Safety Assessment of Sorbitan Esters as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	November 14, 2014
Panel Meeting Date:	December 8-9, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Assistant Director/Senior Scientific Analyst
Date: November 14, 2014
Subject: Safety Assessment of Sorbitan Esters as Used in Cosmetics

Enclosed is the Draft Final Report on the Safety Assessment of Sorbitan Esters as Used in Cosmetics. (It is identified as *sorbes122014rep* in the pdf document.) At the September meeting, the Panel reaffirmed the safe as used conclusions of the 1985 and 2002 safety assessments on sorbitan esters. The Panel also reopened the safety assessment to add four previously unreviewed esters and issued a Tentative Amended Report, concluding that the 21 sorbitan esters are safe the present practices of use and concentration described in this safety assessment.

The Panel noted that a reported function of sorbitan theobroma grandiflorum seedate is skin bleaching agent. Since this is not a cosmetic use in the United States, the Panel emphasized that this review would not include the safety of any of these ingredients for use as skin bleaching agents

Updated concentration of use data were received and incorporated (*sorbes122014data*). Also, comments were received from the Council and have been addressed (*sorbes122014PCPC_1; sorbes122014PCPC_2*).

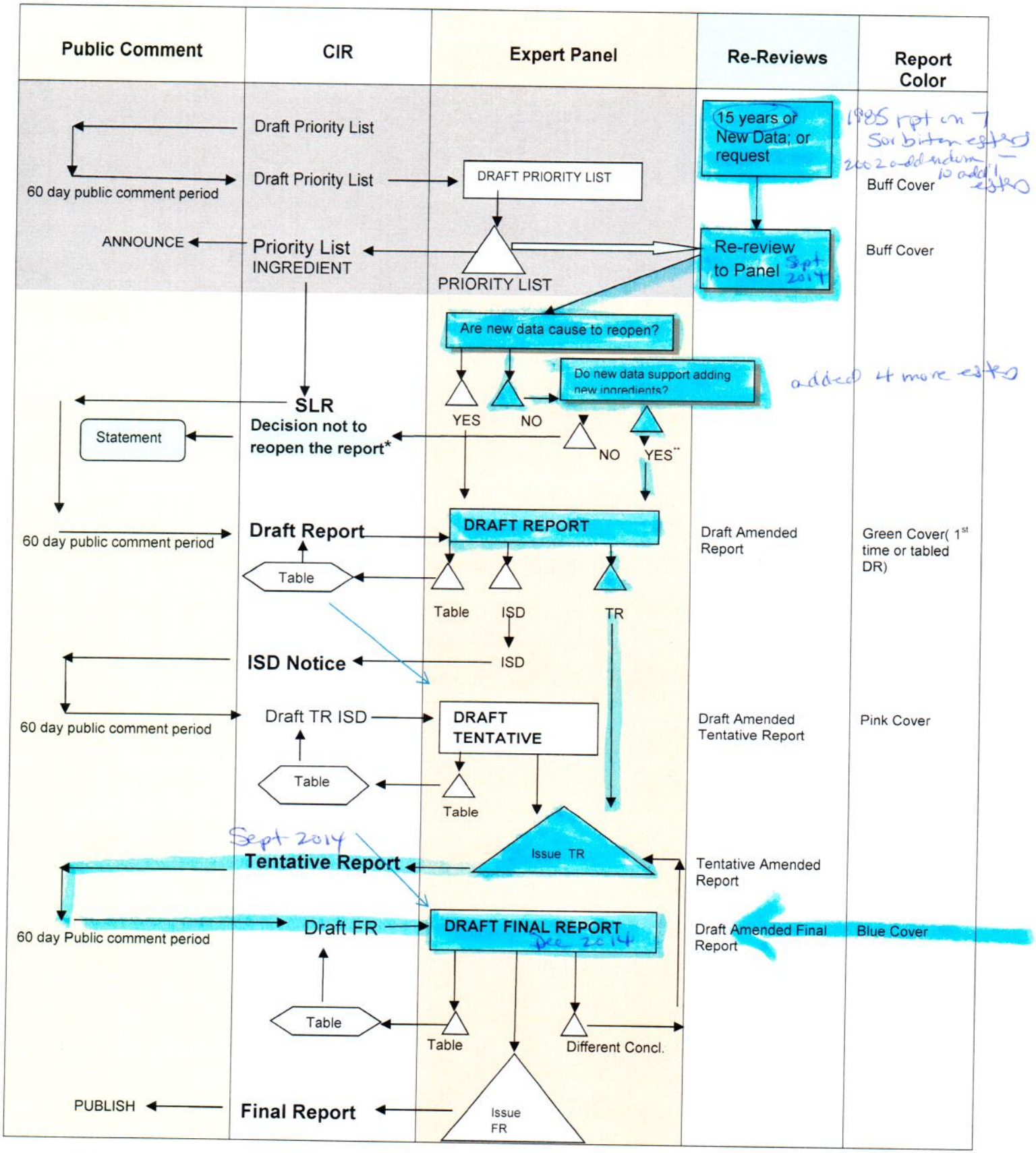
The original 1985 and 2002 safety assessments are provided (*sorbes092014prev_1; sorbes092014prev_2*, respectively) for your use.

The Panel should be prepared to issue a Final Amended Report.

Sorbitan Esters

Dec 2014

SAFETY ASSESSMENT FLOW CHART



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

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

Sorbitan Esters – History

1985: The Panel concluded that sorbitans stearate, laurate, sesquioleate, oleate, tristearate, palmitate, and trioleate are safe as used in cosmetics.

2002: The Panel issued an addendum to the 1985 sorbitan esters report, and reviewed the safety of sorbitans caprylate, cocoate, diisostearate, dioleate, distearate, isostearate, olivate, sesquiisostearate, sesquistearate, and triisostearate. The Panel concluded sorbitan fatty acid esters are safe as used.

September 8-9, 2014: initial Panel review of the re-review.

In addition to the 17 sorbitan esters previously reviewed, the Panel is being asked to consider whether sorbitan undecylenate, sorbitan sesquicaprylate, sorbitan palmate, and sorbitan theobroma grandiflorum seedate should be included in the report.

Unpublished concentration of use data were included in the document.

The Panel combined the two previous reports and added the for new ingredients, and issued a tentative amended report for public comment with the conclusion that the 21 sorbitan esters are safe as used in cosmetics.

December 8-9, 2014: draft Final Amended Report

Sorbitan Esters – Dec 2014 – Monice Fiume																			
	Reported Use	**Method of Mfg**	**Toxicokinetics**	**Dermal Penetration**	**Animal Tox – Acute, Dermal**	**Animal Tox – Acute, Oral**	**Animal Tox, Acute, Inhal.**	**Animal Tox – Rptd Dose, Derm**	**Animal Tox, Rptd Dose, Oral**	**Human – Rptd Dose, Oral**	**Animal Tox – Rptd Dose, Inhal**	**Repro/Dev Tox**	**Genotox**	**Carciniogenicity**	**Photocarc**	**Dermal Irr/Sens**	**Phototoxicity**	**Ocular Irritation**	**Mucous Membrane Irr**
Sorbitan Esters - General		*	*																
Sorbitan Caprylate	X	*																	
Sorbitan Undecylenate																			
Sorbitan Laurate	X*					X*	X	*	*				X	*		X*		*	*
Sorbitan Palmitate	X*					X*		*	X				X			X*		*	
Sorbitan Isostearate	X*					X										X*			*
Sorbitan Oleate	X*					*			*					*		X*	*		*
Sorbitan Stearate	X*		*			X*		*	X*	*		X	X*	*		X*	*	X*	X
Fatty Sorbitan Sesquiesters																			
Sorbitan Sesquicaprylate													X			X		X	X
Sorbitan Sesquiisostearate	X*					*										*			*
Sorbitan Sesquioleate	X*				*	X*		*					X			X*		X*	X
Sorbitan Sesquistearate																			
Fatty Sorbitan Diesters																			
Sorbitan Diisostearate																			
Sorbitan Dioleate																			
Sorbitan Distearate																			
Fatty Sorbitan Triesters																			
Sorbitan Triisostearate	X*																		
Sorbitan Trioleate	X*					*	X	*					X	*		X*		X	X
Sorbitan Tristearate	X*					*			X							X*		*	
Mixed Chain Length Sorbitan Monoesters																			
Sorbitan Cocoate																			
Sorbitan Olivate	X	*																	

Sorbitan Esters – Dec 2014 – Monice Fiume																			
	Reported Use	**Method of Mfg**	**Toxicokinetics**	**Dermal Penetration**	**Animal Tox – Acute, Dermal**	**Animal Tox – Acute, Oral**	**Animal Tox, Acute, Inhal.**	**Animal Tox – Rptd Dose, Derm**	**Animal Tox, Rptd Dose, Oral**	**Human – Rptd Dose, Oral**	**Animal Tox – Rptd Dose, Inhal**	**Repro/Dev Tox**	**Genotox**	**Carciniogenicity**	**Photocarc**	**Dermal Irr/Sens**	**Phototoxicity**	**Ocular Irritation**	**Mucous Membrane Irr**
Sorbitan Palmate	X																		
Sorbitan Theobroma Grandiflorum Seedate																			

*"X" indicates that new data were available in a category for the ingredient
"*" indicates that existing data are summarized for the ingredient

SORBITAN ESTERS RR

PubMed Search – July 10, 2014
Sorbitan AND (Caprylate OR Cocoate OR Diisostearate OR Dioleate OR Distearate OR Isostearate OR Laurate OR Oleate OR Olivate OR Palmate OR Palmitate OR Sesquicaprylate OR Sesquiisostearate OR Sesquioleate OR Sesquistearate OR Stearate OR (Theobroma AND Grandiflorum AND Seedate) OR Triisostearate OR Trioleate OR Tristearate OR Undecylenate) – 233 hits/23 useful

Additional Data Searched
ECHA
HPV/SIDS
CFR
JECFA
FDA – Inactive Drug Ingredients
EU

SORBITAN ESTERS TRANSCRIPTS – September 8-9, 2014

Belsito Team

DR. BELSITO: Okay, last one. Sorbitan esters. So it's a re-review, 1985 we reaffirmed with additional esters in 2002 that they're safe as used. There is some additional four not yet reviewed sorbitan esters and open to add ingredients in safe as used.
DR. LIEBLER: Agree.
DR. BELSITO: This is my comment here under the cosmetic use. It says to function as a skin bleaching agent. I guess it's in the dictionary but that wouldn't be a cosmetic use.
MS. FIUME: No. Let me make sure I'm right. And I think that's why I included it was because it's not normally. It's a little different than normal but let me just double check it right now. Yup, it is listed as one of the functions.
DR. SNYDER: Bad dictionary.
DR. BELSITO: Yeah, so I mean, how do we deal with that? I mean, it is reported to function as a skin bleaching and a skin conditioning agent, emollient. Should we add a sentence after that, however, the panel acknowledges that cosmetic ingredients should not bleach the skin or something to that effect that that's inappropriate for -- or that we're not reviewing it as a skin bleaching agent?
DR. SNYDER: I think we have to say that. We're not reviewing it as a function.
DR. BELSITO: So we need to say it probably there but we need to say it very strongly in the discussion.
DR. SNYDER: Although it's listed as functioning as a skin bleaching agent that it's not what we are reviewing? We're not including in this review?
DR. BELSITO: Right.
MS. FIUME: And I'm wondering if it's there because I clicked on skin bleaching agents. It says that in the EU and other countries skin bleaching products may be considered to be cosmetics.
DR. BELSITO: Yeah, but not in the United States. So I mean, I think we're dealing with the US. So I think just a statement here that, you know, that the use of this material as a skin bleaching agent will not be addressed in this report. And then, in the discussion that the panel felt that the skin bleaching agents were -- would be a non- cosmetic use and did not assess the safety of sorbitan esters as --
DR. SNYDER: Functioning?
DR. BELSITO: -- bleaching agents, skin bleaching agents. And then, Monice, on page 13 of the pdf from the 2002 report summary, I'm assuming it was just a lack of a space but I want to verify that sorbitan isostearate, so it's the 2002 report fourth line last -- it's 10 percent and not 1.0 percent?
MS. FIUME: I'm sorry, what page is that, Don?
DR. BELSITO: Page 13 of the pdf, the 2002 report summary, the fourth line. Just verifying that it was 10 percent and there was just a space and not 1 percent, 1.0 that that's supposed to be.
MS. FIUME: Oh, okay.
DR. SNYDER: 10 percent.
DR. BELSITO: That's what I presume.
DR. SNYDER: Yeah.
DR. BELSITO: I didn't have a chance to go back and look at that report, so.
MS. FIUME: It's irritation and sensitization. It's supposed to say irritation and sensitization.
DR. BELSITO: It's the 2002 report.
MS. FIUME: I'm just trying to find it in the original document.
DR. SNYDER: 10 percent.
DR. BELSITO: 10 percent?
DR. SNYDER: I think so.
MS. FIUME: Yes. It's 10 percent.
DR. BELSITO: Okay. That's all I had.
DR. LIEBLER: I had one comment on the chemical structure for figure two, got that kind of funky representation of the tetrahydropyran. I think you were trying to portray it in a sort of a triglyceride like look with the three acyl chains going up, it just doesn't -- it's not very clear to look at.
DR. HELDRETH: Okay.
DR. LIEBLER: I would recommend doing a flat tetrahydropyran representation and if you have to hang one chain the other way or make a long bond, either way it would be easier for somebody to look at and go, ah, I see.
DR. HELDRETH: Okay. Yeah, I just wanted to be clear that it most likely form a head Al kind of formation and a solution.
DR. LIEBLER: Right, yeah. You can do that with just one extra-long bond to one of the acyl chains.
DR. HELDRETH: Okay, will do.
MS. FIUME: Were there any other items for the discussion on this report, Dr. Belsito?
DR. BELSITO: No, I mean, I guess the only other comment that I had is on page 15 where you -- this is under the summary. The next to the last paragraph where you say recently summary searches have stated that evidence as suggested sensitization

to sorbitan sesquioleate has been increasing and due to increased use as an emulsifier in stearates. I would just strike that. That's pure speculation.
MS. FIUME: Okay.
DR. BELSITO: All of those studies where you're seeing those high numbers are really focused AIM patch testing. You know, sorbitan sesquioleate is very frequently used also in fragrances I tested routinely as part of our fragrance mix as a control and I don't ever see positive reactions to it. So to me it's not increasing and again, I just think that's speculative. You have the data there, they're AIM tested data. We put it in. I would just rid of that speculative comment.
In terms of the discussion, I would just carry it over. It's pretty much the same discussion as we had for the others. I didn't have anything to add to it. There's not much there. And then, just a couple of misspelling. That's it. Excellent. Okay.
MS. FIUME: Before you leave, I don't think it'll be a concern but I just want to point out I forget to earlier, the PEGylated alkyl glycerides, when the original conclusion was done on the 1999 report it said a limit of 10 percent in leave-ons.
DR. BELSITO: Right.
MS. FIUME: It's now used up to 11.3 percent and there's data that have been submitted. I just want to point out that it's increased and that was a question asked by (inaudible).
DR. SNYDER: Not an issue.
DR. BELSITO: Pardon?
DR. SNYDER: Not an issue.
DR. BELSITO: No. Okay.

Marks Team

Okay. Next is the sorbitan esters.
MS. FIUME: You'll note this is also a combination of re-reviews because there were a few that were coming due that could be combined. So it's two combined reports as well as the addition of a few ingredients.
DR. MARKS: So the question is do we reopen or not and reconfirm the safety of these ingredients? I have four add-ons. Are they no brainers, and in the list of 21 ingredients?
DR. SHANK: I say reopen only to add the new ingredients. The conclusion does not change.
DR. SLAGA: I agree the conclusion doesn't change, but add the open and add.
DR. HILL: Can I speak to that before you finalize that decision?
DR. MARKS: Sure.
DR. HILL: Undecylenic acid, I've let this slide by a couple of times in some of the other ingredients, but undecylenic acids, if you go out and look for things to treat, athlete's foot, for example, it has anti-fungal activity.
So, I guess I need to, for my own edification research, as I understand it, the effect relates to an inhibition of fatty acid biosynthesis in fungi. But I haven't gone out to further find out fungi and yeast. I haven't gone out to further find out what is known about trafficking of this particular molecule in human biochemistry.
But compared to the other fatty acids here it's got an unsaturation on the terminal position. I think we're able to shift that in our bodies, but I'm not 100 percent clear. It would matter in terms of this stuff getting into the skin.
I also had a question about the theobroma grandiflora because it's indicative of a skin bleaching agent, so what does that really mean? Dermatologists, is that, like, kojic acid threshold levels, but not drug or what is that?
DR. MARKS: We'll get that clarified. It doesn't appear on my radar, but. Okay. So tomorrow I'll presume I'll second that we reopen this to add on the flora ingredients listed there. Then we'll get more data on that, Ron Hill.
DR. BERGFELD: Could I just make a comment about undecylenic acid, I guess, that you referred to which is used as an anti-fungal. It's an over the counter product. The fungi that we see in skin that this is used on, they're strictly in the stram accordion, and they're not observed. I mean, they're not penetrating, maybe in this top of the follicle, so they have not been of concern to the OTC population. Reviews?
DR. HILL: I'm assuming the FDA has had a good close look at this.
DR. BERGFELD: Right.
DR. HILL: But I guess what I'm getting at is can we somehow capture that information into the report, if nothing else. Like I said, I let this one slide by a couple of times without flagging it, but I have a comment here, and I think I put it in the report. Can we get the computer estimated log P values for at least the component indicated by the structures in table one?
Because I think what we're going to find out is based on molecular weights and based on log Ps these might, at least, penetrate far enough down into the skin to get into the blood stream. I'm not worried about systemic toxicity on any of them, I think. But we don't have composition data on theobroma grandiflora seed, particularly seeing that it has bleaching activity, what else is in there.
Also, I really wanted to know what's the story with undecylenic acid? If we put it down on our -- see, undecylenic acid in those over the counters is just straight undecylenic acid, so it's going to have the free carboxyl group, but that's not what the situation is here. We've got these as triglycerides. So what does that do?
DR. MARKS: Okay. We'll get clarification if it's in our next review of these ingredients. If it's not a no brainer then we, obviously, will delete that particular ingredient from the re-review. Any other comments?
Next is styrene. And, no, I don't plan on going through lunch.

MS. FIUME: Excuse me, Dr. Marks, could I back up a few reports? I forgot to ask about one issue on PEGylated alkyl glycerides. I'm sorry.
DR. MARKS: Mm hmm.
MS. FIUME: The original report, the concentration of use of some of the add-ons is lower than the new concentration of use, and I just wanted to make sure it was going to be okay.
DR. MARKS: When I reviewed it the irritation and sensitization it used concentration for PEG-7, and then the PEG-6 the PEG-7 glyceryl cocoate. Lots of uses, 858, and PEG-6 caprylic and capric glyceride. Again, lots of uses, 500. They were okay.
Then wave 2 showed more irritation and sensitization data which looked okay to me. So it didn't raise a flag in my review. Ron, Ron, Tom? Apparently no.
MS. FIUME: Okay. I just wanted to confirm.
DR. MARKS: Right.
MS. FIUME: I knew we had received data on it, but I just wanted to point out that the concentration of use had increased slightly --
DR. MARKS: Yeah.
MS. FIUME: -- since the last report. Thank you.

Full Panel

DR. BERGFELD: Thank you, unanimous. So now we're moving onto the re-reviews and we have three of these and the first one is sorbitan esters. Dr. Belsito?
DR. BELISTO: So we're looking to combine reports and add ingredients and we thought that was great. And based upon all the information we had, not only did we think we could do that, but go ahead with a tentative final of safe as used.
DR. MARKS: Second.
DR. BERGFELD: Any further discussion? Move the question and all those in favor of this motion?
(All hands raised.)

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ABSTRACT

The CIR Expert Panel assessed the safety of sorbitan ester; this report included sorbitan esters that were reviewed in 1985 and 2002, as well as four previously un-reviewed sorbitan esters. Most of the sorbitan esters are reported to function in cosmetics as surfactant - emulsifying agents. However, a reported function of sorbitan theobroma grandiflorum seedate is skin bleaching agent; the Panel emphasized that function is not cosmetic in the United States, and safety of use as skin bleaching agents is not addressed in this safety assessment. 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 21 sorbitan esters included in this safety assessment are safe as used in cosmetic formulations.

INTRODUCTION

In 1985, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of seven sorbitan esters; based on the data presented in that assessment, the Panel concluded that sorbitan stearate, sorbitan laurate, sorbitan sesqui-oleate, sorbitan oleate, sorbitan tristearate, sorbitan palmitate, and sorbitan trioleate were safe as used in cosmetics.[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 as used in cosmetic ingredients.[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 four 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 re-review 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
sorbitan theobroma grandiflorum seedate

All 21 of these ingredients share an identical sorbitan structural core, and only vary in the number of fatty acid chains and the length of those chains. Most of the sorbitan esters are reported to function as a surfactant – emulsifying agent in cosmetic ingredients[3] (Table 1).

The complete original sorbitan esters reports can be found on the CIR website, http://www.cir-safety.org/ingredients. Therefore, a brief summary of some of the data from each report will be included, as appropriate; this information will be identified by *italicized text*. Please refer to the original reports for detailed information.

Much of the new data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[4] The ECHA website 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 tri-esters, and mixtures thereof, of fatty acids and 1,4-sorbitan. Generally, these ingredients can be depicted using a five-membered ring-shown as the tetrahydrofuran form (Figure 1). However, some of the six-membered ring, tetrahydropyran, may also be present.

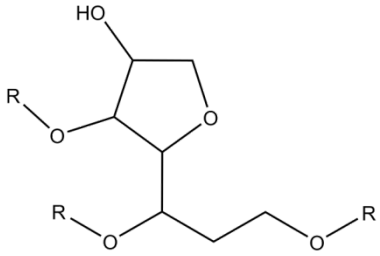


Figure 1. Sorbitan Esters, wherein R represents either a fatty acid residue or hydrogen.

The ingredients in this safety assessment are the reaction products of fatty acids, ranging from eight carbons in length (i.e., sorbitan caprylate) to twenty (e.g., component fatty chain of sorbitan theobroma grandiflorum seedate), with hexitol anhydrides derived from sorbitol (e.g., sorbitan tristearate (Figure2)). "Sorbitan" is a generic name for anhydrides (i.e., cyclic ether tetrahydric alcohols) derived from sorbitol by the removal of one molecule of water with concomitant cyclization.

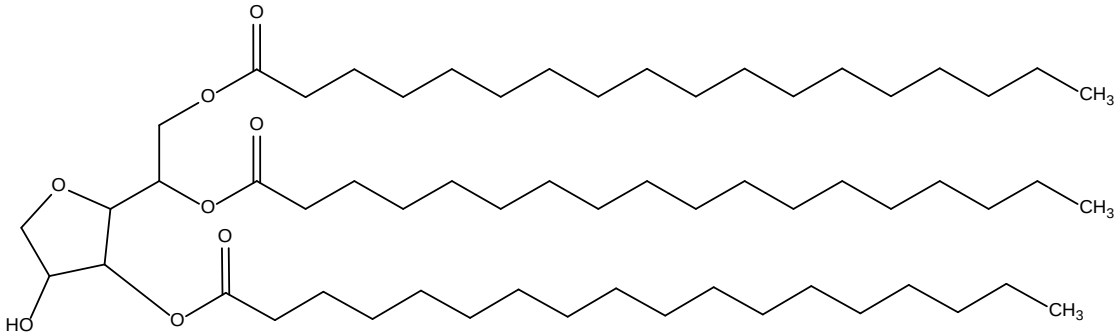


Figure 2. Sorbitan Tristearate

Chemical and Physical Properties

1985 report: Sorbitan esters are waxy solids or viscous liquids soluble inorganic solvents.[1] Sorbitan esters 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.

Sorbitol, the compound from which the hexitol anhydrides of the sorbitan esters are derived, is a crystalline, hexahydric alcohol.[5]

Methods of Manufacture

1985 report: Sorbitan esters are manufactured by combining sorbitol with the appropriate fatty acid at elevated temperatures.[1]

Composition and Impurities

1985 report: 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 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). 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 21 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 seven sorbitan esters included in the 1985 report were updated in the 2002 report; that 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 (e.g., 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 (e.g., 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 with 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 (i.e., 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 esters named in this report are listed in the European Union inventory of cosmetic ingredients.[12]

Non-Cosmetic

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).

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 non-ionic surface-active agent bilayers, and the intended use of these vesicles is as a drug delivery system.

Sorbitan theobroma grandiflorum may function as a skin bleaching agent.[3] This is considered a drug function in the United States, but is considered a cosmetic function in some parts of the world.

TOXICOKINETICS

1985 report: Sorbitan stearate is hydrolyzed to stearic acid and anhydrides of sorbitol when ingested.[1] 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 given 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.

TOXICOLOGICAL STUDIES

1985 report: The results of oral toxicity studies of sorbitan fatty acid esters indicated that these sorbitans in low concentration were relatively nontoxic via ingestion.[1] The lowest rat 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 sorbitans stearate, laurate, and oleate. At a 5% dietary concentration, sorbitan laurate and sorbitan oleate had no adverse effect on rats over a 2-yr period. Dogs fed 5% sorbitan stearate for 20 mos had no compound-related 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. 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 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.

2002 report: The no-effect dose of sorbitan stearate was 7.5 g/kg/day using rats fed the ingredient for 2 yrs.[2] The acute oral LD_{50} of sorbitan sesquiisostearate was 25 ml/kg in a study using female ddY mice.

Single Dose (Acute) Toxicity

The original safety assessments of the sorbitan esters included data that indicated that this group of ingredients was relatively non-toxic upon ingestion of a single dose. Additional oral studies in mice and rats on sorbitan laurate, palmitate, isostearate, stearate, sesquioleate, and tristearate support that finding (Table 6).[17-22] In 4-h exposure studies, sorbitan laurate and sorbitan trioleate had an 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 yrs.[18] The no-observable adverse effect level (NOAEL) was 5%. Thirty male rats were fed a diet with 5% sorbitan stearate, equivalent to 5000 mg/kg bw/day, for 2 yrs.[20] No effects on clinical signs, mortality, body weight, feed consumption, hematology, clinical chemistry, gross or microscopic lesions, or pathology were reported. Sorbitan tristearate, 5% (equivalent to 5000 mg/kg bw/day), was also administered in the diet to a group of 30 male rats for 2 yrs.[22] No effects on clinical signs or mortality, body weight or weight gains, or gross or microscopic lesions were reported.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

2002 report: 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 (~7% sorbitol) were not reproductive toxins at doses of 3000 to 7000 mg/kg/day for 2 years.

Gravid female Wistar rats, 20 per group, were dosed once daily by gavage with 0, 500 or 1000 mg/kg bw/day sorbitan stearate on days 0-20 of gestation, and the animals were killed.[20] The NOAEL for maternal toxicity and for teratogenicity was 1000 mg/kg bw/day. No test article-related embryotoxic results were reported.

Groups of 12 male and 12 female Sprague-Dawley rats were dosed by gavage once daily with 0, 40, 200, or 1000 mg/kg bw/day sorbitan stearate in water.[20] The females were dosed 2 wks prior to mating until day 4 of lactation; the males were dosed for 42 days. No signs of toxicity, no effects on mortality, body weight, or body weight gains, and no gross or microscopic lesions were observed. Effects on feed consumption, hematology, and clinical chemistry were not examined.

GENOTOXICITY

1985 report: 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.

2002 report: 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 PK 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

1985 report: Mice fed ≤4% sorbitan stearate for 80 wks had no difference in tumor type and incidence as compared to control animals.[1] Sorbitan laurate was inactive as a carcinogen or tumor promoter when painted on mice skin for 70 wks. 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%).

2002 report: The sorbitan fatty acid esters had no antitumor activity against Ehrlich ascites tumors in mice. Sorbitan stearate was neither a mouse skin carcinogen or tumor promoter. Sorbitans laurate and trioleate were co-carcinogens in one mouse skin study, but the latter ester and sorbitan oleate were not tumor promoters in another.

IRRITATION AND SENSITIZATION

Dermal

Non-Human

1985 report: 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 day 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 is minimal. Undiluted sorbitan oleate was minimally irritating to rabbit skin when applied for 24 h. Sorbitan palmitate, 50%, was not irritating to rabbit skin when applied for 24 h. Sorbitan tristearate, 30%, was nonirritating when applied to the skin of rabbits for 24 h.

2002 report: The sorbitan fatty acid esters (concentrations up to 100%) were generally minimal to mild skin irritants in various animal studies.[2] Sorbitan isostearate, however, was a moderate irritant in one study using rabbits and intradermal injections of the ingredient caused mild to severe irritation in a study using guinea pigs. Concentrations up to 100% sorbitan isostearate had low sensitization potential in guinea pigs. Sorbitan isostearate and sorbitan sesquiisostearate (10%) were non- to weak irritants to the intact and abraded skin of rabbits. The same concentrations caused weak cumulative irritation in a study using guinea pigs. In other studies, the ingredient did not produce significant irritation, sensitization, or comedone formation.

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-h occlusive patches,[18-20] sorbitan sesquioleate was applied for 24-h using a semi-occlusive patch,[21] 40% aq. sorbitan tristearate was applied using a 24-h occlusive patch,[22] and undiluted sorbitan sesquicaprylate and sorbitan trioleate were applied with a 4-h semi-occlusive 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, the concentrations used for intradermal induction, topical induction, challenge, re-challenge were 2%, 100%, 50 and 100%, and 25 and 50%, respectively.[23] Slight to moderate erythema and slight edema were observed in test and control animals; at re-challenge, slight erythema was observed in two test animals.

Human

1985 report: The sorbitans are minimal to mild skin irritants in humans.[1] Results from three repeated insult patch tests (RIPTs) (involving a total of 420 subjects) indicated that up to 4% sorbitan stearate is not a sensitizer. Products containing 2-4% 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; two Schwartz prophetic patch tests with undiluted sorbitan sesquioleate produced no reactions, and in five RIPTs, products containing 1-3 % sorbitan sesquioleate were not sensitizer, but some subjects did experience mild irritation. Several products containing 1.75-2.0% sorbitan oleate have been tested on human subjects. 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 non-sensitizers in several RIPTs. No irritation was observed in maximization test with a formulations containing 1.75% sorbitan oleate, but in a product usage test with a cream containing 1.75% sorbitan oleate produced mild irritation in 2/53 individuals. A Schwartz prophetic patch test with undiluted sorbitan tristearate produced no irritation in 201 subjects. Formulation containing 4% sorbitan palmitate 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 4% sorbitan palmitate was non-irritating and non-sensitizing. Several products containing 5% sorbitan trioleate were tested on human subjects; these products were slightly irritating in 21-day cumulative irritation tests, Shelanski/Jordan RIPT, modified Schwartz-Peck predictive patch tests, and in a 4-wk usage test.

Photosensitization assessments on products containing 2% sorbitan stearate or 2% sorbitan oleate classified both products as non-phototoxic and non-photoallergenic. Sorbitans laurate, sesquioleate, palmitate and trioleate did not absorb radiation in the UVA and UVB range in ultraviolet spectral analysis.

2002 report: 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 1206 patients with eczema were treated with 5% to 20% sorbitans stearate, oleate, and sesquioleate, and two polysorbates. Sorbitan isostearate and sorbitan sesquiisostearate (10%) were non-irritating in a 24-h occlusive patch test using 56 subjects.

In clinical testing, 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 7-10 days (Table 8).[18,20,21,23] Sorbitan palmitate, 50%, also was not an irritant after a 72-h occlusive application.[18] Positive reactions were observed in numerous provocative tests in contact allergy and contact dermatitis patients with sorbitan laurate (0.4% incidence),[25] sorbitan oleate (0.6% incidence with 5%; up to 2.7% incidence with 20%),[14,25-28] sorbitan stearate(2.3% incidence with 5%),[27] and sorbitan sesquioleate (up to 9.8% incidence with 20%).[14,26-29]

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.[14,30] 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.[14,30-34]

Effect on Non-Immunologic Immediate Contact Reactions

A 10 x 20 cm 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) three times per day for 2 days, and a contralateral site was treated in a similar manner with petrolatum only.[35] 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 min 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 and 250 mM benzoic acid in petrolatum only were stronger on the sites that were pretreated with sorbitan sesquioleate, as 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 and 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.

Case Reports

Case reports of contact dermatitis to sorbitan laurate, sorbitan oleate, and sorbitan sesquioleate have been described. For example, studies reported reactions to 2%[36] or 5% aq. sorbitan laurate[37] used as an emulsifier in a hydrocortisone cream; one reported that three of 23 patients with chronic leg ulcers had an allergic reaction to 20% sorbitan oleate in petrolatum;[38] one reported that three patients with recalcitrant wounds from sensitization to a non-adhering dressing had positive reactions to sorbitan sesquioleate, a component of the dressing;[39] and one reported that six pediatric patients with recalcitrant dermatitis had positive reactions to 20% sorbitan sesquioleate in petrolatum.[40]

Ocular Irritation

1985 report: Draize and modified Draize ocular irritation studies using rabbits were performed with all of the sorbitans in this 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.

2002 report: The sorbitan fatty acid esters were generally not ocular irritants.[2] In one study, sorbitan isostearate (10%) was non-irritating to the eyes of rabbits, whereas the same concentration of sorbitan sesquiisostearate was minimally irritating.

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 9).[20,21,23,24]

SUMMARY

In 1985, the Panel reviewed the safety of the cosmetic use of seven 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 four sorbitan esters have been identified and are reviewed in this assessment; all 21 of

these esters share an identical sorbitan structural core, and only vary in the number of fatty acid chains and the length of those chains,. Most of the sorbitan esters are reported to function as a surfactant – emulsifying agent in cosmetic ingredient

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 21 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 non-toxic in mice and rats following a single oral exposure. In single-exposure inhalation studies, the LC_{50} in rats was ≥5mg/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 yrs did not result in any adverse effects.

In oral reproductive toxicity studies in rats, the NOAEL for sorbitan stearate was 1000 mg/kg bw/day; this was the highest dose administered.

Sorbitan laurate, palmitate stearate, sesquicaprylate, sesquioleate, and 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, but the results of a chromosomal aberration assay in Chinese hamster cells with sorbitan stearate were ambiguous.

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-h occlusive patches, sorbitan sesquioleate was applied for 24-h using a semi-occlusive patch, 40% aq. sorbitan tristearate was applied under a 24-h occlusive patch, and undiluted sorbitan sesquicaprylate and sorbitan trioleate were applied with a 4-h semi-occlusive patch. Sorbitan sesquicaprylate was not a sensitizer in a guinea pig maximization test; 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 re-challenge. Slight to moderate erythema and slight edema were observed in test and control animals; at re-challenge, slight erythema was observed in only two test animals.

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 7-10 days. Sorbitan palmitate, 50%, also was not an irritant after a 72-h occlusive application. Positive reactions were observed in numerous provocative tests in contact allergy and contact dermatitis patients 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 seven 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 four additional esters that had not yet been reviewed, and the Panel reopened the safety assessment to add these esters.

The Panel did note that a reported function of sorbitan theobroma grandiflorum seedate is as a skin bleaching agent. Because this is not a cosmetic use in the United States, the Panel emphasized that this review would not include the safety of any of these ingredients for use as skin bleaching agents.

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-h inhalation studies of sorbitan laurate and sorbitan trioleate reported LC_{50} values >5 mg/l, and because sorbitan trioleate is permitted for use as an inactive ingredient in drugs at a maximum concentration of 0.0694%, 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% – 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 CIR Expert Panel concluded that the following 21 sorbitan esters are safe 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 theobroma grandiflorum seedate*
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.

TABLES

Table 1. Definition, Structure, and Function

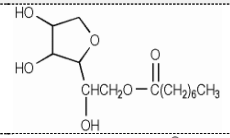
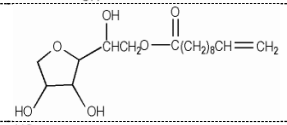
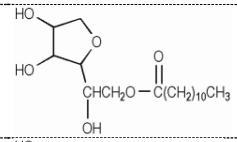
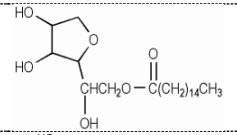
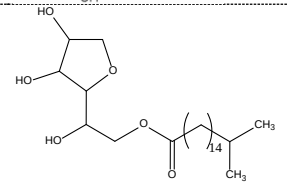
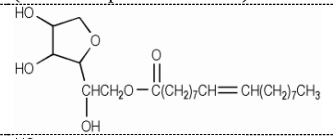
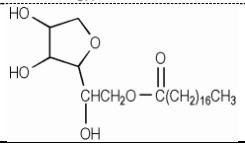
Ingredient (CAS No, if available)	Definition[3,*]	Structure[3,**]	Function(s)[3]
	Fatty Sorbitan Monoesters		
Sorbitan Caprylate [95508-00-2]	the monoester of caprylic acid and hexitol anhydrides derived from sorbitol		surfactant - emulsifying agent
Sorbitan Undecylenate (93963-92-9)	the monoester of 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

Table 1. Definition, Structure, and Function

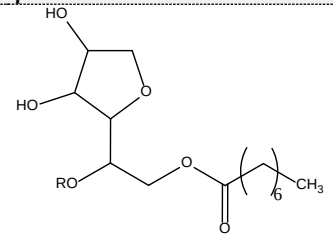
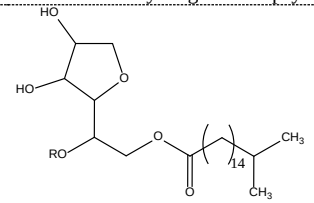
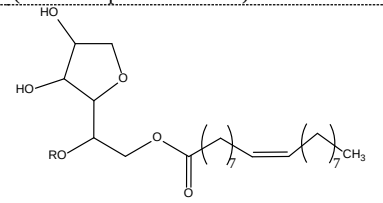
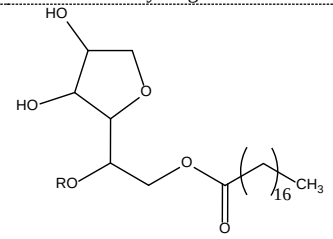
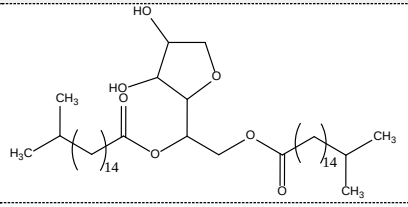
Ingredient (CAS No, if available)	Definition[3,*]	Structure[3,**]	Function(s)[3]
		Fatty Sorbitan Sesquiesters	
Sorbitan Sesquicaprylate (91844-53-0)	a mixture of mono and diesters of caprylic acid and hexitol anhydrides derived from sorbitol	 wherein R is hydrogen or caprylate**	skin-conditioning agent – misc.; surfactant - solubilizing agent; viscosity increasing agent – aq.
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")**	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**	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**	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

Table 1. Definition, Structure, and Function

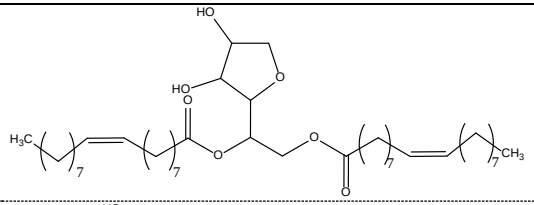
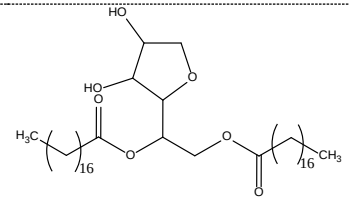
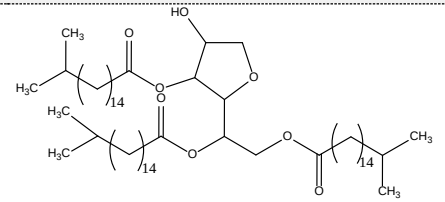
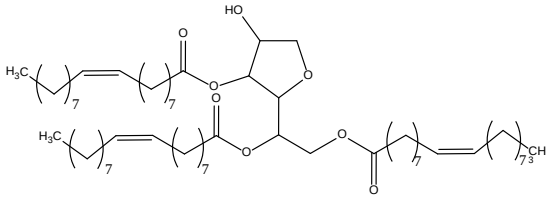
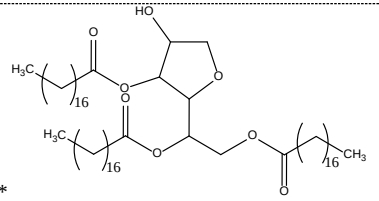
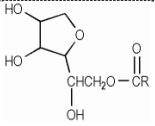
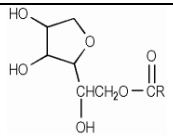
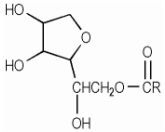
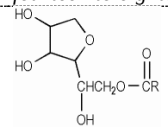
Ingredient (CAS No, if available)	Definition[3,*]	Structure[3,**]	Function(s)[3]
Sorbitan Dioleate (29116-98-1)	the diester of oleic acid and hexitol anhydrides derived from sorbitol.		surfactant - emulsifying agent
Sorbitan Distearate (36521-89-8)	the diester of stearic acid and the hexitol anhydrides 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")**	surfactant - emulsifying agent
Sorbitan Trioleate (26266-58-0)	he triester of oleic acid and hexitol anhydrides derived from sorbitol	** 	surfactant – emulsifying agent
Sorbitan Tristearate (26658-19-5)	the triester of stearic acid and hexitol anhydrides derived from sorbitol	 **	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 eight to eighteen carbons**)	surfactant - emulsifying agent

Table 1. Definition, Structure, and Function

Ingredient (CAS No, if available)	Definition[3,*]	Structure[3,**]	Function(s)[3]
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 sixteen to eighteen carbons**)	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 fourteen to eighteen carbons**)	emulsion stabilizer; skin-conditioning agent - emollient
Sorbitan Theobroma Grandiflorum Seedate	the monoester of the fatty acids derived from theobroma grandiflorum seed butter and hexitol anhydrides derived from sorbitol *the fatty acid residues from theobroma grandiflorum seed butter primarily consist of palmitate, stearate, oleate, linoleate, and arachidate*	 where RCO- represents the fatty acid radical derived from *Theobroma grandiflorum* seed butter (*ranging in chain length from sixteen to twenty carbons**)	skin-conditioning agent – emollient; skin bleaching agent (not considered a cosmetic function in the United States)

*information in italics was provided by the CIR Chemist
**these structures were provided by the CIR Chemist

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	5
solubility	soluble in mineral oil, cottonseed oil, methanol, ethanol, isopropyl alcohol, ethylene glycol; insoluble in water and propylene glycol	5
	dispersible in hot and cold water	41
	Sorbitan Palmitate	
physical characteristics	light cream to tan beads or flakes, or a hard waxy solid with a slight odor	42
congealing range	45-47ºC	42
solubility	soluble at temperatures above its melting point in ethanol, methanol, ether, ethylacetate, aniline, toluene, dioxane, petroleum ether, and carbon tetrachloride	42
	insoluble in cold water; dispersible in warm water	
	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	5
solubility	soluble in ethanol and isopropyl alcohol; miscible with mineral and vegetable oils; insoluble in water and propylene glycol	5
	soluble at temperatures above its melting point in ethanol, ether, ethylacetate, aniline, toluene, dioxane, petroleum ether, and carbon tetrachloride; insoluble in cold water; dispersible in warm water	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	5
melting point	49-65ºC	5
congealing range	50-52ºC	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 50ºC 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	47-50ºC	45
solubility	slightly soluble in toluene, ether, carbon tetrachloride, and ethyl acetate	45
	dispersible in petroleum ether, mineral oil, vegetable oils, acetone, and dioxane	
	insoluble in water, methanol, and ethanol	

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*	**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[a]	NA	2; 33[c]	7[c]	0.03-1[a]	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 - Non-Coloring	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*	**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,#]	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,#]	1[c]	0.03-1.5[a]	1-5[c]	4; 1[a]; 45[c]	1[c]	0.001-1; 0.001-2.6[a]	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 - Non-Coloring	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
	Sorbitan Oleate				**Sorbitan Stearate**			
	2014[6]	**1998[2]**	**2014[7]**	**1981[1]**	**2014[6]**	**1998[2]**	**2014[7]**	**1981[1]**
Totals*	**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	0.0042-3.2	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,#]	9; 78[b]; 78[c,#]	0.00000072; 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[a]	0.1-1; 0.1-5[c]	15; 6[a]; 217[c,#]	78[c,#]	0.001-2.1; 0.013-4[a]	≤0.1-5[c]
Dermal Contact	200	59	0.0025-7	≤0.1-25	757	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 - Non-Coloring	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

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 Sesquiisostearate				**Sorbitan Sesquioleate**			
	2014[6]	**1998[2]**	**2014[7]**	**1999[2]**	**2014[6]**	**1998[2]**	**2014[7]**	**1981[1]**
Totals*	**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[a]	NA	31; 17[c]	10; 2[a]; 9[c]	0.016-1; 0.25-2[a]	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 - Non-Coloring	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
	Sorbitan Triisostearate				**Sorbitan Trioleate**			
	2014[6]	**1998[2]**	**2014[7]**	**1999[2]**	**2014[6]**	**1998[2]**	**2014[7]**	**1981[1]**
Totals*	**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[a]	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 - Non-Coloring	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*	**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[a]	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 - Non-Coloring	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

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 Palmate					
	2014[6]	**2014[7]**				
Totals*	**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 - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Mucous Membrane	NR	NR				
Baby Products	NR	NR				

*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.

[a] Includes products that can be powders, but it is not known whether the reported uses are powders

[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

[#] - has reported use is as a foot powder/spray

NR – no reported use

NA - at the time of the original safety assessment, concentration of use data were not reported by the FDA

Table 4. Ingredients not reported to be used

sorbitan undecylenate
sorbitan sesquicaprylate
sorbitan sesquistearate
sorbitan diisostearate
sorbitan dioleate
sorbitan distearate
sorbitan cocoate
sorbitan theobroma grandiflorum seedate

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%

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] *
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] *
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] *
sorbitan stearate	Wistar rats	10/sex	water	90%; 16 g/kg by gavage (high application dose administered in two portions)	>16 g/kg	[20] *
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] *
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] *
sorbitan tristearate	Wistar rats	5/sex	CMC	100g/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-h nose-only exposure; 40% particles were <4 µm; MMAD/ GSD: 4.6 and 4.7 µm /2.0 and 2.1µm	>5 mg/l	[17]
sorbitan trioleate	Wistar rats	3/sex	air	5.27 mg/l; 4-h 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]

* study disregarded by ECHA applicant because only a short abstract was available (reason may have included no data on analytical purity of test substance, no gross pathology performed, no necropsy)

Abbreviations: CMC – carboxymethylcellulose; GSD – geometric standard deviation; MMAD – mean mass aerodynamic diameter

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	3-5000 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	8-5000 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	313-5000 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] *
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*	*Salmonella typhimurium* TA98, TA100	negative	[24] *
sorbitan sesquicaprylate	3-5000 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 - 5000 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]

* study disregarded by ECHA applicant

Abbreviations: CMC – carboxymethylcellulose; DMSO – dimethyl sulfoxide; stat. sig. – statistically significant

Table 8. Dermal irritation and sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
sorbitan palmitate	neat	6 male NZW rabbits	24-h occlusive application to shaved and abraded skin; the test sites were scored at 24 and 72 h	not irritating	[18]
sorbitan isostearate	neat; 0.5 ml	6 albino rabbits	24-h occlusive application to shaved and abraded skin; the test sites were scored at 24 and 72 h	erythema score – 1.78/4; edema score – 0.94/4 neither erythema or edema were fully reversible after 72 h	[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] *
sorbitan stearate	neat, 0.5 g	6 NZW rabbits	4-h semi-occlusive patches to shaved and abraded skin	not irritating erythema score – 0.3/4, fully reversible after 72 h edema score – 0/4	[20]
sorbitan stearate	0.5 ml	NZW rabbits, 3/sex	24-h occlusive patch to intact and abraded skin	not irritating erythema score – 0.7/4, fully reversible after 72 h in 4/6 animals; edema score – 0/4	[20]
sorbitan sesquicaprylate	neat; 0.5 ml	NZW rabbits, 1 male and 2 females	4-h semi-occlusive application to clipped skin; test sites scored at 1, 24, 48, and 72 h 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-h patch 7 days after intradermal induction challenge: after 14 days, 24-h patch	not a sensitizer no reactions were observed during induction or challenge	[24]
sorbitan sesquioleate	neat; 0.5 ml	6 male NZW rabbits	24-h semi-occlusive application to shaved and abraded skin; the test sites were scored at 24 and 72 h	classified as not irritating erythema score – 1.89/4; edema score – 0.78/4 neither erythema or edema were fully reversible after 72 h	[21]
sorbitan trioleate	neat, 0.5 ml	2 NZW rabbits	4-h semi-occlusive application to clipped skin; test sites scored at 1, 24, 48, and 72 h after patch removal	classified as not irritating erythema and edema scores – 0/4	[23]
sorbitan trioleate	Induction: intradermal, 2% in olive oil; topical, 100% in liquid paraffin challenge: 50 and 100% in liquid paraffin re-challenge: 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, 2 48-h patches challenge: on day 20, 24-h patches re-challenge: on day 28, 24-h 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 h, and slight edema at 24 h only was reported for both control and test groups Re-challenge: slight erythema was observed in test animals at 24 h (25%, 1 animal; 50%, 2 animals) and at 48 h (50%, 1 animal); no reactions were observed in the negative controls	[23]
sorbitan tristearate	40% aq.; 0.5 ml	6 NZW rabbits	24-h occlusive application to shaved and abraded skin; the test sites were scored at 24 and 72 h	not irritating erythema and edema scores – 0/4	[22]

Table 8. Dermal irritation and sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			HUMAN		
sorbitan laurate	not specified, but assumed neat	475 contact allergy patients	European retrospective survey of allergic contact reactions to cosmetics	2 patients had a positive reaction (0.4%)	25
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-h occlusive application using a 1 sq. in cotton pad	not an irritant	18
sorbitan oleate	not specified, but assumed neat	475 contact allergy patients	European retrospective survey of allergic contact reactions to cosmetics	2 patients had a positive reaction (0.4%)	25
sorbitan oleate	5% (vehicle not specified)	945 contact dermatitis patients	occlusive patches using Finn chambers were applied for 48 h; reactions were evaluated at 48-72 h and 96-168 h	6 patients reacted positively (0.6%); 3 reactions were identified as macular erythema, 3 react5ions were weak, 1 was strong	28
sorbitan oleate and sorbitan sesquioleate	sorbitan oleate: 20% in petrolatum sorbitan sesquioleate: 5% pet	112 dermatitis patients	48-h occlusive application using Finn chambers; test sites were scored at 48 and 72 h; 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 h, 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 contact dermatitis patients	sites were scored at 48 and 72 h; a modified NACDG standard and a cosmetic series was 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 h, all but 2 reactions were +; 2 subjects had a ++ reaction to sorbitan oleate	26
sorbitan oleate and sorbitan stearate	5% (each) in petrolatum	86 dermatoses patients	patch test; 24-h occlusive application using Finn chambers	+,++ reaction in 2 subjects (2.3%)	27
		the 2 patients with positive reactions	ROAT; 0.1 ml applied 2x/day for 7 days to a 5 cm^2 area of the forearm	positive reaction in both	
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-h challenge performed after a 10-day non-treatment period	not a sensitizer	20
sorbitan stearate	30% aq.	50 subjects	3-day initial occlusive patch, 3-day challenge performed after a 7-day non-treatment period	not an irritant or sensitizer	20
sorbitan sesquioleate	30% aq.	10 subjects	occlusive patch test; 5-day initial application, 48-h challenge after a 10-day non-treatment period	not an irritant or sensitizer	21
sorbitan sesquioleate	20% in petrolatum	86 dermatoses patients	patch test; 24-h occlusive application using Finn chambers	equivocal reaction – 2 subjects (2.3%) questionable reaction – 2 subjects (2.3%) positive (++,+++) reaction – 5 subjects (5.8%)	27
		the 9 patients with positive reactions	ROAT; 0.1 ml applied 2x/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	4469 patients with eczematous dermatitis	24 h occlusive application using Finn chambers; test sites were scored at 72 or 96 h	25 patients had an allergic response, + or stronger (0.6%)	29

Table 8. Dermal irritation and sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
sorbitan sesquioleate	20% (vehicle not specified)	870 contact dermatitis patients	TRUE test; occlusive patches using Finn chambers were applied for 48 h; reactions were evaluated at 48-72 h and 96-168 h	9 patients reacted positively (0.7%); 6 reactions were identified as macular erythema, 2 reactions were weak, 1 was strong	[28]
sorbitan trioleate	30% aq.	10 subjects	patch test; 5-day initial application, 48-h challenge performed after a 10-day non-treatment period	not a sensitizer	[23]
sorbitan trioleate	30% aq.	50 subjects	3-day initial occlusive patch, 3-day challenge performed after a 7-day non-treatment period	not an irritant or sensitizer	[23]

* study disregarded by ECHA applicant

Abbreviations: 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

Table 9. 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]
			NON-HUMAN 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] *
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] *
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 h 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] *
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] *
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] *
sorbitan trioleate	neat, 0.1 ml	2 NZW rabbits	single instillation; eyes were not rinsed	not irritating	[23]

* study disregarded by ECHA applicant
Abbreviations: NZW – New Zealand White

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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

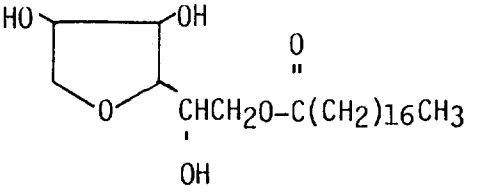
The Sorbitan fatty acid ester group includes the following ingredients: Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate. They are surfactants and are used primarily as emulsifiers, solubilizers, and stabilizers.[1-4]

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)



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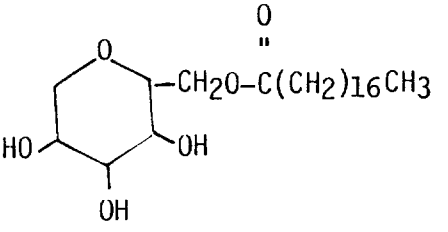
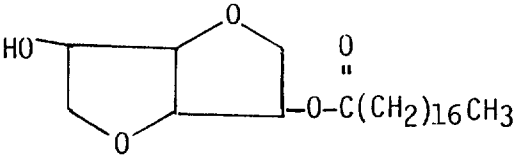


(c)

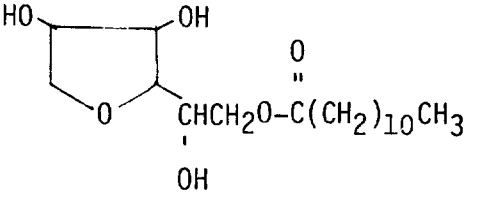


Sorbitan Stearate

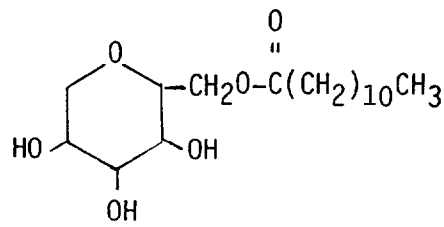
Synonyms include: Arlacel 60, Armotan MS, Copmul S, Emsorb 2505, Glycomul S, Hodag SMS, Liposorb S, Liposorb SC, Protachem SMS, Sorbitan Monostearate, Span 60.[2,4,5,7-9]

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

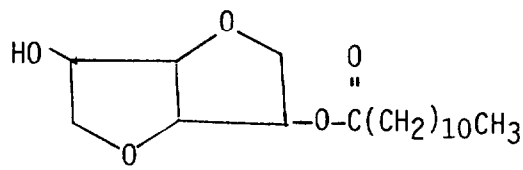
(a)



(b)



(c)

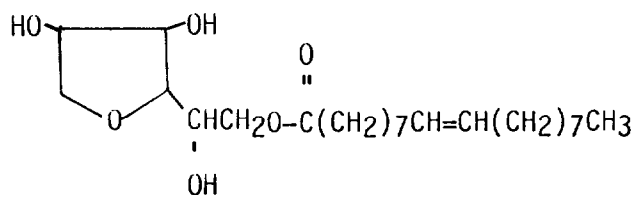


Sorbitan Laurate

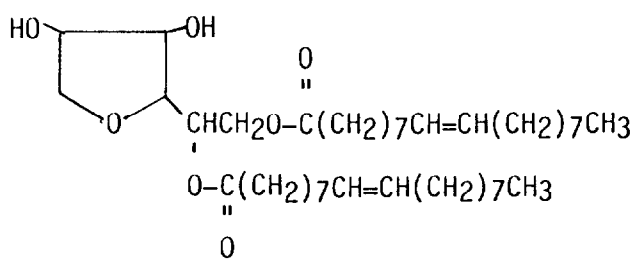
Other names include: Arlacel 20, Armotan ML, Emsorb 2515, Glycomul L, Glycomul LC, Liposorb L, Protachem SML, Sorbitan Monolaurate, Span 20.[2,4,5,7-9]

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)



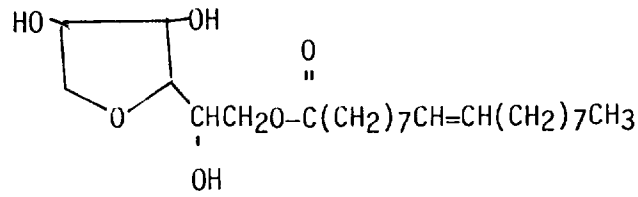
Sorbitan Sesquioleate

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

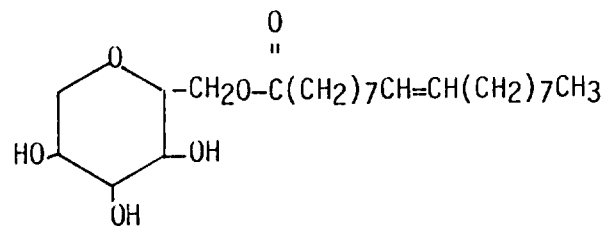
Sorbitan Oleate is the monoester of oleic acid and heixtol mono- and dianhy-

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

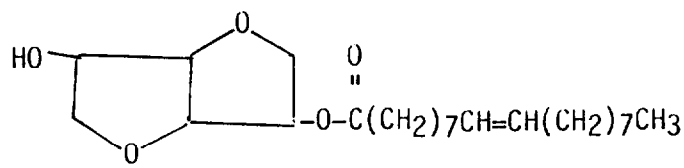
(a)



(b)



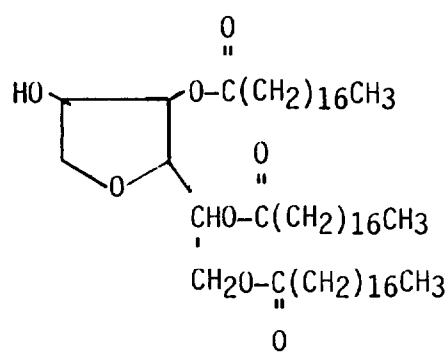
(c)



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:

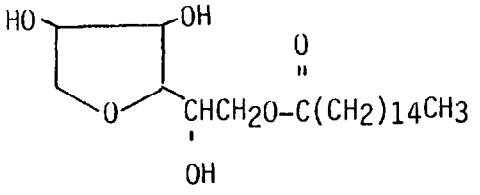


Sorbitan Tristearate

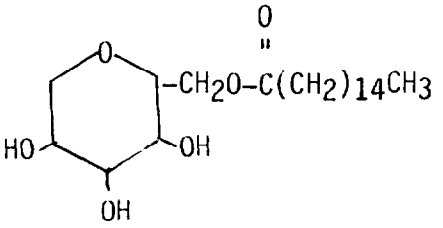
Other names include: Emsorb 2507, Glycomul TS, Liposorb TS, Protachem STS, Span 65.[2,5,7]

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

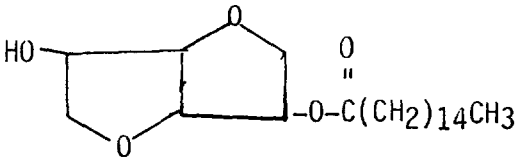
(a)



(b)



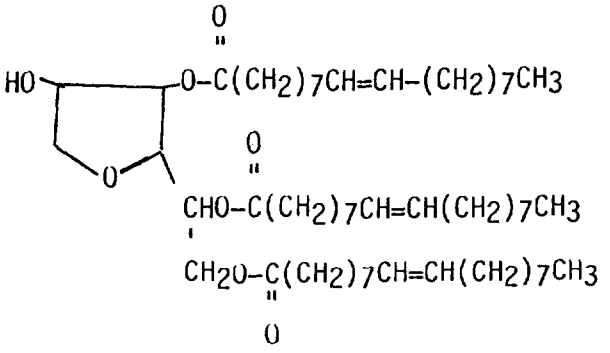
(c)



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.

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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).*

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

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

CHEMISTRY

Definition and Structure

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

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

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

Chemical and Physical Properties

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

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

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

Reactivity

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

Analytic Methods

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

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

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

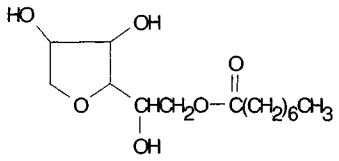
where C is the Sorbitan Stearate content (%); $W1$, $W2$, and $W3$ are isosorbide, 1,4-sorbitan, and D-sorbitol contents (μg), respectively; W is the sample weight (g); and f is a conversion factor of 0.27 (Tsuda et al. 1984).

Method of Manufacture

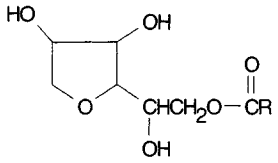
In general, Sorbitan Fatty Acid Esters are prepared by the dehydration of sorbitol (Figure 2) to form a hexitan, which is then esterified with the desired fatty acid (Gennaro 1990; Canterbery 1997).

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

SORBITAN CAPRYLATE
No CAS No. or Synonyms

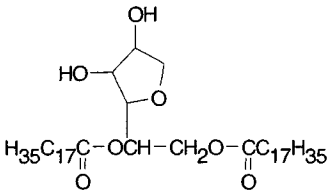


SORBITAN COCOATE
CAS No. 68154-36-9
Synonyms: Anhydrosorbitol Monococoate
Fatty Acids, Coco, Monoesters with Sorbitan
Sorbitan Monococoate

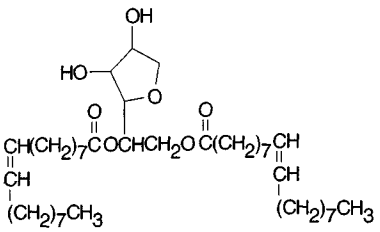


where RCO- represents the fatty acids derived from coconut oil

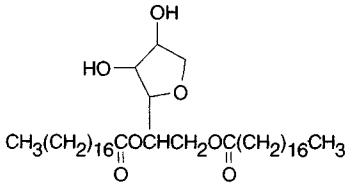
SORBITAN DIISOSTEARATE
CAS No. 68238-87-9
Synonym: Anhydrohexitol Diisostearate



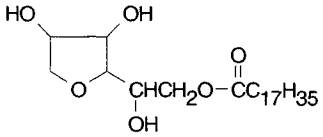
SORBITAN DIOLEATE
CAS No. 29116-98-1
Synonyms: Anhydrosorbitol Dioleate
Sorbide Dioleate
Sorbitan, Di-9-Octadecanoate



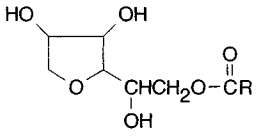
SORBITAN DISTEARATE
CAS No. 36521-89-8
Synonyms: Anhdrosorbitol Distearate
Sorbitan Dioctadecanoate



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

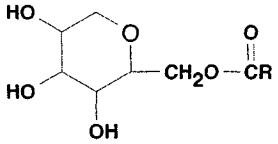


SORBITAN OLIVATE
No CAS No.
Synonyms: Anhydrosorbitol Monoolivate
Fatty Acids, Olive, Monoesters with Sorbitan
Sorbitan Monoolivate



where RCO- represents the fatty acids derived from olive oil

GENERIC STRUCTURE - TETRAHYDROPYRAN FORM



where RCO⁻ equals the fatty acid moiety

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

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

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

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

Impurities

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

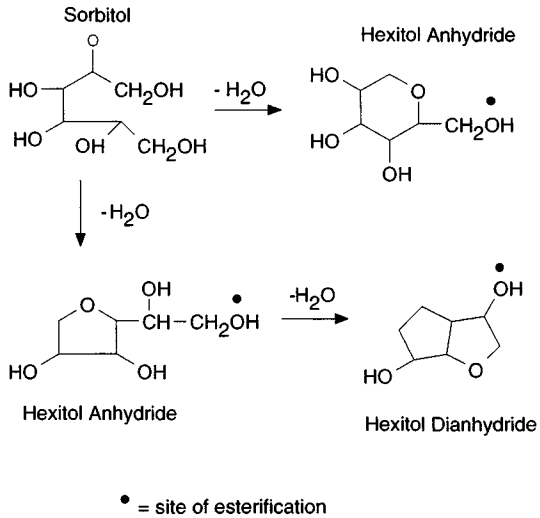


FIGURE 2
Mechanisms of Hexitol Anhydride Derivation (Canterbery 1997).

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

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

Ultraviolet Absorption

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

USE

Cosmetic

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

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

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

TABLE 2
Product formulation data (FDA 1998)

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

(Continued on next page)

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

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

(Continued on next page)

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

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

(Continued on next page)

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

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

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

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

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

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

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

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

Noncosmetic

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

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

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

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

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

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

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

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

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

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

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

Cytotoxicity

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

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

ANIMAL TOXICOLOGY

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

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

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

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

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

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

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

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

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

Dermal Irritation and Sensitization

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

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

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

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

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

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

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

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

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

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

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

Ocular Irritation

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

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

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

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

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

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

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

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

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

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

GENOTOXICITY

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

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

An unspecified Sorbitan Fatty Acid Ester (maximum dose = 5.0 mg/plate, in DMSO) was tested for mutagenicity in the Ames test using *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537. In the chromosomal aberration test using Chinese hamster fibroblasts, a maximum dose of 0.3 mg/ml of the test compound (in DMSO) resulted in 5.0% polyploid cells and 8.0% structural aberrations 48 hours after treatment. The results were considered equivocal, and polyploidization effects were observed (Ishidate et al. 1984).

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

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

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

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

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

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

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

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

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

CARCINOGENICITY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cocarcinogenicity

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

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

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

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

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

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

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

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

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

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

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation and Sensitization

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Comedogenicity

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

Photosensitization

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

Ocular Irritation

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

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

Case Reports

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

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

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

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

CONCLUSION

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

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Sorbitan Caprylate - conc of use, but no VCRP

SORBITAN LAURATE	01C - Other Baby Products	1
SORBITAN LAURATE	02A - Bath Oils, Tablets, and Salts	1
SORBITAN LAURATE	03A - Eyebrow Pencil	1
SORBITAN LAURATE	03B - Eyeliner	3
SORBITAN LAURATE	03D - Eye Lotion	2
SORBITAN LAURATE	03F - Mascara	9
SORBITAN LAURATE	03G - Other Eye Makeup Preparations	2
SORBITAN LAURATE	04E - Other Fragrance Preparation	1
SORBITAN LAURATE	05A - Hair Conditioner	1
SORBITAN LAURATE	05F - Shampoos (non-coloring)	1
SORBITAN LAURATE	05I - Other Hair Preparations	1
SORBITAN LAURATE	07A - Blushers (all types)	2
SORBITAN LAURATE	07B - Face Powders	2
SORBITAN LAURATE	07C - Foundations	12
SORBITAN LAURATE	07E - Lipstick	1
SORBITAN LAURATE	07F - Makeup Bases	2
SORBITAN LAURATE	07I - Other Makeup Preparations	3
SORBITAN LAURATE	10E - Other Personal Cleanliness Products	1
SORBITAN LAURATE	11A - Aftershave Lotion	2
SORBITAN LAURATE	11G - Other Shaving Preparation Products	1
SORBITAN LAURATE	12A - Cleansing	2
SORBITAN LAURATE	12C - Face and Neck (exc shave)	12
SORBITAN LAURATE	12D - Body and Hand (exc shave)	21
SORBITAN LAURATE	12F - Moisturizing	21
SORBITAN LAURATE	12G - Night	3
SORBITAN LAURATE	12H - Paste Masks (mud packs)	5
SORBITAN LAURATE	12J - Other Skin Care Preps	3
SORBITAN LAURATE	13B - Indoor Tanning Preparations	2

SORBITAN PALMITATE	03A - Eyebrow Pencil	7
SORBITAN PALMITATE	03B - Eyeliner	9
SORBITAN PALMITATE	03D - Eye Lotion	2
SORBITAN PALMITATE	03G - Other Eye Makeup Preparations	4
SORBITAN PALMITATE	05A - Hair Conditioner	3
SORBITAN PALMITATE	07E - Lipstick	3
SORBITAN PALMITATE	07I - Other Makeup Preparations	1
SORBITAN PALMITATE	10A - Bath Soaps and Detergents	1
SORBITAN PALMITATE	10E - Other Personal Cleanliness Products	2
SORBITAN PALMITATE	11G - Other Shaving Preparation Products	1
SORBITAN PALMITATE	12A - Cleansing	8
SORBITAN PALMITATE	12C - Face and Neck (exc shave)	15
SORBITAN PALMITATE	12D - Body and Hand (exc shave)	13
SORBITAN PALMITATE	12E - Foot Powders and Sprays	1
SORBITAN PALMITATE	12F - Moisturizing	27
SORBITAN PALMITATE	12G - Night	5
SORBITAN PALMITATE	12H - Paste Masks (mud packs)	2
SORBITAN PALMITATE	12J - Other Skin Care Preps	5

SORBITAN ISOSTEARATE	01B - Baby Lotions, Oils, Powders, and Cream	1
SORBITAN ISOSTEARATE	03A - Eyebrow Pencil	3
SORBITAN ISOSTEARATE	03B - Eyeliner	3
SORBITAN ISOSTEARATE	03C - Eye Shadow	11
SORBITAN ISOSTEARATE	03D - Eye Lotion	12
SORBITAN ISOSTEARATE	03F - Mascara	10

SORBITAN ISOSTEARATE	03G - Other Eye Makeup Preparations	10
SORBITAN ISOSTEARATE	05A - Hair Conditioner	1
SORBITAN ISOSTEARATE	05G - Tonics, Dressings, and Other Hair Groo	4
SORBITAN ISOSTEARATE	05I - Other Hair Preparations	4
SORBITAN ISOSTEARATE	06B - Hair Tints	8
SORBITAN ISOSTEARATE	07A - Blushers (all types)	2
SORBITAN ISOSTEARATE	07B - Face Powders	4
SORBITAN ISOSTEARATE	07C - Foundations	23
SORBITAN ISOSTEARATE	07E - Lipstick	119
SORBITAN ISOSTEARATE	07F - Makeup Bases	2
SORBITAN ISOSTEARATE	07G - Rouges	1
SORBITAN ISOSTEARATE	07H - Makeup Fixatives	3
SORBITAN ISOSTEARATE	07I - Other Makeup Preparations	32
SORBITAN ISOSTEARATE	10E - Other Personal Cleanliness Products	1
SORBITAN ISOSTEARATE	11A - Aftershave Lotion	2
SORBITAN ISOSTEARATE	12A - Cleansing	2
SORBITAN ISOSTEARATE	12C - Face and Neck (exc shave)	27
SORBITAN ISOSTEARATE	12D - Body and Hand (exc shave)	18
SORBITAN ISOSTEARATE	12F - Moisturizing	58
SORBITAN ISOSTEARATE	12G - Night	6
SORBITAN ISOSTEARATE	12H - Paste Masks (mud packs)	7
SORBITAN ISOSTEARATE	12I - Skin Fresheners	1
SORBITAN ISOSTEARATE	12J - Other Skin Care Preps	12
SORBITAN ISOSTEARATE	13A - Suntan Gels, Creams, and Liquids	2
SORBITAN ISOSTEARATE	13B - Indoor Tanning Preparations	8
SORBITAN ISOSTEARATE	13C - Other Suntan Preparations	4

SORBITAN OLEATE	03C - Eye Shadow	4
SORBITAN OLEATE	03D - Eye Lotion	2
SORBITAN OLEATE	03E - Eye Makeup Remover	1
SORBITAN OLEATE	03G - Other Eye Makeup Preparations	5
SORBITAN OLEATE	05A - Hair Conditioner	7
SORBITAN OLEATE	05G - Tonics, Dressings, and Other Hair Groo	9
SORBITAN OLEATE	05I - Other Hair Preparations	4
SORBITAN OLEATE	06A - Hair Dyes and Colors (all types requiring	64
SORBITAN OLEATE	06B - Hair Tints	23
SORBITAN OLEATE	07B - Face Powders	1
SORBITAN OLEATE	07C - Foundations	3
SORBITAN OLEATE	07E - Lipstick	2
SORBITAN OLEATE	07H - Makeup Fixatives	1
SORBITAN OLEATE	07I - Other Makeup Preparations	7
SORBITAN OLEATE	08B - Cuticle Softeners	1
SORBITAN OLEATE	08G - Other Manicuring Preparations	1
SORBITAN OLEATE	10E - Other Personal Cleanliness Products	1
SORBITAN OLEATE	11A - Aftershave Lotion	4
SORBITAN OLEATE	12A - Cleansing	9
SORBITAN OLEATE	12C - Face and Neck (exc shave)	21
SORBITAN OLEATE	12D - Body and Hand (exc shave)	13
SORBITAN OLEATE	12F - Moisturizing	108
SORBITAN OLEATE	12G - Night	3
SORBITAN OLEATE	12H - Paste Masks (mud packs)	1
SORBITAN OLEATE	12I - Skin Fresheners	3
SORBITAN OLEATE	12J - Other Skin Care Preps	2
SORBITAN OLEATE	13A - Suntan Gels, Creams, and Liquids	2
SORBITAN OLEATE	13B - Indoor Tanning Preparations	7
SORBITAN OLEATE	13C - Other Suntan Preparations	2

SORBITAN STEARATE	01B - Baby Lotions, Oils, Powders, and Cream	6
SORBITAN STEARATE	03A - Eyebrow Pencil	10
SORBITAN STEARATE	03B - Eyeliner	2
SORBITAN STEARATE	03C - Eye Shadow	41
SORBITAN STEARATE	03D - Eye Lotion	15
SORBITAN STEARATE	03E - Eye Makeup Remover	2
SORBITAN STEARATE	03F - Mascara	27
SORBITAN STEARATE	03G - Other Eye Makeup Preparations	12
SORBITAN STEARATE	04A - Cologne and Toilet waters	1
SORBITAN STEARATE	04C - Powders (dusting and talcum, excluding	5
SORBITAN STEARATE	04E - Other Fragrance Preparation	2
SORBITAN STEARATE	05A - Hair Conditioner	6
SORBITAN STEARATE	05F - Shampoos (non-coloring)	1
SORBITAN STEARATE	05G - Tonics, Dressings, and Other Hair Groo	12
SORBITAN STEARATE	06A - Hair Dyes and Colors (all types requiring	108
SORBITAN STEARATE	06B - Hair Tints	23
SORBITAN STEARATE	06H - Other Hair Coloring Preparation	29
SORBITAN STEARATE	07A - Blushers (all types)	11
SORBITAN STEARATE	07B - Face Powders	10
SORBITAN STEARATE	07C - Foundations	12
SORBITAN STEARATE	07D - Leg and Body Paints	3
SORBITAN STEARATE	07E - Lipstick	5
SORBITAN STEARATE	07I - Other Makeup Preparations	10
SORBITAN STEARATE	08C - Nail Creams and Lotions	1
SORBITAN STEARATE	10B - Deodorants (underarm)	9
SORBITAN STEARATE	10E - Other Personal Cleanliness Products	4
SORBITAN STEARATE	11A - Aftershave Lotion	5
SORBITAN STEARATE	11E - Shaving Cream	2
SORBITAN STEARATE	11G - Other Shaving Preparation Products	11
SORBITAN STEARATE	12A - Cleansing	31
SORBITAN STEARATE	12C - Face and Neck (exc shave)	59
SORBITAN STEARATE	12D - Body and Hand (exc shave)	156
SORBITAN STEARATE	12E - Foot Powders and Sprays	2
SORBITAN STEARATE	12F - Moisturizing	253
SORBITAN STEARATE	12G - Night	27
SORBITAN STEARATE	12H - Paste Masks (mud packs)	13
SORBITAN STEARATE	12I - Skin Fresheners	1
SORBITAN STEARATE	12J - Other Skin Care Preps	29
SORBITAN STEARATE	13A - Suntan Gels, Creams, and Liquids	2
SORBITAN STEARATE	13B - Indoor Tanning Preparations	10
SORBITAN SESQUIISOSTEARATE	03A - Eyebrow Pencil	11
SORBITAN SESQUIISOSTEARATE	03B - Eyeliner	21
SORBITAN SESQUIISOSTEARATE	03C - Eye Shadow	192
SORBITAN SESQUIISOSTEARATE	03D - Eye Lotion	2
SORBITAN SESQUIISOSTEARATE	03G - Other Eye Makeup Preparations	13
SORBITAN SESQUIISOSTEARATE	07A - Blushers (all types)	26
SORBITAN SESQUIISOSTEARATE	07B - Face Powders	13
SORBITAN SESQUIISOSTEARATE	07C - Foundations	22
SORBITAN SESQUIISOSTEARATE	07E - Lipstick	2
SORBITAN SESQUIISOSTEARATE	07F - Makeup Bases	11
SORBITAN SESQUIISOSTEARATE	07G - Rouges	2
SORBITAN SESQUIISOSTEARATE	07H - Makeup Fixatives	1
SORBITAN SESQUIISOSTEARATE	07I - Other Makeup Preparations	16
SORBITAN SESQUIISOSTEARATE	12A - Cleansing	1
SORBITAN SESQUIISOSTEARATE	12C - Face and Neck (exc shave)	6
SORBITAN SESQUIISOSTERATE	03C - Eye Shadow	1

SORBITAN SESQUIOLEATE	01B - Baby Lotions, Oils, Powders, and Cream	5
SORBITAN SESQUIOLEATE	02D - Other Bath Preparations	1
SORBITAN SESQUIOLEATE	03A - Eyebrow Pencil	1
SORBITAN SESQUIOLEATE	03B - Eyeliner	12
SORBITAN SESQUIOLEATE	03C - Eye Shadow	29
SORBITAN SESQUIOLEATE	03D - Eye Lotion	2
SORBITAN SESQUIOLEATE	03E - Eye Makeup Remover	2
SORBITAN SESQUIOLEATE	03F - Mascara	32
SORBITAN SESQUIOLEATE	03G - Other Eye Makeup Preparations	13
SORBITAN SESQUIOLEATE	05A - Hair Conditioner	3
SORBITAN SESQUIOLEATE	05G - Tonics, Dressings, and Other Hair Groo	3
SORBITAN SESQUIOLEATE	07A - Blushers (all types)	13
SORBITAN SESQUIOLEATE	07B - Face Powders	31
SORBITAN SESQUIOLEATE	07C - Foundations	55
SORBITAN SESQUIOLEATE	07E - Lipstick	18
SORBITAN SESQUIOLEATE	07F - Makeup Bases	9
SORBITAN SESQUIOLEATE	07G - Rouges	4
SORBITAN SESQUIOLEATE	07H - Makeup Fixatives	1
SORBITAN SESQUIOLEATE	07I - Other Makeup Preparations	20
SORBITAN SESQUIOLEATE	08C - Nail Creams and Lotions	1
SORBITAN SESQUIOLEATE	10A - Bath Soaps and Detergents	2
SORBITAN SESQUIOLEATE	10E - Other Personal Cleanliness Products	1
SORBITAN SESQUIOLEATE	11A - Aftershave Lotion	1
SORBITAN SESQUIOLEATE	12A - Cleansing	9
SORBITAN SESQUIOLEATE	12C - Face and Neck (exc shave)	14
SORBITAN SESQUIOLEATE	12D - Body and Hand (exc shave)	3
SORBITAN SESQUIOLEATE	12F - Moisturizing	11
SORBITAN SESQUIOLEATE	12G - Night	5
SORBITAN SESQUIOLEATE	12J - Other Skin Care Preps	14
SORBITAN SESQUIOLEATE	13A - Suntan Gels, Creams, and Liquids	6
SORBITAN SESQUIOLEATE	13C - Other Suntan Preparations	2
SORBITAN TRIISOSTEARATE	03B - Eyeliner	1
SORBITAN TRIISOSTEARATE	07E - Lipstick	2
SORBITAN TRIISOSTEARATE	12H - Paste Masks (mud packs)	1
SORBITAN TRIOLEATE	02A - Bath Oils, Tablets, and Salts	4
SORBITAN TRIOLEATE	03B - Eyeliner	1
SORBITAN TRIOLEATE	03C - Eye Shadow	2
SORBITAN TRIOLEATE	03D - Eye Lotion	1
SORBITAN TRIOLEATE	05A - Hair Conditioner	6
SORBITAN TRIOLEATE	07A - Blushers (all types)	1
SORBITAN TRIOLEATE	07C - Foundations	3
SORBITAN TRIOLEATE	07F - Makeup Bases	2
SORBITAN TRIOLEATE	07I - Other Makeup Preparations	4
SORBITAN TRIOLEATE	11D - Preshave Lotions (all types)	1
SORBITAN TRIOLEATE	12A - Cleansing	9
SORBITAN TRIOLEATE	12J - Other Skin Care Preps	2
SORBITAN TRISTEARATE	03A - Eyebrow Pencil	2
SORBITAN TRISTEARATE	03B - Eyeliner	11
SORBITAN TRISTEARATE	03D - Eye Lotion	8
SORBITAN TRISTEARATE	03F - Mascara	9
SORBITAN TRISTEARATE	03G - Other Eye Makeup Preparations	6
SORBITAN TRISTEARATE	07C - Foundations	4

SORBITAN TRISTEARATE	07E - Lipstick	2
SORBITAN TRISTEARATE	08C - Nail Creams and Lotions	1
SORBITAN TRISTEARATE	12C - Face and Neck (exc shave)	11
SORBITAN TRISTEARATE	12D - Body and Hand (exc shave)	6
SORBITAN TRISTEARATE	12F - Moisturizing	21
SORBITAN TRISTEARATE	12G - Night	15
SORBITAN TRISTEARATE	12H - Paste Masks (mud packs)	1
SORBITAN TRISTEARATE	12J - Other Skin Care Preps	1
SORBITAN TRISTEARATE	13A - Suntan Gels, Creams, and Liquids	2

SORBITAN OLIVATE	01B - Baby Lotions, Oils, Powders, and Cream	3
SORBITAN OLIVATE	03B - Eyeliner	10
SORBITAN OLIVATE	03C - Eye Shadow	1
SORBITAN OLIVATE	03D - Eye Lotion	10
SORBITAN OLIVATE	03F - Mascara	9
SORBITAN OLIVATE	03G - Other Eye Makeup Preparations	6
SORBITAN OLIVATE	05A - Hair Conditioner	2
SORBITAN OLIVATE	05I - Other Hair Preparations	1
SORBITAN OLIVATE	07B - Face Powders	1
SORBITAN OLIVATE	07C - Foundations	4
SORBITAN OLIVATE	07E - Lipstick	10
SORBITAN OLIVATE	07F - Makeup Bases	5
SORBITAN OLIVATE	07I - Other Makeup Preparations	4
SORBITAN OLIVATE	10B - Deodorants (underarm)	3
SORBITAN OLIVATE	10E - Other Personal Cleanliness Products	5
SORBITAN OLIVATE	11A - Aftershave Lotion	2
SORBITAN OLIVATE	11E - Shaving Cream	5
SORBITAN OLIVATE	11G - Other Shaving Preparation Products	1
SORBITAN OLIVATE	12A - Cleansing	19
SORBITAN OLIVATE	12C - Face and Neck (exc shave)	22
SORBITAN OLIVATE	12D - Body and Hand (exc shave)	19
SORBITAN OLIVATE	12F - Moisturizing	41
SORBITAN OLIVATE	12G - Night	12
SORBITAN OLIVATE	12H - Paste Masks (mud packs)	3
SORBITAN OLIVATE	12I - Skin Fresheners	4
SORBITAN OLIVATE	12J - Other Skin Care Preps	8
SORBITAN OLIVATE	13A - Suntan Gels, Creams, and Liquids	3
SORBITAN OLIVATE	13B - Indoor Tanning Preparations	1

Sorbitan Palmate - conc of use, but no VCRP

Concentration of Use by FDA Product Category – Sorbitan Esters*

Sorbitan Stearate
Sorbitan Laurate
Sorbitan Sesquioleate
Sorbitan Oleate
Sorbitan Tristearate
Sorbitan Palmitate
Sorbitan Trioleate
Sorbitan Caprylate
Sorbitan Cocoate
Sorbitan Diisostearate
Sorbitan Dioleate
Sorbitan Distearate
Sorbitan Isostearate
Sorbitan Olivate
Sorbitan Palmate
Sorbitan Sesquicaprylate
Sorbitan Sesquiisostearate
Sorbitan Sesquistearate
Sorbitan Theobroma Grandiflorum Seedate
Sorbitan Triisostearate
Sorbitan Undecylenate

Ingredient	Product Category	Maximum Concentration of Use
Sorbitan Stearate	Baby lotions, oils and creams not powder	0.8-0.99%
Sorbitan Stearate	Eyebrow pencil	0.25-1%
Sorbitan Stearate	Eye liner	0.006-3.2%
Sorbitan Stearate	Eye shadow	0.017-2.1%
Sorbitan Stearate	Eye lotion	0.001-1.9%
Sorbitan Stearate	Eye makeup remover	0.0042%
Sorbitan Stearate	Mascara	0.017-2.8%
Sorbitan Stearate	Other eye makeup preparations	1.3%
Sorbitan Stearate	Colognes and toilet waters	0.00000072%
Sorbitan Stearate	Perfume	1.7%
Sorbitan Stearate	Hair conditioners	1%
Sorbitan Stearate	Hair sprays pump spray	0.4%
Sorbitan Stearate	Tonics dressings and other hair grooming aids	0.0002-2.4%
Sorbitan Stearate	Other hair preparations (noncoloring)	3%
Sorbitan Stearate	Hair dyes and colors	0.0026-1.5%
Sorbitan Stearate	Hair bleaches	0.0013%
Sorbitan Stearate	Blushers	1-1.3%
Sorbitan Stearate	Face powders	0.001-2.1%
Sorbitan Stearate	Foundations	1.6-4%
Sorbitan Stearate	Makeup bases	0.75-3.8%
Sorbitan Stearate	Cuticle softeners	1.5%
Sorbitan Stearate	Nail creams and lotions	1%
Sorbitan Stearate	Deodorants not spray	0.5%
Sorbitan Stearate	Aftershave lotions	0.9-1.2%
Sorbitan Stearate	Shaving cream	2%

Sorbitan Stearate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1.2-3%
Sorbitan Stearate	Face and neck products not spray	0.013-3.5%
Sorbitan Stearate	Body and hand products not spray	0.02-4%
Sorbitan Stearate	Foot products Not spray or powder	0.95-1.6%
Sorbitan Stearate	Moisturizing products not spray	0.2-3.8%
Sorbitan Stearate	Night products not spray	0.15-2%
Sorbitan Stearate	Paste masks and mud packs	0.0013-3.5%
Sorbitan Stearate	Other skin care preparations	0.1%
Sorbitan Stearate	Suntan products not spray	1.6-5%
Sorbitan Stearate	Indoor tanning preparations	1.5%
Sorbitan Laurate	Bath oils, tablets and salts	0.02%
Sorbitan Laurate	Eyebrow pencil	0.01%
Sorbitan Laurate	Eye liner	0.00003-0.3%
Sorbitan Laurate	Eye shadow	0.01-0.1%
Sorbitan Laurate	Eye lotion	0.2%
Sorbitan Laurate	Other eye makeup preparations	0.066%
Sorbitan Laurate	Hair dyes and colors	0.0009%
Sorbitan Laurate	Foundations	0.02-0.3%
Sorbitan Laurate	Makeup fixatives	0.06%
Sorbitan Laurate	Nail polish and enamel	0.000075%
Sorbitan Laurate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	2%
Sorbitan Laurate	Face and neck products not spray	0.03-0.3%
Sorbitan Laurate	Body and hand products not spray	0.3-1%
Sorbitan Laurate	Moisturizing products not spray	0.01-0.75%
Sorbitan Laurate	Paste masks and mud packs	0.1-3%
Sorbitan Laurate	Other skin care preparations	0.2-3%
Sorbitan Laurate	Suntan products not spray	0.0073-0.03%
Sorbitan Sesquioleate	Baby lotion, oils and creams not powder	4%
Sorbitan Sesquioleate	Eyebrow pencil	1-5%
Sorbitan Sesquioleate	Eyeliner	0.01-2.9%
Sorbitan Sesquioleate	Eye shadow	0.25-2.2%
Sorbitan Sesquioleate	Mascara	0.02-2%
Sorbitan Sesquioleate	Other eye makeup preparations	1.9-2%

Sorbitan Sesquioleate	Tonics, dressings and other hair grooming aids	8%
Sorbitan Sesquioleate	Blushers (all types)	1.4-1.7%
Sorbitan Sesquioleate	Face powders	0.016-1%
Sorbitan Sesquioleate	Foundations	0.015-4%
Sorbitan Sesquioleate	Lipstick	0.0051-3%
Sorbitan Sesquioleate	Makeup bases	0.005-2%
Sorbitan Sesquioleate	Rouges	1.7%
Sorbitan Sesquioleate	Makeup fixatives	0.02%
Sorbitan Sesquioleate	Deodorants not spray aerosol	 0.009-2% 0.0064%
Sorbitan Sesquioleate	Aftershave lotions	0.1%
Sorbitan Sesquioleate	Face and neck products not spray	 0.25-2%
Sorbitan Sesquioleate	Body and hand products not spray	 0.9-1%
Sorbitan Sesquioleate	Foot products not spray or powder	 0.87%
Sorbitan Sesquioleate	Night products not spray	 0.2%
Sorbitan Sesquioleate	Paste mask and mud packs	0.35%
Sorbitan Sesquioleate	Suntan products not spray	 0.2%
Sorbitan Oleate	Eye liner	0.0081%
Sorbitan Oleate	Eye lotion	0.009-0.08%
Sorbitan Oleate	Hair conditioner	0.015-0.5%
Sorbitan Oleate	Hair sprays aerosol pump spray	 0.018% 0.02%
Sorbitan Oleate	Hair straighteners	0.01%
Sorbitan Oleate	Tonics, dressings and other hair grooming aids	0.05-3%
Sorbitan Oleate	Other hair preparations (noncoloring)	0.08-2.5%
Sorbitan Oleate	Foundations	0.0045-1%
Sorbitan Oleate	Lipstick	0.8%
Sorbitan Oleate	Makeup fixatives	0.005%
Sorbitan Oleate	Nail creams and lotions	0.0063%
Sorbitan Oleate	Deodorants not spray	 0.06%
Sorbitan Oleate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.013-7%
Sorbitan Oleate	Face and neck products not spray	 0.063-2.7%
Sorbitan Oleate	Body and hand products not spray	 0.0025-2%
Sorbitan Oleate	Moisturizing products not spray	 0.01-0.5%

Sorbitan Oleate	Night products not spray	2.4%
Sorbitan Oleate	Suntan products not spray	0.07-1%
Sorbitan Tristearate	Eyebrow pencil	2%
Sorbitan Tristearate	Eye liner	0.75-1.5%
Sorbitan Tristearate	Eye shadow	0.4-1.1%
Sorbitan Tristearate	Eye lotion	0.5-1%
Sorbitan Tristearate	Mascara	1-2.2%
Sorbitan Tristearate	Other eye makeup preparations	2.6%
Sorbitan Tristearate	Foundation	0.9%
Sorbitan Tristearate	Lipstick	0.7-1%
Sorbitan Tristearate	Other makeup preparations	1%
Sorbitan Tristearate	Other personal cleanliness products	0.13%
Sorbitan Tristearate	Face and neck products not spray	0.77-2%
Sorbitan Tristearate	Body and hand products not spray	0.5-1%
Sorbitan Tristearate	Moisturizing products not spray	0.13-1%
Sorbitan Tristearate	Night products not spray	1.4-1.5%
Sorbitan Tristearate	Other skin care preparations	0.15-0.5%
Sorbitan Tristearate	Suntan products not spray	1.2-3.5%
Sorbitan Palmitate	Eyebrow pencil	0.028-5.5%
Sorbitan Palmitate	Eyeliner	0.00003-5.4%
Sorbitan Palmitate	Eye shadow	0.25-2.5%
Sorbitan Palmitate	Eye lotion	0.75-1.4%
Sorbitan Palmitate	Mascara	1%
Sorbitan Palmitate	Foundation	1%
Sorbitan Palmitate	Lipstick	2.3-5.3%
Sorbitan Palmitate	Other makeup preparations	5.7%
Sorbitan Palmitate	Nail polish and enamel	0.000075%
Sorbitan Palmitate	Bath soaps and detergents	1.8%
Sorbitan Palmitate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1.8%
Sorbitan Palmitate	Face and neck products not spray	0.03-1.5%
Sorbitan Palmitate	Body and hand products not spray	0.3%
Sorbitan Palmitate	Moisturizing products not spray	1.5%
Sorbitan Palmitate	Night products not spray	0.5-0.7%
Sorbitan Palmitate	Suntan products	

	not spray	0.3%
Sorbitan Trioleate	Eyeliner	0.00001-0.00002%
Sorbitan Trioleate	Eye makeup remover	2.5%
Sorbitan Trioleate	Face powder	0.3%
Sorbitan Trioleate	Foundation	0.3-1.7%
Sorbitan Trioleate	Lipstick	0.3%
Sorbitan Trioleate	Nail polish and enamel	0.000025%
Sorbitan Trioleate	Beard softener	1%
Sorbitan Trioleate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1-5%
Sorbitan Trioleate	Face and neck products not spray	 0.5-2.5%
Sorbitan Caprylate	Eye lotion	1.5%
Sorbitan Caprylate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1%
Sorbitan Caprylate	Face and neck products not spray	 1.5%
Sorbitan Caprylate	Body and hand products not spray	 1%
Sorbitan Caprylate	Paste masks and mud packs	1%
Sorbitan Isostearate	Eyebrow pencil	1%
Sorbitan Isostearate	Eyeliner	1-1.5%
Sorbitan Isostearate	Eye shadow	0.0021-3.2%
Sorbitan Isostearate	Eye lotion	0.00038-4%
Sorbitan Isostearate	Other eye makeup preparations	0.05%
Sorbitan Isostearate	Hair sprays pump spray	 2.3%
Sorbitan Isostearate	Hair straighteners	2.3%
Sorbitan Isostearate	Tonics, dressings and other hair grooming aids	0.09%
Sorbitan Isostearate	Blushers	0.14-1.5%
Sorbitan Isostearate	Face powders	0.001-1%
Sorbitan Isostearate	Foundation	0.05-5%
Sorbitan Isostearate	Lipstick	0.0005-2.2%
Sorbitan Isostearate	Makeup bases	2.5%
Sorbitan Isostearate	Makeup fixatives	0.45-6.5%
Sorbitan Isostearate	Aftershave lotions	0.0007-0.07%
Sorbitan Isostearate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.068%
Sorbitan Isostearate	Face and neck products not spray	 0.004-2.6%
Sorbitan Isostearate	Body and hand products not spray spray	 0.001-2.5% 0.03-3%
Sorbitan Isostearate	Moisturizing products not spray	 0.042-3%
Sorbitan Isostearate	Night products	

	not spray	0.068-0.1%
Sorbitan Isostearate	Paste masks and mud packs	0.003-1%
Sorbitan Isostearate	Other skin care preparations	0.003-0.02%
Sorbitan Isostearate	Suntan products not spray aerosol	 0.0004-2% 1.4%
Sorbitan Isostearate	Other suntan preparations	2.5%
Sorbitan Olivate	Eyebrow pencil	0.014-7%
Sorbitan Olivate	Eye shadow	0.016%
Sorbitan Olivate	Eye lotion	1-2%
Sorbitan Olivate	Mascara	0.012-7.7%
Sorbitan Olivate	Tonics, dressings and other hair grooming aids	1.6-4%
Sorbitan Olivate	Foundations	1-1.2%
Sorbitan Olivate	Lipstick	0.018-1%
Sorbitan Olivate	Other makeup preparations	1%
Sorbitan Olivate	Shaving cream	0.88%
Sorbitan Olivate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.25-0.7%
Sorbitan Olivate	Face and neck products not spray	 0.2-1.9%
Sorbitan Olivate	Body and hand products not spray	 0.015-1.4%
Sorbitan Olivate	Moisturizing products not spray	 0.004-1.8%
Sorbitan Olivate	Night products not spray	 0.4-1.6%
Sorbitan Olivate	Suntan products not spray	 0.3-1.8%
Sorbitan Palmate	Eye lotion	0.75%
Sorbitan Palmate	Face and neck products not spray	 0.75%
Sorbitan Palmate	Body and hand products not spray	 0.45%
Sorbitan Sesquiisostearate	Eyebrow pencil	1-3%
Sorbitan Sesquiisostearate	Eyeliner	3%
Sorbitan Sesquiisostearate	Eye shadow	0.005-3%
Sorbitan Sesquiisostearate	Eye lotion	2%
Sorbitan Sesquiisostearate	Mascara	2%
Sorbitan Sesquiisostearate	Hair tints	1%
Sorbitan Sesquiisostearate	Blushers	3%
Sorbitan Sesquiisostearate	Face powders	2%
Sorbitan Sesquiisostearate	Foundations	1.5-3%
Sorbitan Sesquiisostearate	Lipstick	3%
Sorbitan Sesquiisostearate	Makeup bases	3%
Sorbitan Sesquiisostearate	Deodorant not spray	 3%

Sorbitan Sesquiisostearate	Face and neck products not spray	3%
Sorbitan Sesquiisostearate	Body and hand products not spray	2%
Sorbitan Sesquiisostearate	Moisturizing products not spray	1%
Sorbitan Sesquiisostearate	Suntan products not spray	0.5%
Sorbitan Triisostearate	Foundations	4.2%
Sorbitan Triisostearate	Lipstick	0.24-2%
Sorbitan Triisostearate	Rouges	9.1%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2014

Table prepared July 16, 2014

Updated October 27, 2014: Sorbitan Stearate: baby lotions, oils and creams added low concentration 0.8%; eye lotion high concentration increased from 0.9% to 1.9%; foundations high concentration increased from 2.1% to 4%; added shaving cream; Sorbitan Laurate: moisturizing products added low concentration 0.01%; Sorbitan Sesquioleate: added baby lotions, oils and creams; Sorbitan Oleate: other hair preparations (noncoloring) added low concentration 0.08%; face and neck products changed low concentration from 0.075% to 0.063%; suntan products added low concentration 0.07%; Sorbitan Trioleate: skin cleansing high concentration increased from 2.5% to 5%; Sorbitan Isostearate: added skin cleansing; moisturizing products high concentration increased from 2% to 3%; night products added 0.68% low concentration; suntan products added aerosol; Sorbitan Olivate: skin cleansing added 0.25% low concentration; moisturizing products added 1.8% high concentration; suntan products added 1.8% high concentration

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 3, 2014

SUBJECT: Comments on the Re-Review on Sorbitan Esters Prepared for the September 8-9, 2014 CIR Expert Panel Meeting

Toxicological Studies, 1985 report - What dose (or concentration) was used in the dermal studies of Sorbitan Palmitate and Sorbitan Trioleate?

Single Dose Exposure - What was the duration of exposure for the inhalation exposure studies?

Carcinogenicity, 1985 report - Rather than stating that mice were fed "low concentrations of sorbitan stearate", please state the concentration, as it is not clear what is meant by "low". What concentrations of Sorbitan Laurate and Sorbitan Trioleate were inactive as tumor promoters?

2002 report - What doses/concentrations were used in the studies described in this section?

Irritation and Sensitization - As both types of studies are described in this section, the subheading, "Dermal Irritation" is not necessary. Please include the concentrations tested throughout this section.

Ocular Irritation - Please state the concentrations tested as it is not clear what is meant by "high concentration".

Table 1 - Please include a reference for the fatty acid distribution of Theobroma Grandiflorum Seed Butter.

Table 3 - The footnote in the powder row for Sorbitan Laurate should be "a" not "b" ("b" is: "Includes products that can be sprays, but it is not known whether the reported uses are sprays" - which is not appropriate for the powder row.

Sorbitan Stearate - What is the source of the 0.0026% concentration in the Incidental Ingestion row? Hair coloring products was the only category with a use concentration of 0.0026% reported in the Council's use survey.

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Sorbitan Olivate - The foot note in the spray row should be "b", not "2".

Tables 6-9 - It is not necessary to include the studies that are disregarded on the ECHA website in these tables. The Introduction of the report should note that there were studies in the ECHA submissions that did not meet criteria and were disregarded by the applicants, and that these studies are not summarized in the CIR report. If the "disregarded" studies are left in the tables, the footnotes need to be revised. ECHA has not reviewed the submissions. It is the applicant (the companies submitting the data) that has indicated that the studies should be disregarded.

Table 8 - Please correct "react5ions"

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 26, 2014

SUBJECT: Comments on the Tentative Amended Report: Safety Assessment of Sorbitan Esters as Used in Cosmetics

Key Issue

Text, Tables 6-9 - It is not necessary to include the studies that are disregarded on the ECHA website in this report. The Introduction of the report should note that there were studies in the ECHA submissions that did not meet criteria for study quality and were disregarded by the applicants, and that these studies are not summarized in the CIR report.

If the "disregarded" studies are left in the text and the tables, the report needs to be revised. In addition to indicating that the results of the chromosomal aberration assay with Sorbitan Stearate were ambiguous, the Genotoxicity section should state that the companies providing the information to ECHA considered this study to be deficient and disregarded the study. The footnotes of Tables 7, 8 and 9 need to be revised. ECHA has not reviewed the submissions, so it is not appropriate to indicate that ECHA disregarded the studies. It is the applicant (the companies submitting the data) that has indicated that the studies should be disregarded.

Summary - As this is now a tentative report, the inclusion of all of the ingredients in the report should no longer be a proposal. The first paragraph of the Summary needs to be revised to remove "it is proposed that all of these ingredients be reviewed in a single safety assessment."

Discussion - As there were acute (4 hour) inhalation studies of Sorbitan Laurate and Sorbitan Trioleate, it is not appropriate to state that "there were no inhalation data available". The Discussion in the paragraph on potential inhalation exposure from spray cosmetics, should also note that Sorbitan Trioleate is permitted to be used in drug products intended to be inhaled with a maximum concentration of 0.0694% reported (Table 5).

Table 5 - If the CIR Expert Panel finds Table 5 (use as inactive ingredients in drug) helpful, perhaps the FDA data base on drug inactives

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(http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm) should routinely be used to prepare a similar table for other CIR reports such as PEG Alkyl Glycerides and Lecithin and related ingredients.

Additional Comments

Introduction, Summary - Both the Introduction and Summary state that the sorbitan esters are "safe as used in cosmetic ingredients." The original (1985) conclusion actually stated "safe as cosmetic ingredients". Sorbitan esters are cosmetic ingredients; therefore, the conclusion should be "safe as cosmetic ingredients" or "safe as used in cosmetics".

Introduction - In the Introduction, it would be helpful to explain the meaning of the prefix "sesqui".

Non-Cosmetic Use - Please also state that skin bleaching is considered a drug function in the United States. It is a cosmetic function in other parts of the world.

Toxicological Studies - Correct "10%t"

Irritation and Sensitization, Dermal, Non-Human, 1985 report - There is not one indication of a concentration tested in the summary from the 1985 report. Please provide some indication of concentrations tested.

Irritation and Sensitization, Dermal, Human, 1985 report - Please provide some indication of concentrations tested in the photosensitzation studies.

Table 1 - The structure of Sorbitan Triisostearate is not correct as it is missing the "iso" (one example) portions of the compound (see structure of Sorbitan Isostearate).

There is one digit missing from the CAS No. for Sorbitan Cocoate - it should be 68154-36-9.

Table 3 - The Council concentration of use survey indicated that the deodorant products containing Sorbitan Oleate, Sorbitan Stearate, Sorbitan Sesquiisostearate and Sorbitan Sesquioleate were not sprays. Please add this information to Table 3.

Table 5 - Please add a reference to this table and add the reference to the Reference section of the report.

Reference 33 - Correct "sorbitsn"

Reference 35 - Correct "fo sorbitan"