclusion

The Panel concluded that the following 20 sorbitan esters are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Sorbitan caprylate
Sorbitan cocoate*
Sorbitan diisostearate*
Sorbitan dioleate*
Sorbitan distearate*
Sorbitan isostearate
Sorbitan laurate
Sorbitan oleate
Sorbitan olivate
Sorbitan palmate
Sorbitan palmitate
Sorbitan sesquicaprylate*
Sorbitan sesquiisostearate
Sorbitan sesquioleate
Sorbitan sesquistearate*
Sorbitan stearate
Sorbitan triisostearate
Sorbitan trioleate
Sorbitan tristearate
Sorbitan undecylenate*

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

Author's Note

Unpublished sources cited in this report are available from the Executive Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Author Contributions

M. Fiume contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, and critically revised manuscript. W. Bergfeld contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. D. Belsito contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. R. Hill contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. C. Klaassen contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. D. Liebler contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. J. Marks contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. R. Shank contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. T. Slaga contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. P. Snyder contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. L. Gill contributed to analysis and interpretation and critically revised the manuscript. B. Heldreth contributed to analysis and interpretation and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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