Safety Assessment of Ethers and Esters of Ascorbic Acid as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 19, 2017
Panel Date:	June 12-13, 2017

The 2017 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 report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, Ivan Boyer, Ph.D., Senior Toxicologist, and Bart Heldreth, Ph.D., Chemist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 19, 2017
Subject: Draft Final Report on Ethers and Esters of Ascorbic Acid

A tentative report with a conclusion stating that 7 ethers and esters of Ascorbic Acid are safe in the present practices of use and concentration described in the safety was issued at the December 5-6 Expert Panel meeting. Comments on the tentative report (*ethasb062017pcpc2*) were received from the Council and have been addressed. It should be noted that a CIR Final Report on 3 of the ascorbic acid esters included in this safety assessment, Ascorbyl Palmitate, Ascorbyl Dipalmitate, and Ascorbyl Stearate, was published in 1999. The safety of these 3 ingredients is being reevaluated in the current safety assessment, taking into consideration data that have been identified in the published literature since the final report was published.

The safety assessment has been revised to include 2017 FDA VCRP data. The greatest increase in ingredient use frequency is being reported for Ascorbyl Palmitate (522 additional product uses, compared to 2016 FDA VCRP data), followed by Tetrahexyldecyl Ascorbate (135 additional product uses). For Ascorbyl Palmitate, 133 additional product uses are being reported for the Lipstick category and 105 additional product uses are being reported for the Eye Shadow category. An increase of ≥100 product uses is not being reported for any of the other ingredients in any product category. For Tetrahexyldecyl Ascorbate, the greatest increase in additional product uses is being reported for the Lipstick category (44 additional product uses), followed by the Foundations category (35 additional product uses). Of the few new use ingredient categories that are being reported, it should be noted that Ascorbyl Palmitate is now being used in 6 dentifrices.

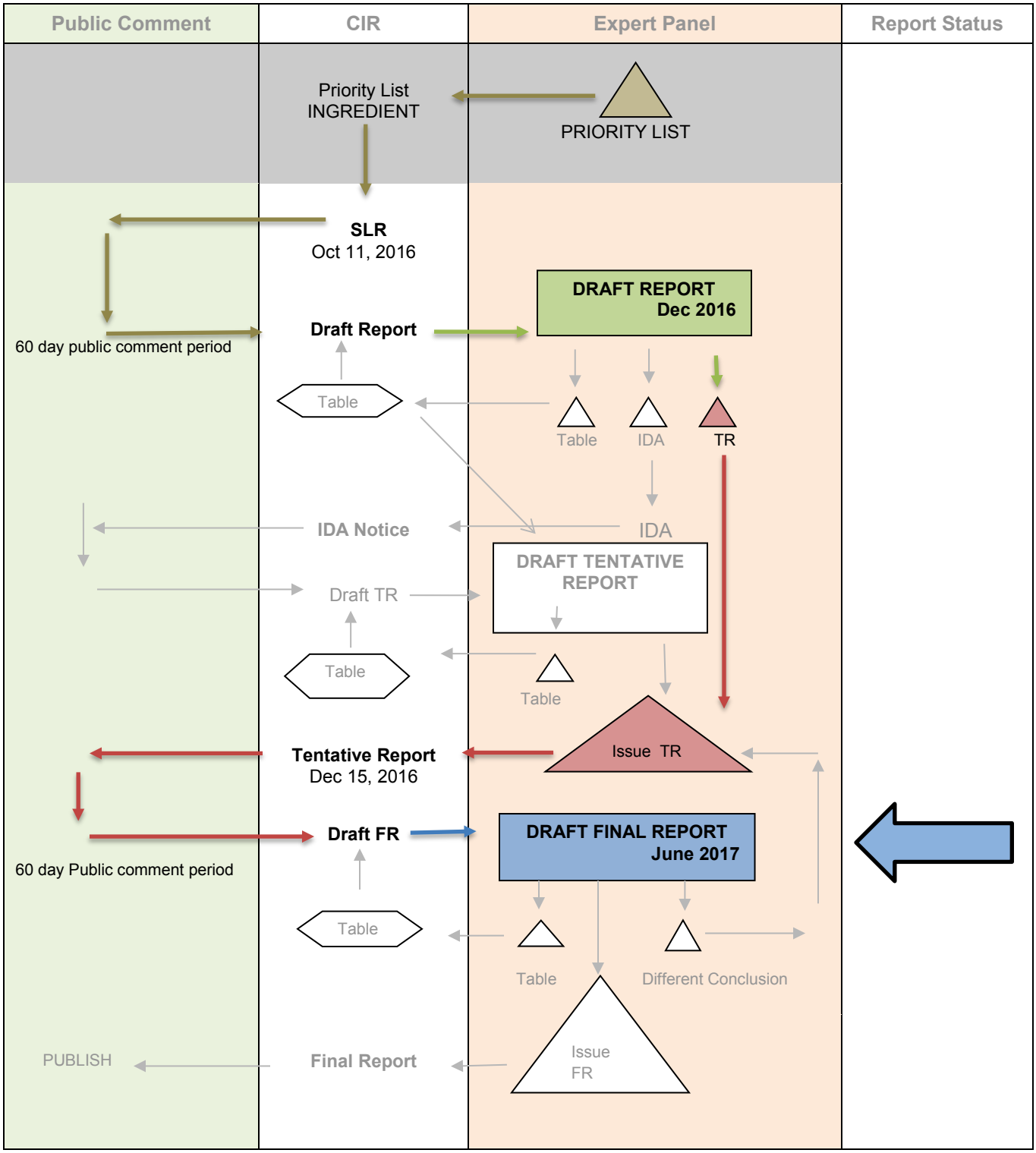
Included in this package for your review is the Draft Final Report (*ethasb062017rep*), the CIR report history (*ethasb062016hist*), Literature search strategy (*ethasb062017strat*), Ingredient Data profile (*ethasb062017prof*), 2017 FDA VCRP data (*ethasb062017FDAdata*), Comments that were received from the Council (*ethasb062017pcpc1 and ethasb062017pcpc2*), and Minutes from the December 5-6, 2016 Expert Panel Meeting (*ethabs062017min*).

After reviewing the available safety test data and 2017 FDA VCRP data, the Panel needs to determine whether a final report with a safe as used conclusion should be issued at this Panel meeting.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Ethers and Esters of Ascorbic Acid

MEETING June 2017



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CIR History of:

Ethers and Esters of Ascorbic Acid

The Scientific Literature Review (SLR) was announced on 10-11-2016.

Draft Report, Teams/Panel: December 5-6, 2016

Comments on the SLR and use concentration data were received from the Council and have been addressed/added to the Draft Report.

A tentative report with the following conclusion was issued:

The CIR Expert Panel concluded that the following 7 ethers and esters of ascorbic acid are safe in the present practices of use and concentration, as described in this safety assessment:

Tetrahexyldecyl Ascorbate
Ascorbyl Isostearate*
Ascorbyl Linoleate
Ascorbyl Tetraisopalmitate
Ascorbyl Palmitate
Ascorbyl Dipalmitate
Ascorbyl Stearate

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

Draft Final Report, Teams/Panel: June 12-13, 2017

Comments on the Tentative Report that were received from the Council have been addressed. The safety assessment has been updated to include 2017 FDA VCRP data.

Ethers and Esters of Ascorbic Acid Check List for June 2017 Panel. Analyst – Wilbur Johnson																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr.	Dermal Irr Human	Sensitization	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Tetrahexyldecyl Ascorbate													X							
Ascorbyl Isostearate																				
Ascorbyl Linoleate																				
Ascorbyl Tetraisopalmitate	X			X									X		X	X		X		
Ascorbyl Palmitate	X	X	X														X	X	X	
Ascorbyl Dipalmitate	X		X																	
Ascorbyl Stearate																	X	X	X	

[Ethers and Esters of Ascorbic Acid (6/20/2016]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Tetrahexyldecyl Ascorbate	1445760-15-5	1/1	27/2	4/4	2/0	0	0	0	0	0	0	0	0	0	0	0	0	
Ascorbyl Isostearate		1/1	26/0	0/0	0/0	0	0	0	0	0	0	0	0	0	0	0	0	
Ascorbyl Linoleate	121869-32-7	1./1	23/0	3/3	0/0	0	0	0	0	0	0	0	0	0	0	0	0	
Ascorbyl Tetraisopalmitate	161436-56-2 183476-82-6	1/1	155/8	9/4	2/2	0	0	1 on-6	0	0	0	1	0	0	0	0	0	
Ascorbyl Dipalmitate	28474-90-0	1/1	139/0	6/0	5/0	0	0	0	0	0	0	0	0	0	0	0	0	
Ascorbyl Palmitate	137-66-6	1/1	131/4	158/18	105/0	5	0	1	0	0	1	0	0	0	1	0	0	
Ascorbyl Stearate	25395-66-8	1/1	332/4	8/5	18/0	3	0	1 on -8	0	0	0	0	0	0	1	0	0	

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

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Ethers and Esters of Ascorbic Acid

Next one is ethers and esters of ascorbic acid. So see whether we have any definition issues with ethers and esters.

So this is a draft report. There are seven ingredients. And as a routine, is there any ingredient in these seven that we should delete? And I might note here that three of these ascorbic acid esters are included in a safety report from 1999. That's in Wilbur's memo. The first paragraph, the middle, the palmitate, the dipalmitate and the stearate. In the table, they're the last three ingredients.

So all the ingredients okay? Tom, Ron, Ron? Good. Any needs?

MR. JOHNSON: May I interrupt, Dr. Marks? We received data late on ascorbic dipalmitate. A human RIPT on a face powder containing 20 percent ascorbic dipalmitate.

DR. MARKS: Dipalmitate. So let me see. Where is that in here? I see tetrahexyl. Oh, that's one that's already been -- that was previously declared as safe, right?

MR. JOHNSON: Right.

DR. MARKS: In the '99 paper?

MR. JOHNSON: Yes.

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DR. MARKS: So you've got some more data to reinforce its safety. Is that --

MR. JOHNSON: Yes. And the data are negative.

DR. MARKS: Okay.

MR. JOHNSON: But the 20 percent ascorbyl dipalmitate in a face powder was tested at a concentration of

percent. So the actual test concentration was six percent and the results are negative in that study.

DR. MARKS: This is ascorbyl dipalmitate?

MR. JOHNSON: Yes. Mm-hmm.

DR. MARKS: And that was six percent was okay?

MR. JOHNSON: Yeah.

DR. HILL: What's the maximum use?

DR. MARKS: Twenty percent.

DR. HILL: Yeah.

DR. MARKS: So it's not adequate for that but I actually --

DR. EISENMANN: That's how they test

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face powders as I understand it. It's 30 percent dilution. So that's, I mean, we went to the company report and the 20 percent.

DR. MARKS: And the reasoning for that? Because you're putting on the face powder. Neat, whatever concentration is in the face powder, you don't dilute it, do you, to put the face powder on?

DR. EISENMANN: No, but I think to get it to stick for purposes of HRIPT tests, they need to put -- I don't know if they need to dilute it. I mean, that's --

MS. JONAS: It's got to be a bowl of some sort to apply.

DR. EISENMANN: Mm-hmm.

DR. MARKS: They need what? Pardon.

MS. JONAS: I'm thinking it must just be the vehicle to make it stick to the skin.

DR. EISENMANN: For the purposes of the test.

DR. MARKS: You would think you could

get it up close to the use concentration. That's what sticks to the skin. So the use concentration is 20 percent. I would think you could test it at 20 percent. If they used whatever product it was and did the HRIPT on that. At any rate, that was

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safe before so I didn't concentrate on it very much since it was declared safe. One hundred percent it's nonirritating. Okay, that's fine. It doesn't have a lot of uses but it has the highest concentration.

DR. HILL: That kind of belies the whole issue with that kind of testing because you've got the percentage in the ingredient but what really matters is what's the concentration and what's the surface area.

DR. MARKS: That's a whole (inaudible).

DR. HILL: So you can pile it. Yeah, I mean, you can pile a bunch of face powder on there and get the amount up but is that really telling you the right thing anyway? I mean, I know we've talked about this sporadically.

DR. MARKS: And it's interesting because

I picked that up for me for the skin toxicity. I wanted the tetrahexyldecyl ascorbate and HRIPT or local lymph node assay, some sensitization at three percent. It has lots of uses but there's no sensitization data. So I would have probably said insufficient data. And then I did have the ascorbyl dipalmitate at 20 percent. It only has four uses but there was no data on sensitization

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in the original report so I question -- I still question that even at six percent it's safe.

DR. HILL: Why? Yeah, that is what I was going to ask Woodward. In that read-across table, does that capture all the data from the old report or is that only new data?

MR. JOHNSON: The old and new data.

DR. HILL: That's what I thought.

DR. MARKS: Well, somewhere I had the old report. Was it Wave 2? I have under irritation the dipalmitate 100 percent was okay. Where did I get that?

MS. FIUME: PDF page 26.

DR. MARKS: Yeah, I have 26. Why wasn't

it checked down here as okay? Notice on the box on the table there's no X? If you look at the table on whatever page, four or five, it's the usual table that puts everything.

MR. JOHNSON: Okay.

DR. MARKS: So I need to put an X in there for that. Yeah.

MR. JOHNSON: Okay.

DR. MARKS: That's page five is the table.

MR. JOHNSON: Okay.

DR. MARKS: X under it because that was

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100 percent. Yeah.

And then the other question --

MR. JOHNSON: Are you talking about the ascorbyl tetraisopalmitate?

DR. MARKS: No, the dipalmitate. I have that 100 percent was okay with an irritation study. That was ocular. Is that correct on page 19 where it began? I assume that since I wrote it in here but who knows?

MR. JOHNSON: The human data are only on

ascorbyl tetraisopalmitate.

MS. FIUME: Wilbur, does your data profile only include new data or does it include --

MR. JOHNSON: It should include both.

DR. MARKS: Yeah, that's --

MS. FIUME: PDF page 26?

MR. JOHNSON: Not to say that it does but it's supposed to.

DR. MARKS: That's where probably -- yeah, I have a comment about matching the text with the tables, actually. Twenty-six, let's see here.

DR. HILL: Dermal sensitization. Ascorbyl poly --

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DR. MARKS: Oh, yeah, there it is. That's where I got it from. If you look on Table 1, thanks, Monice, on page 26, if you go down to the third line. Undiluted ascorbyl dipalmitate in albino rabbits was nonirritating.

MR. JOHNSON: I see.

DR. MARKS: And that's why I put a check

in that box. So yeah, that was one of my comments is when I compared Table 1 with the text, it wasn't quite -- they didn't quite match up. The text on page 19 and the table on page 26.

MR. JOHNSON: Now that I think about it, I think that the data in that table are only on the new data. I didn't include those --

DR. MARKS: Right.

MR. JOHNSON: -- from the old report. That's why they put both of them --

DR. MARKS: And I think it would be helpful to put all of it. Yeah.

DR. HILL: Say what you just said again.

MR. JOHNSON: I think the profile table only has the data in the current report, not those from the published report.

DR. MARKS: Yeah, that's why I had in there it was okay for irritation but it was from the table, not from the text. So I would match

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the table and the report, get the profile.

So I would -- for me, I would have an insufficient data notice for sensitization studies

on tetrahexyldecyl ascorbate and ascorbyl dipalmitate even though that had been safe prior looking at the data here. Any other toxic concerns for any other of these?

DR. SLAGA: It could be formulated to be nonsensitizing.

DR. MARKS: We do that with the plants. Yeah, this one -- Tom? That would make -- we could probably have our meeting in a half an hour or less. Everything is formulated to be nonsensitizing.

DR. HILL: Of course, give it 10 years and --

DR. MARKS: So this would be insufficient -- so, but --

DR. SLAGA: Its first time.

DR. MARKS: Yeah. Tom, Ron, Ron, were there any other tox needs?

DR. SHANK: I had questions about the phototoxicity. I didn't write down the page number but in the report it says ascorbyl palmitate increased the phototoxicity of UVB

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radiation to human keratocytes (inaudible).

MR. JOHNSON: PDF 19.

DR. SHANK: That's page 19?

MR. JOHNSON: Right.

DR. SHANK: Thank you.

DR. MARKS: I actually had under phototox okay. So let me see. Let's also -- do you have phototox in the table in the back? Because --

MS. JONAS: I don't think phototox. I thought it was lipid peroxidation.

MR. JOHNSON: Lipid peroxidation. That's what it is.

MS. JONAS: Right. It's very different. Lipid peroxidation can be catalyzed by metals or anything in the system so it's probably nonspecific to the ascorbyl.

DR. HILL: I thought it was oxygen in the air.

DR. SHANK: That's the same thing that Dr. Liebler explained in September about the alkoxysilanes.

DR. HILL: Well, but in this case we've

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got the ascorbic moiety has redux activity and so reaction with oxygen could come into play but that's not really direct phototoxicity. So how do we think about that?

DR. MARKS: Was this this last one, ascorbyl palmitate where they applied it to UV damaged skin? Is that what you were talking about, Ron Shank? It's page 21. The paragraph right before Summary.

DR. SHANK: Page 21. Okay, I was on 19.

MR. JOHNSON: Under lipid peroxidation.

DR. MARKS: When I looked at that it looked like it helped.

DR. HILL: The last line right before dermal irritation and sensitization says they noted that the data in the study suggests that despite its antioxidant properties, ascorbyl palmitate may intensify skin damage following physiologic doses of UV radiation. That's reference 50. So I didn't know how to think about that.

MS. JONAS: I believe the reference is actually a keratinocyte culture where they exposed it to UVB radiation causing oxidation and they saw an increase in lipid peroxidation. They had

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ascorbyl -- whichever ascorbic acid derivative --

DR. SHANK: Palmitate.

MS. JONAS: Palmitate present. But in talking to Dr. Liebler, he and I both agreed that ascorbyl palmitate is typically an antioxidant and that it was nonspecific. It wasn't a phototoxic reaction; it was probably just some sort of lipid peroxidation. So if there were metals present, you could have had redox and Fenton chemistry occurring but he wasn't concerned about it.

DR. MARKS: Yeah, if you look where I was, Ron Shank, on page 21, when compared to untreated skin, either the absence or erythema or decreased erythema was observed after pretreatment with three percent ascorbyl palmitate before UVB exposure. So that would go along with the antioxidant type of mechanism. And then in the second experiment, again, when you treat it with

this lotion, it got better sooner. That was a five percent ascorbyl palmitate. So it seems I have an anti- UVB damage rather than a phototoxic property.

Did you see someplace where it had a phototoxic property, Ron Shank?

DR. HILL: What it's saying here is it doesn't -- it's increasing in their test system

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lipid peroxidation --

DR. SHANK: Right.

DR. HILL: -- while it is reducing levels of reactive oxidant species. So it's an in vitro system without all the usual skin defenses that would be there, so how do we interpret that? I think it's an interesting piece of information.

MR. JOHNSON: And also, Dr. Liebler disagreed with that last sentence in the last paragraph in that section.

DR. HILL: He thinks it's not an accurate statement?

MR. JOHNSON: Right, he does not, and he said that he was going to, you know, study that

publication and then, you know, send the text for the discussion.

DR. GILL: Wilbur, you're talking about that right before the summary, the last sentence under ascorbyl palmitate?

MR. JOHNSON: This is on PDF page 19.

DR. GILL: Nineteen, okay.

MR. JOHNSON: The last sentence in that section just before irritation and sensitization studies.

DR. MARKS: Okay. So, the second --

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DR. SHANK: I think we should clarify that in the discussion.

DR. HILL: I had a couple of other things by the way before you totally leave this.

DR. MARKS: Okay. So that will be under discussion, clarify -- how do I want to put it? Photo studies in discussion. Okay. And Wilbur, you've got our discussions on what Dan said, too? Okay.

Ron Hill?

DR. HILL: So I realize this ship maybe

sailed but --

DR. MARKS: No, it isn't. We're just beginning --

DR. HILL: I feel like --

DR. MARKS: It hasn't left the dock yet.

DR. HILL: The first compound in Table 2, that's the tetrahexyldecyl that you asked about. That's an ether and the rest of these are esters. So I know we encountered this situation earlier. I don't understand why the ether is lumped with the esters at all.

DR. MARKS: Because that's in the title.

DR. HILL: Yeah, I know it is but why are we lumping them together? I mean, they don't go together. We wouldn't expect chemically that

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they'd do anything similar other than being something greasy tacked onto an ascorbate. The ethers would be predicted to be stable or at least relatively stable, much more so than esters which could come off. I don't know why we were lumping them other than for administrative convenience in a way that I'm not sure matters.

DR. GILL: We may want to go back to the priority document because many times Bart will indicate why they won't as the panel walks through them.

DR. HILL: Well, I will ask Kim that question tomorrow but I object. I don't think that reading across on anything from the esters to the ether here makes good sense. Well, I say not anything; some things.

DR. MARKS: Okay. I'll actually --

DR. HILL: That was just one thing.

DR. MARKS: Okay. All right. So why combine ether and ester? And Bart will -- we'll direct that at Bart. Do you want me to mention that or do you want to mention it? Since you have several points, maybe you can just --

DR. HILL: Well, they're not all related. Yeah, we have no method of manufacture

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for the ether but we won't. Apparently, it's not in use. But even the method of manufacture for the stearate I thought was completely noninformative, which I think is the only one we

have.

DR. MARKS: So you would want method of manufacture?

DR. HILL: For the tetraisopalmitate, there is no such thing as tetroisopalmitic acid, so this method of manufacture is either misreported here or it's erroneously described in the source.

1DR. HILL: Dr. Hill?

DR. HILL: Yes? 1DR. HILL: You can in theory make isopalmitic acid

--

DR. HILL: No, no. I'm saying it's saying that you're using -- one of the reactants is tetroisopalmitic acid. That's what it says. There is no such thing as tetroisopalmitic acid.

MR. STEINBERG: There is.

DR. HILL: There is?

MR. STEINBERG: Yeah. When you do the reaction to create isostearic acid based on tallow-based oleic acid.

DR. HILL: Okay.

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MR. STEINBERG: You can -- you will get the natural stearic because oleic acid has stearic but you're also going to have some palmitic, probably in the area of about 10 percent.

DR. HILL: How do you get the tetra?

MR. STEINBERG: But that's the stearification. I mean, they have to start with the isopropyl.

DR. HILL: No, it says the reacting -- they say with their reacting tetroisopalmitic acid.

MR. STEINBERG: Well, they have --

DR. HILL: It's got to be --

MR. STEINBERG: That doesn't -- that's not possible.

DR. HILL: Okay, so --

MR. STEINBERG: But isopalmitic is possible to make it but it's extremely -- it would cost a fortunate. I don't think they actually are doing that.

DR. HILL: Well, I'm just saying this is a mythical ingredient so something is wrong with

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this write-up. It might be a translation problem I'm guessing but something is amiss.

If lipase is commonly used for acylating across this group, how is purification accomplished to remove all the potentially antigenic enzymes or is it using immobilized enzymes of some sort? And I'm curious because lipase is usually cleaved, not esterified. So that's interesting.

DR. MARKS: Is that under --

DR. HILL: This is all method of manufacture. The method of manufacture given for the stearates completely noninformative. Is this a reaction run neat, that is in the melt or is there some catalyst? What about the potential impurities if there are catalysts and so forth present?

From the subheader ascorbyl palmitate and ascorbyl linoleate, what is written does not seem to be a method of manufacture at all, and certainly not a means of production of those ingredients in any pure form. So that has to be

deleted or moved.

I had concerns about that ether in particular. We don't have any toxicology data at all other than dermal irritation. And it's in

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nearly 400 formulations, many leave- on concentrations up to three percent. We need some tox data.

Let's see. Composition impurities. There's no such thing as L-stearate so something is wrong with that write-up. Please check the original source. If it says that, it's erroneous. It probably means L-ascorbyl stearate but we should confirm that.

DR. GILL: So Ron, you're saying there's no such thing as ascorbyl L-stearate?

DR. HILL: No, I say there is but in the write-up, the composition impurities, they say L-stearate. Do they mean L-ascorbyl stearate? Maybe that's --

DR. GILL: I see ascorbate --

DR. HILL: Page 11. Page 11. Let me see where that is.

MR. JOHNSON: Yeah, I see ascorbyl L-stearate.

DR. GILL: Yeah.

DR. HILL: There's somewhere where it says -- yeah, ascorbyl L-stearate. There is no such thing as L-stearate.

MR. JOHNSON: Oh, okay.

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DR. HILL: I'm assuming it means L-ascorbyl stearate.

MR. JOHNSON: Oh, okay.

DR. HILL: But if that's, yeah, again, that might be a sort of translation error.

And then the other thing is there's that computational paper that's in there and I pulled it and I looked at it and with all due respect, it's completely noninformative as it is. I will look at the cross-references in that paper but I didn't feel it was a useful data point at all for safety assessment here. I guess we can't completely ignore it because it's out there but I don't like it being prominently in the report, especially any suggestion that it tells us

anything whatsoever about safety assessment because it doesn't.

MR. JOHNSON: The other team said to delete that.

DR. HILL: Okay, great. I'm glad I'm not the only one. I was able to get the paper and I -- okay.

DR. MARKS: So this is going to go out, depending on what the other team decides, insufficient data notice. Ron Hill, I'm going to call on you tomorrow to make a lot of these points

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where that's been deleted.

DR. HILL: Okay. I'll try to shorten up the other things. If we know that we're deleting that, I don't have to say anything about that.

DR. MARKS: And then the other -- yeah, I guess you should mention it for us and for the full panel before Wilbur makes changes --

DR. HILL: Okay.

DR. MARKS: -- between this draft report and the next -- the next, either whether it be --

MR. JOHNSON: But for right now, with

respect to the need for method of manufacturing impurities data, Dr. Hill, do you have a list of ingredients for which those data are needed?

DR. HILL: I believe we have nothing informative on method of manufacture to speak of for anything here.

MR. JOHNSON: Okay. Okay.

DR. HILL: With the exception of the ascorbyl palmitate and linoleate I think that's okay except -- no, that's the one where I commented there doesn't seem to be a method of manufacture. I take that back. So we really produced bio reaction of this and this that, you know, okay. I mean, the whole reason we need

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method of manufacture is to get some sense of what impurities might be there and that's the issue I had except for the palmitoyl chloride with ascorbic acid in pyridine. So that one -- that would make sense. That one's good.

MR. JOHNSON: So we need method of manufacturing impurities on --

DR. HILL: I wanted it for the ether,

which if it's not in use according to -- I mean, we don't see it reported being in use, we're not likely to get except that it is, right? I mean, we had -- where did I -- I know what it was. It wasn't X'd in use for -- hang on. I'm sorry.

MR. JOHNSON: This used up to 2.5 percent.

DR. HILL: All right. Okay. Yes. So we don't have anything about method of manufacture. I didn't go too far with this because I felt strongly it should not be in this report with the esters.

MR. JOHNSON: Right.

DR. HILL: But if we're keeping it then I would like to see method of manufacture for that guy.

MR. JOHNSON: Okay. And all the others except for ascorbyl palmitate?

DR. HILL: Yeah.

MR. JOHNSON: Okay.

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DR. MARKS: Okay?

DR. SHANK: I have a mysterious note to

self here. Much of the systemic toxicity data are from computational toxicology predictions by the European Food Safety Authority. I can't find where I saw that but if that's true we should mention that in the discussion.

MR. JOHNSON: You decided to delete that; right?

DR. HILL: No, that's a different one. That was the last issue I was going to raise for myself is it seems the FDA and the USDA both have evaluated systemic toxicology of these compounds because they somehow came to the conclusion of GRAS, as well as safe for use in animal feed stuff. But we don't seem to capture any of that toxicology in this report.

DR. SHANK: Okay. Aside from that, somewhere, unless I missed something.

DR. GILL: No.

DR. SHANK: A lot of the systemic tox data are from computer computational model predictions which is a bit thing now in toxicology. And this was done by the European

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Food Safety Authority, but I don't -- I can't find it right now.

DR. GILL: Well, it's here. I just wanted to make sure if you guys were comfortable with that --

DR. SHANK: Oh, it's in your notes?

DR. GILL: -- large amount of (inaudible) data.

DR. MARKS: That's where you read it.

DR. SHANK: That's where I read it.

DR. MARKS: You got the annotated notes.

DR. SHANK: It's very helpful. So I would mention that in the discussion.

DR. MARKS: Yeah. That's -- well, I think to Lillian's point is do you feel comfortable with those as supporting systemic toxicity, lack of systemic toxicity? Because that's the important --

DR. SLAGA: It's better I have no data.

DR. SHANK: Correct.

DR. SLAGA: It gives you some idea.

DR. SHANK: It's supportive.

DR. MARKS: And there is no -- well, it's not only supportive with that but then I

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always looked at real life that these things are being -- compounds are being used, is there any case reports or endemics of systemic toxicity from it is another alert. Obviously, it wouldn't want to get to that point but that's reassuring when we talked about the carbonate in the last set of ingredients. There were no case reports, just like the alert for the wheat -- hydrolyzed wheat protein was an endemic of type one reactions to it from a topical.

DR. HILL: Surely, if this thing was improved -- I say surely -- surely, if this stuff was -- some of these things were approved for routine addition to food at substantial concentrations and animal feed stuffs, there's more data here than we're getting. And it's got to be something else other than just computational prediction.

DR. EISENMANN: Well, you know, it's in Table 1 from the old report, some of it.

DR. HILL: Okay, right. So that's --

DR. EISENMANN: Because there's carcinogenicity studies. Two percent is ascorbyl palmitate in the diet. I mean, there's a bunch of studies in Table 1.

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DR. HILL: Right. I remember --

DR. EISENMANN: I presume that's the studies that support food use.

DR. HILL: Right.

DR. MARKS: Okay. I still think we can include that in the discussion. So let me see if -- Ron Hill, did you have any more comments? Or Ron Shank or Tom?

DR. SHANK: No.

DR. MARKS: So we'll see what happens tomorrow. If an insufficient data notice is moved by the Belsito team, I will second that. Otherwise, I'll propose that we have an insufficient data notice, and really what we need is a sensitization study for the tetrahexyl ascorbate at three percent has lots of uses. We don't know if that's -- how many are three percent

but that's a maximum leave-on. And ascorbyl dipalmitate at 20 percent, even though it has few uses. Then we'll bring up the issues whether this should also be included. Certainly the issue of why combining ether and ester in this report, that's your concern, Ron Hill?

DR. HILL: It is.

DR. MARKS: Method of manufacture issues, and that could be part of the insufficient

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data notice. And those would be the needs, and then in the discussion we'll clarify the photo studies and that the systemic toxicity safety came from -- at least part of it came from computational studies. And we'll match the text on page 19 with the table on page 26 on irritation and sensitization.

Is there anything I left out?

MR. JOHNSON: I just want to be clear. I thought that we had decided to delete the computational toxicology data from the safety assessment.

DR. MARKS: No. Since it's going to be

in the discussion.

MR. JOHNSON: We're not going to? You're going to adjust --

DR. MARKS: Did I interpret that right, Ron?

DR. SHANK: I would put it --

DR. HILL: Are we talking about that one paper that I was --

MR. JOHNSON: Yes, the DMI?

DR. HILL: Oh, throw that thing out. Sorry, it's worthless.

DR. MARKS: Well --

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DR. HILL: It's worthless.
DR. MARKS: I can, yeah.
DR. SHANK: Show me where you are in your report, please?
DR. HILL: Let's make sure we're talking about the same thing.
MR. JOHNSON: Starting on page 16.
DR. SHANK: Sixteen?
MR. JOHNSON: Yes. Under acute toxicity studies oral.

DR. MARKS: You can't throw out papers with a reason of worthless. That won't fly in the --
DR. SHANK: I'm sorry, Wilbur.
DR. HILL: Pull it up and look at it and then see if you can --
MR. JOHNSON: Under toxicity studies.
MR. BOYER: It's basically -- it looks like a summary of a bunch of computational calculations that were made. It's like an executive summary of the report, so it doesn't give any of the details that you would expect to see or want to see. You really don't know how they conducted the analysis.
DR. HILL: And you can't find any specific mentions of the compounds in question

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here at all. And again, as I say, I was going to go into the cross references and I didn't get that far. But in looking at the ways that they're talking about what they did, they're just relying on whatever happens to be in the database and popping out with some -- and that's the worst

possible use of computation without some way of validating or assuring that something meaningful is actually coming out of that. If you look at the paper you'll see what I'm saying.

DR. MARKS: Yeah. So Ron Shank, you talked about -- you brought up the issue of computational studies. We have to handle that either -- now, normally, we don't delete papers; we comment about them. But --

DR. SLAGA: Yeah, we made comment in the discussion that there were a number of computational studies found but, you know, the panel didn't see any supporting information or however you want to phrase that, and therefore, you still found the need for the data. If it's going out as an insufficient, we could certainly put that as a message.

DR. MARKS: Well, even if it goes out as a tentative, we'll have another shot at it for

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sure.

DR. SLAGA: Well, yeah.

DR. MARKS: Ron Shank, you brought up

having it in the discussion. Now the discussion goes to how the paper is worthless.

MR. JOHNSON: Dr. Marks, this is it.

DR. SHANK: Not having read the paper I can't say it's worthless.

DR. MARKS: Yeah, okay.

DR. HILL: The point is, if it's computation only and those softwares don't have compounds in this class in there so that we're interpolating instead of completely extrapolating, then I object. It's like reading across from those esters to the ether in terms of toxicology is completely bogus. Completely bogus. And so if they're doing that computationally and saying, well, this is safe because those are safe, forget it.

DR. MARKS: Here's the paper. That will be good. Is this -- we'll let Ron review it between now and tomorrow, Ron Shank, and then tomorrow when it comes up in a discussion, Ron, your comments will be really important.

Okay. I don't think right now -- I'm

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not going to expect you to read it right now, Ron Shank, because they have methods and manufacture. It's several pages long, so rather than -- let's -- but I'll bring it up tomorrow if the Belsito team doesn't bring it up and then we'll go from there.

MR. JOHNSON: Dr. Marks, just one last -- you mentioned the need for skin sensitization data on tetrahexyldecyl ascorbate at three percent?

DR. MARKS: Right. Three percent. Yep.

MR. JOHNSON: And ascorbyl dipalmitate at which concentration?

DR. MARKS: Twenty percent.

MR. JOHNSON: Twenty percent. Okay.

DR. MARKS: Yeah. Both of them are the highest use concentration on leave-ons. Yep.

Okay. Any other comments? That was robust.

DR. HILL: I don't know if robust is the right word.

DR. MARKS: It was. That's okay. Okay,

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Ethers and Esters of Ascorbic Acid

DR. BELSITO: Okay. So again, we're going to go safe as used when formulated to be non-irritating. Okay. Moving along, ethers and esters of ascorbic acid. So this is the first time we're seeing this report, seven ethers and esters of ascorbic acid that are alkylator or acylated derivatives of ascorbic acid, a function mostly as antioxidants, skin-conditioning agents, skin protectants, fragrance ingredients, and a skin-bleaching agent which obviously is not a cosmetic function so we will not be looking at that aspect of these ascorbates.

Yes, I want to save my changes, okay.

MR. JOHNSON: Dr. Belsito, may I make one comment before I forget?

DR. BELSITO: Sure.

MR. JOHNSON: We received a late data submission on ascorbyl dipalmitate, you know, basically we have negative clinical skin sensitization data on a face powder containing 20 percent ascorbyl dipalmitate.

DR. BELSITO: Uh-huh.

MR. JOHNSON: And it was tested at a concentration of 30 percent so the effect of concentration was 6 percent. But those results are negative and they will be included in the next draft of the report.

DR. BELSITO: Right.

MR. JOHNSON: And also one more item is the fact that the ingredient ascorbyl palmitate is now being used at concentrations up to 0.01 percent and not the 11 percent that is being reported in the table.

DR. BELSITO: Okay. Okey-doke. So --

DR. SNYDER: The sensitization data, the highest concentration that they tested was negative but we didn't have test concentrations at 20 percent. The highest test concentration was six percent, is that what you're saying?

MR. JOHNSON: Right, yeah.

DR. SNYDER: Okay.

MR. JOHNSON: It was a face powder containing 20 percent ascorbyl dipalmitate but it was tested at a concentration of 30 percent. So --

DR. SNYDER: Yeah.

MR. JOHNSON: -- actually six percent was actually tested.

DR. SNYDER: Okay.

DR. BELSITO: Right. So we don't have a 20 percent sensitization on ascorbyl dipalmitate?

DR. SNYDER: Correct.

MR. JOHNSON: No, we don't.

DR. BELSITO: Okay. But just to go back, so just starting from the beginning, you know, if ascorbyl linoleate is a bleaching agent, how do we deal with that because we're not given the data that tells us the no effect level on skin bleaching? So I -- that was one of the things that I thought do we say insufficient or if formulated into a cosmetic product should not have an effect on skin pigmentation?

I mean, we don't have the data that allow us to say it can be safely used because we don't know at what point it creates hypopigmentation. You see what I'm getting at?

DR. LIEBLER: Yeah. I don't think we saw any data that said that it was. I mean, it was simply listed as a function, right?

MR. JOHNSON: Right.

DR. BELSITO: Okay. But if it's listed as a function do we want to see that data or, I mean, I know the, you know, that's the problem with this cosmetic dictionary. Someone can throw anything in there and without any, you know, it's just like when we heard about reproductive or endocrine endpoints. Someone puts it on a list and it may or may not have data to support it but then how do we deal with that then simply in the discussion say that we were unable to find any data showing that ascorbyl linoleate in fact did have any effect on pigmentation? However, formulators should be aware of this supposedly reported use and assure that products

containing it do not have an effect on skin pigmentation?

DR. LIEBLER: Yeah, I'd be okay with that.

DR. BELSITO: Okay.

DR. LIEBLER: That we could add that to the discussion.

DR. SNYDER: Or could Carol go back and confirm what that is?

DR. BELSITO: Well, this comes straight out of the dictionary, right, Wilbur? It's not a matter of confirming.

MR. JOHNSON: Right.

DR. BELSITO: It's in the dictionary. Okay. So we have the other issue is ascorbyl dipalmitate up to 20 percent in leave-ons without the sensitization data to support it. Does that bother anyone? The highest sensitization data we have is what six percent if I recall?

DR. LIEBLER: If it bothers you it bothers me.

DR. BELSITO: I mean, it doesn't bother me, I mean --

DR. LIEBLER: Really?

DR. BELSITO: Yeah, I mean, what I was thinking is can't we look at -- don't we have data on -- well, we have data on ascorbic acid and don't we have data on dipalmetic?

DR. JONAS: Actually, three of them have been previously reviewed and found to be safe. It's the ascorbyl palmitate, the ascorbyl dipalmitate, and ascorbyl stearate.

DR. BELSITO: Right. Yeah. I didn't have a problem with it. It's just I wanted to point out that we don't have data supporting that concentration of use for sensitization. I'm fine. Down on pdf page 14, the heading says penetration enhancement. I guess that was the purpose of the study.

DR. LIEBLER: Right.

DR. BELSITO: But it's sort of misleading because if anything, it doesn't enhance penetration, it reduces penetration.

DR. LIEBLER: Right, I have the same comment. Yeah.

DR. BELSITO: So I don't know how you want to deal with it, but, I mean, if you just look at it and see penetration enhancement ascorbyl palmitate, you know, if you don't really read what it says your assumption is it enhances penetration. So I mean, other biological effects because it decreases penetration, you know, in a penetration enhancement study ascorbyl palmitate was found to decrease the penetration of ibuprofen as compared to whatever the vehicle was.

DR. LIEBLER: Is penetration enhancement one of our standard subheads?

DR. SNYDER: Boilers, yeah.

DR. BELSITO: When -- yeah, I mean, when there are studies looking at penetration enhancement on it, yes.

DR. LIEBLER: So this is kind of akin to having acute toxicity as a heading and then, showing that it's not toxic at any of the doses tested. So perhaps you could simply add a sentence to the end saying thus ascorbyl palmitate did not enhance the penetration of ibuprofen.

DR. BELSITO: Okay. So the next issue that I just wanted to point out is we have no DART studies here or in the prior review. Does that bother any of you?

DR. SNYDER: Have no what?

DR. BELSITO: No developmental and reproductive tox studies for these in this or any of the prior reviews.

DR. SNYDER: I didn't have any issues with that in my notes so.

DR. LIEBLER: And these have such an overall favorable safety profile.

DR. BELSITO: Okay, but it will have to be --

DR. LIEBLER: There is a data gap --

DR. BELSITO: It will have to be something we address in the discussion --

DR. LIEBLER: Yes, it is a data gap.

DR. BELSITO: -- if we go ahead so how do we address that?

DR. BERGFELD: Can you address it on the basis of the no skin absorption, reduced skin absorption? You have it delivered -- the ascorbyl palmitate delivered only to the epidermis. In the rabbit study you have an in vivo study. Didn't show any absorption.

DR. BELSITO: I don't see those, Wilma, under --

DR. BERGFELD: There I'm picking them up under the summary there. They

are listed --

DR. BELSITO: Under --

DR. BERGFELD: -- skin penetration let me see --

DR. LIEBLER: It's pdf 13 is the--

DR. BERGFELD: -- under summary.

DR. BELSITO: Okay.

DR. LIEBLER: So these appear to penetrate at least into the epidermis.

DR. BERGFELD: Right.

DR. LIEBLER: And are hydrolyzed to ascorbic acid to a limited extent. So I don't think we can make the big molecule argument saying that it wouldn't get in.

DR. BELSITO: So what argument do we use to say that we don't want some reproductive toxicity, that vitamin C is a vitamin and we're not concerned about the hydrolysis product?

DR. BERGFELD: Well, it's an antioxidant, minimally absorbed, natural in the skin.

DR. BELSITO: No, I understand but we're not just looking at vitamin C.

DR. BERGFELD: Yeah, we're --

DR. BELSITO: Right? I mean, it's conjugated to something.

DR. LIEBLER: So all the ascorbic esters and are essentially fatty acid esters?

DR. SNYDER: Yes.

DR. LIEBLER: So there's no concern there with the components, the ascorbic acid and the fatty acids?

DR. BERGFELD: On your table 4 you have low use concentrations.

DR. BELSITO: Well, except the dipalmitate at 20 percent. Just, you know, I guess I'm asking, I mean, this is not my area of expertise if you're concerned and if you're not concerned --

DR. SNYDER: I didn't see anything. I just consider it to be vitamin C and a fatty acid. I mean, I didn't see anything there that would signal a --

DR. BELSITO: Do we have any data on the fatty acids that we could bring in to support that? Or --

DR. SNYDER: I mean, I didn't go back and look at all of those three ingredients that this is basically a re-review of but, I mean, we could go back and look at those and see was there data in there?

DR. BELSITO: No.

DR. SNYDER: No?

DR. BELSITO: No, I went back and looked. There's no -- we have no repro or tox data in the original report or this report. So I mean, again, I'm just throwing this out because we don't have it. Then I think we need to address it in the discussion and I don't know how to craft that language since this is not an area of expertise that I have.

DR. SNYDER: Well, either the parent or the constituents were of no concern and then, they had that in silico stuff that said it was not predicted to be a reproductive toxicant, right?

DR. BELSITO: Okay.

DR. SNYDER: So I think we can craft something.

DR. BELSITO: Okay.

DR. LIEBLER: You know, these chemically would be most similar to mono and di-fatty acylglycols, small glycols because basically you've got a small molecule with a bunch of hydroxyl groups on it one or two of which are esterified or even a couple form ethers. And we know about their -- I think we might know more about their uptake in metabolism (inaudible). They are chemically virtually identical. I put them in the same bin in terms of their solubilities, ability to penetrate the epidermis extent of hydrolysis, other things.

And I think that's another thing we can look at is a potential read across for repro. Because I think we're all kind of stuck on look this is -- these are the essentially synthesized from two innocuous molecules. Therefore, the ascorbityl esters should then also be innocuous but we don't have any data so but I think that with some read across data, I think we can

make a stronger case.

DR. BELSITO: Read across from what again, Dan?

DR. LIEBLER: Well, I would say like glycol esters, mono and di-esters of single glycols.

DR. HELDRETH: Would something like --

DR. LIEBLER: Like propylene glycol or something like that, you know --

DR. HELDRETH: Would something like isolated sugars since this is like a pure --

DR. LIEBLER: Also very similar, yes, exactly. In fact, there's NO2R saccharide -- our saccharide report that we have going, yeah. Both of those would be sources of read across.

DR. BELSITO: Okay. So could we bring those in?

DR. HELDRETH: Yeah, we have --

DR. BELSITO: Whatever data we have for them? So read across from mono and what did you say? Mono and --

DR. LIEBLER: Mono and diacyl either saccharides or --

DR. BELSITO: Glycols --

DR. LIEBLER: -- glycols. For example, like propylene glycol stearate, mono and distearate, things like that so --

DR. BELSITO: Okay. We certainly have that data so if we could bring that in, Wilbur?

MR. JOHNSON: Okay.

DR. BELSITO: And use that as read across to help us with the repro. So with the sensitization we have for the tetraisopalmitate that 100 percent is sensitizing, 10 percent is non-sensitizing, and 100 percent was said to be a strong sensitizer. So again, yeah, I'm okay with it but I just wanted to point that out that the tetraisopalmitate was said to be a strong sensitizer at 100 percent and negative at 10 but we don't have 20.

DR. LIEBLER: Yeah.

DR. SNYDER: So back to the depigmentation, so ascorbic acid in related molecules that they use for depigmentation of hyperpigmentation --

DR. BERGFELD: You're right.

DR. SNYDER: So is that -- that's different than depigmentation.

DR. BELSITO: No, I mean it's --

DR. BERGFELD: It's different of the (inaudible). Yes.

DR. BELSITO: You know, I think it quite honestly I think it comes from the "" although I know this term it doesn't have any bearing on legally, the cosmeceutical industry and their vitamin C derivatives that reduce aging effects.

DR. SNYDER: Right.

DR. BELSITO: Okay. And so that's probably why it got thrown into the dictionary. I've never been really overwhelmed with the cost-benefit analysis of topical vitamin C on the skin. When you look at the photographs, you know, photographs can lie depending upon lighting. So I --

DR. SNYDER: But I wonder if we should capture that in the discussion of why we consider it to be -- why it may be in there and how it's maybe not in the classic sense it --

DR. BELSITO: No, I mean, what we simply say is that it's listed as a function in the cosmetic dictionary. We saw no data in the literature to support that it acted that way but we wanted to remind manufacturers that a bleaching effect would be a non-cosmetic effect and we would not expect that this specific ascorbyl --

DR. SNYDER: Okay.

DR. BELSITO: -- ester had that effect when used in a cosmetic. I think that can be put into the discussion.

DR. JONAS: Just a comment. There are some regulatory bodies, in particular Asia, Korea, and Japan, that recognize ascorbic acid in this way. So if you include it in the product then you can make a skin-lightening claim. So it's listed along with placental extract and all sorts of things that Asians believe have a skin-lightening benefit.

DR. BELSITO: Okay. So go ahead, Wil --

DR. BERGFELD: Pinnell has some interesting information.

DR. BELSITO: Oh, Sheldon, oh.

DR. BERGFELD: Sheldon Pinnell, early on it must have been in the nineties on collagen, increase collagen, decrease pigmentation, dysmorphic pigmentation from Duke.

DR. BELSITO: Okay. So the only other thing that I thought we could use to support a lack of data on the dipalmitate at 20 percent was that we did have in 44 patients the tetrahexyldecyl ascorbate used at 30 percent in an HRIPT. So we can point that out I think as well although we usually ask for 100.

The one thing that bothered me in this report and in another report was that a lot of the data that was brought forth from other reports was summarized in a table up front and then I had to keep going back to that table to see what was there for the toxicity endpoints. It took not an insignificant amount of my time in reviewing the report because first I had to print out this page to see, okay, when I'm looking at acute tox I need to go back to table 1. I liked it better when you put it italicized at the beginning of each section rather than in a table. So I'm wondering why you did it this way.

MR. JOHNSON: Dr. Belsito, if you click on the table like table 1, you go directly to the table at the end of the report.

DR. BELSITO: I understand but I --

MR. JOHNSON: Yeah.

DR. BELSITO: -- it just was a lot of clicking back and forth.

MR. JOHNSON: Okay.

DR. BELSITO: I just -- I don't understand what you elected to put it in a table at the beginning rather than simply putting it like you used to do italicized at the beginning of each heading.

MS. FIUME: Part of it, I believe, is so that the panel will understand that when the report is published those data come out. So with it being in a table we are hoping that the panel sees the report in a form more like what will be going to the publisher. I believe we can leave the table in but the text that would be italicized in each section would come out.

So part of our hope is that you review it in a form that is going to be later on published so that if some of that information was critical and you've seen it in the report but didn't necessarily comment on it, that if it was taken out at the publishing stage, that it -- that something wasn't missing. That you assumed it was going to be there.

DR. BELSITO: But this table would be present in the publishing stage?

MS. FIUME: I think we can keep the table in the publishing stage, yes.

DR. BELSITO: Well, if that's the case it still would be easier I think when the panel was reviewing it to have these italicized at the beginning of the appropriate section. And then, when you submit it to publication, taking those italicized things out and creating this table that you had. I know it's a little bit more work for you but it was a little bit more work for, I think, all of us to work with it that way. I don't know how the others of you thought but --

DR. LIEBLER: So I basically agree. You know, the nice thing -- it's nice to be able to click on the table 1 and go to table 1 but that doesn't take you back. You have to remember what page you were on or scroll back to wherever the heck you were. So it's helpful to be able to do that but it's a one way trip.

DR. BELSITO: Yeah. And in fact, I didn't use those clicks for the same reason because it just -- then I had to keep scrolling back. I just split my screen and got to tables and just kept scrolling down the tables like I did the old way. So the hyperlinks in terms of time for me didn't help. But the biggest drawback was having all the prior data in a table --

DR. LIEBLER: Yes.

DR. BELSITO: -- that preexisted all of the tox endpoints I was looking at.

DR. HELDRETH: Related to that just maybe for clarification for Wilbur's purpose in the next draft. For the DART data that we're going to pull as read across from the isolated saccharides or glycols, would you like Wilbur to present that as in the body of the report under those headings where it's reading read across to or simply as a table at the end that these are ingredients we feel may be useful for read across?

DR. LIEBLER: I think it should be in the body of the report.

DR. BELSITO: Yeah. I mean, I think that we can introduce in the introduction

that there was essentially no specific data on DART and that we would be using these or you could refer to, you know, you always want to justify why you think it's appropriate read across. So perhaps there should be a table showing why the panel felt that these were appropriate read across materials or whatever.

But then, the information about them I think should be under the repro and tox -- developmental tox section.

DR. HELDRETH: Okay, thanks.

DR. LIEBLER: You know, we might want to have a -- go ahead, Wilbur. I'm sorry you had a question on that.

MR. JOHNSON: Yeah. Would any development on reproductive toxicity data on ascorbic acid be relevant to this safety assessment?

DR. BELSITO: Of course.

DR. LIEBLER: Yeah.

DR. BELSITO: Just, you know, I mean, there's going to be reams of it. So just a brief summary or you could even say that it's grass --

MS. FIUME: There's an existing report.

MR. JOHNSON: Yeah. So if you have those data on ascorbic acid, would you need data on propylene glycol?

DR. BELSITO: It would support --

DR. LIEBLER: You don't need it on propylene glycol but we want to have -- so there are different ways of looking at these. You could look at these as these are fatty acid derivatives that deliver ascorbic acid. Or they're ascorbic acid that delivers fatty acids, okay?

So you've got the ascorbic acid piece covered I presume by some data in the literature on repro. And then -- but to cover for the other version where you've got the, you know, the small highly hydroxylated molecule delivering a fatty acid that's where the propylene glycol fatty acyl ester could be useful read across, okay?

MR. JOHNSON: Okay.

DR. LIEBLER: That make sense?

MR. JOHNSON: Yes, it does.

DR. LIEBLER: You know, I was going to say my other point about in the RIFM we do tons of read across and we have a framework in our reports at the end where we actually have sort of an appendix with the justification of the read across, a listing of what they are, or the analogs. You can see the structures. You can see the endpoints that they were used for. And then, kind of a systematic set of considerations that we edit slightly but it's almost a boilerplate. And we might -- if we start using much read across here we might want to adopt that sort of framework in our reports.

DR. BELSITO: Yeah. And we could send you an example of the type of appendix that Dan is referring to.

DR. LIEBLER: You can just pull one out of any of our recent --

DR. BELSITO: Right.

DR. LIEBLER: -- publications. They're all pretty much the same now.

MS. FIUME: Definitely, but that was going to be my next question because actually in my butyl polyoxyethylene ethers report I didn't get the framework from you yet but I was trying to develop something similar because we did use read across data and it was put into a table because I remember when we did discuss formatting it was recommended that that information go into a table which I think also is part of the reason that some of the information in this report was in a table.

DR. BELSITO: Right.

MS. FIUME: So --

DR. LIEBLER: I noticed what you were doing there and I thought oh, it would be better if it was, you know, the RIFM format or something like that. And it's simply because A) I'm used to it. But B) I helped to develop it and it's, I think we've already climbed the learning curve on that.

DR. BELSITO: (Inaudible) Dan.

DR. LIEBLER: You know.

DR. BELSITO: I actually can send it to you, Monice.

MS. FIUME: That would be great, thank you.

DR. BELSITO: And why don't you give me and Wilbur's -- your and Wilbur's address because it's actually on my computer to work on the way home because I'm now shifting gears to the RIFM reviews. So mfiume?

MS. FIUME: fiumem.

DR. BELSITO: @cir and I always forget it's --

MS. FIUME: -safety.org.

DR. BELSITO: Right.

MS. FIUME: That was my (inaudible).

DR. LIEBLER: That's okay. It's a good start.

DR. BELSITO: And Wilbur is johnsonw?

MR. JOHNSON: Right, that's right.

DR. BELSITO: Anything else?

DR. BERGFELD: Can I see it?

DR. BELSITO: bergfew?

DR. LIEBLER: So one other comment I had, Wilbur, on -- we have several spots here where we have computational analyses predictions and these are ridiculous. Ascorbyl palmitate on pdf 16 predicted to be moderately toxic. Ascorbyl stearate, two carbons longer, predicted not to be slightly toxic. Moderately toxic versus not to be slightly toxic.

MR. JOHNSON: And both results are not explained anywhere --

DR. LIEBLER: Yeah, just I would trash that. I mean, it's not really useful. It's nonsensical on its face.

MR. JOHNSON: Okay. So basically I guess all the data included in the safety assessment that or included in that publication should be deleted?

DR. LIEBLER: I think so. I wouldn't even call them data.

MR. JOHNSON: Okay.

DR. LIEBLER: If you say something is not slightly toxic --

DR. BELSITO: So where are you, Dan?

DR. LIEBLER: -- I would call that non- quantifiable.

MR. JOHNSON: Under toxicity.

DR. BELSITO: And what's the pdf page?

DR. LIEBLER: Oh, pdf 16, Don, in the middle of the page under where it says computational analyses predictions.

DR. BELSITO: Okay. So you want those -- that computational analysis totally removed?

DR. LIEBLER: Right. Then you have it again a little further down. Then you have it under repro and developmental. That's all we have in repro right there so we're going to beef that up anyway.

DR. SNYDER: So on this appendix is that -- I've raised this before and I'm going to raise it again because there was a comment in a report and I don't think it was this one but it was one coming up in which we had the statement after an exhaustive review and I -- what I pinged it because what is exhaustive review? I think it's important that we have some data or some information into the -- what was reviewed, I mean, because it is pretty extensive. I think it is an important aspect of these reports at what lengths we go to to find data on the ingredients being reviewed but yet we don't really have any information in the report that specifically says to what degree a literature review was done.

DR. BELSITO: Right.

DR. SNYDER: So do you do that with the RIFM? I mean, do you do that, you know, do you have an appendix that says here's -- because we have it -- you have the data because we see it in the pre --

DR. BELSITO: I'm trying to remember in the -- well, I just pulled up a study to send off so I can tell you. I don't think that we do do that but let me look.

DR. SNYDER: Because I think it is very important that you spend an enormous amount of time and effort to find data. And so when we say there are no published reports, I, as a reviewer, have a great deal of confidence that there isn't anything out there.

DR. BELSITO: Because you have that scheme of what was searched and --

DR. SNYDER: Right. Right but somehow that never gets captured in any of these reports.

DR. BERGFELD: Where would you put that?

DR. SNYDER: Well, that's what made me think about it now again is this idea that --

DR. BELSITO: Yeah, so in the RIFM reports we say so in the introduction that each endpoint discussed in the safety assessment da, da, da, dah, used information in the RIFM database consisting of publicly available and proprietary data and through publicly available information sources. And then, it lists the sources. It says for example, SciFinder, PubMed.

DR. SNYDER: Right.

DR. BELSITO: So yeah, I mean, it -- you could just simply list the search engines you used to look for this data.

DR. SNYDER: Or it could be referenced to a --

DR. BELSITO: Or it could be a boilerplate.

DR. SNYDER: Yeah.

DR. BELSITO: You know, we could create a boilerplate of what search engines CIR typically uses because it's almost always the same.

DR. SNYDER: It's pretty consistent, exactly. It's pretty consistent.

DR. BELSITO: You know, so that people can go back and look and say, okay, when we say after an exhaustive, you know, search of the data this is what we used. And if someone has a comment, well, why didn't you use this? We could reconsider using that going forward.

DR. HELDRETH: So then something akin to what's on pdf page 7?

DR. SNYDER: Yes.

DR. LIEBLER: Yeah.

DR. BELSITO: Yeah, but create a, you know, like so it doesn't have to occur in each report. We could --

DR. HELDRETH: But --

DR. BELSITO: -- set up an independent document of this is when RIFM does a scientific literature research this is what we're looking at.

DR. SNYDER: I think some of these boilerplates have uses both for --

DR. BELSITO: Or when (inaudible).

DR. SNYDER: -- the writers, for the reviewers, and for the end users. And so just like I said this morning with the endocrine disruption boiler, it's the writer says did I do all these things that we normally do, and, you know, and so I think it's just kind of due diligence that it kind of is a QA, your own kind of QA'ing of did you go through all the procedures for what you normally do for reviewing? I always look at that. I mean, I always look to see to what extent and it just -- this wording that somebody used, exhaustive and I went, I pinged it again saying what entails exhaustive? Because sometimes there's a not so exhaustive.

DR. BERGFELD: Would you put an asterisk to that and then have that appear somewhere in the document or --

DR. SNYDER: Well, I think as Don said if we just had a statement in there saying, you know, in accordance with procedures used by the CIR and reference a boilerplate that says these are the typical literature searches.

DR. BERGFELD: Where would you put that, though, in the document?

DR. SNYDER: Well, on the website and then --

DR. BERGFELD: Oh, at the website?

DR. SNYDER: I would put it at the intro because always say --

DR. BELSITO: Right.

DR. SNYDER: -- it always in the intro. We always say, you know, a search of the published information and unpublished information but I never -- I always -- I pinged that many times over saying what does this mean?

DR. LIEBLER: So you could have something like this pdf 7 list of link to the sources.

DR. SNYDER: Yeah.

DR. LIEBLER: And that could go on the CIR website with -- and then, you add

a sentence in the introduction to state essentially what Paul just said which would be a standard sentence and it would end with the link to the CIR page that has this information on it. And if there is anything peculiar to a particular set of ingredients for a particular report, we can add additional language pointing to additional resources.

DR. SNYDER: And it also goes to then the re- reviews so in the re-review process I assume you go back through all of that same list.

DR. BELSITO: Wilma, for some reason your -- it's bergfew@ --

DR. BERGFELD: ccf -- ccf.org.

DR. BELSITO: Okay. Normally it pops up. Okay. Mostly getting that it's not recognizing you.

DR. LIEBLER: So, we'll bear --

DR. BELSITO: And if --

DR. LIEBLER: -- another point. Under carcinogenicity studies, PDF 17, you have inhibition of tumor promotion and then you have data for ascorbyl palmitate. Shouldn't that logically go under anti- carcinogenicity studies or do we simply have -- are we locked in by our own organizational boilerplate, that inhibition of tumor promotion goes under carcinogenicity? Because, logically, it's anti-carcinogenicity.

MR. JOHNSON: I can move it to the --

DR. LIEBLER: Okay. Yeah, if we can do that, that's --

DR. SNYDER: I think you might want to ask Tom about that because I think that promotion is only one aspect of tumorigenicity, so.

DR. LIEBLER: I mean it could belong under carcinogenicity if it were data on tumor promotion.

DR. SNYDER: Right.

DR. LIEBLER: But it's actually explicitly data in inhibition of tumor promotion.

DR. BELSITO: Okay, Dan, let me get this straight again though. So, you want all of the references to the in silico deleted?

DR. LIEBLER: It's that reference 42. And it comes up beginning on PDF 17, I believe it is. The middle of PDF 17 under acute tox comb (inaudible).

DR. BELSITO: I have 16.

DR. LIEBLER: Sixteen, sorry. Thank you. Yes, 16.

DR. BELSITO: So, all of the references 42 should be dropped.

DR. LIEBLER: Yes.

DR. BELSITO: Including for the developmental and re(inaudible)?

DR. LIEBLER: Yeah, that's all we have there, but it's -- again, ascorbyl palmitate predicted not to be reproductive toxicant. And then ascorbyl stearate, not to be reproductive toxicant.

But the ones that bothered me were the ones under -- on PDF 16 where under acute toxicity were ascorbyl palmitates predicted to be moderately toxic and ascorbyl stearate is not slightly toxic. So --

DR. BELSITO: Okay.

DR. LIEBLER: I just thought that those were nonsensical.

DR. BELSITO: Okay. So, I had we're going to go safe as used. We'll bring in the reprobe data on ascorbic acid and the mono and decyl glycols. Is that correct, Dan?

DR. LIEBLER: Yeah.

DR. BELSITO: And saccharides?

DR. LIEBLER: Correct.

DR. BELSITO: And then explain the fact that while we don't have 20 percent sensitization in dipalmitate, we do have some data at 10 percent. And the tetraisopalmitate. And then we also have the HRIPT in 44 patients with the tetrahexyldecyl at 30 percent. And I guess we could also throw in lack of case reports indicating sensitization of these esters and ethers of ascorbic acid.

Other comments? Yes.

MR. BEST: I was just curious. Do you all have a sense of why the Australians limited the concentration of tetrahexyldecyl so low? I was just curious. And it's used higher. And

you said there is a clinical study at higher. But I was curious if you knew why they decided to do that?

DR. BELSITO: What page are you on?

MR. BEST: Sorry, it's under PDF 12, use.

DR. BELSITO: Okay.

MR. BEST: The last paragraph.

DR. BELSITO: Right.

MR. BEST: Yeah.

DR. BELSITO: For dermal use only, the concentration should not exceed one percent. Not for the eye. I don't know. Wilbur, this is --

MR. JOHNSON: I would have to, you know, consult that to see if I can determine the basis for those, you know, conditions of use.

DR. BELSITO: What is the concentration of use that we're looking at here?

MR. BEST: Three percent and 1.5 percent around the though, not in the eye. So, I wasn't sure if that's the same.

DR. BELSITO: Yeah, well this says in the eye, so.

MR. BEST: Right. Yeah.

DR. BELSITO: Yeah, that would be different. But the three percent was in what kind of product? Table 3.

DR. LIEBLER: It's a leave on.

DR. BELSITO: It's a leave on.

DR. LIEBLER: After shave. Shave cream.

MR. JOHNSON: Yeah, that's tetrahexyldecyl ascorbate is up to 2.5 percent in after shave, lotion, shaving cream, and moisturizing products. Not spray and night products. Not spray.

DR. BELSITO: I don't -- I mean based upon the data we have here, I don't see a reason why they would restrict it.

MR. BEST: Yeah, fair enough. I know you work in the walls of this. But I mean I guess, I guess it would be good if you're going to have it in there to at least, to have some sort of response to it in the report because it had raised a red flag for me, as, you know, you just say oh it's just really weird, some other body has decided that, you know.

DR. LIEBLER: No, it's a good point. It doesn't make sense.

DR. BELSITO: Okay. Anything else?

MR. JOHNSON: Yes, Dr. Belsito, on PDF page 19 under Promotion of Lipid Peroxidation, you know, are those studies, you know, useful? Particularly, the last statement at the end of that section that ascorbyl palmitate may intensify skin damage following physiologic doses of UV radiation.

DR. LIEBLER: Yeah, I don't agree with that. I don't agree with that interpretation. In antioxidant chemistry, there is an interesting history of studies that suggest that some antioxidants promote lipid peroxidation. But they're under very unphysiologic conditions. Vitamin E can be shown to promote lipid peroxidation under very unphysiologic conditions, such as when you have a great excess of the antioxidant relevant to the physiological normally -- if there's a physiologic amount.

But they're extrapolating from observations that I don't think justify their assertion that ascorbyl palmitate will intensify skin damage upon UV radiation.

MR. JOHNSON: Should these studies remain in the safety assessment?

DR. LIEBLER: I think that they probably should be there, but I think that we don't necessarily need to accept the conclusion that's offered as you quoted it there. We can deal with it in discussion.

I have to go back and look at this reference, actually. And I could do that and help you with some wording on that.

MR. JOHNSON: Okay. Thank you.

DR. LIEBLER: Reference 50. Do you have it handy? Is it a published paper? I think it probably -- [Drs. Jonas and Liebler converse in a whisper].

DR. BELSITO: F-I-U-M-E- M at C-I-R safety -- dash safety dot org. It's not recognizing you. It says Microsoft Office --

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Anything else? Okay, so is everyone happy with safe as used?
DR. LIEBLER: Yes.

Day 2 of the December 5-6, 2016 CIR Expert Panel Meeting – Full Panel

Ethers and Esters of Ascorbic Acid

DR. BELSITO: There are seven ethers and esters of Ascorbic Acid and, let me scroll down here. We thought that we could do with a safe as used conclusion for all seven of these.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. MARKS: We'll have a discussion first. We felt that perhaps an insufficient data notice. I was concerned that we didn't sensitization studies for the Tetrahexyldecyl Ascorbate. It's used at 3% leave-ons with 397 uses. So a lot of uses at 3%. We didn't know whether at 3% it was safe or not from a sensitization point of view. And then even though Ascorbyl Dipalmitate has few uses for it, it's up to 20% in a leave-on and again, I'd like to see some sensitization data that confirms its safety.

DR. BELSITO: We discussed that. So the Dipalmitate, is 20%. 100% we know that there was some sensitization. 10% there was no sensitization. We do have on the Tetrahexyldecyl, a study, granted only in 44 patients, but where 30% was used and it was completely negative.

DR. MARKS: Oh, okay.

DR. BELSITO: And we felt that we could use that as read across, plus the absence of case reports of these causing sensitization. So, we thought we actually had the 20% Dipalmitate covered.

DR. MARKS: Okay. Thanks, Don. Then I will second your motion.

DR. BERGFELD: Any further discussion? Ron Hill?

DR. HILL: I have a problem with that ether. That same ingredient that he's asking about. It's an ether. The rest of them are esters. I'm not sure what the basis for reading across from one to the other could possibly be in this particular case. But I can't, and I won't. And I'm not sure we have all the pertinent safety information in here because this is one of the ones that is allegedly, well, I guess is, GRAS. At least it's approved for use in food stuffs and in diet. I don't have the original information. I could just abstain at this point and see what else I can get, dredge up on that. Or see what else staff dredges up on that. But I feel like we're missing some pieces of the puzzle here. And because this is an ether and we don't really know anything about the bio-handling of this, I feel a high degree of uncertainty.

DR. BERGFELD: Thank you. Ron Shank. Tom.

DR. SYNYDER: I didn't have any problems.

DR. SHANK: I think that the discussion should probably explain phototoxicity because we have phototoxicity data here. And as Dr. Liebler explained the (inaudible) had the same problem from a toxicity data, that you said it was irrelevant in terms of cosmetic formulations.

MR. JOHNSON: On PDF, page 19 and PDF page 21.

DR. SHANK: Another thing I think that should be in the discussion is an indication that some of the data in the report are from a computational prediction. I read the paper, the technology is old. The paper is not old, but the technology is. It's based on LD50s and non-quantitative structure activity relationships. A lot of contradictions within it. I don't think we should ignore it. It's an international information source. But I don't think it's relevant to evaluation of cosmetic ingredients.

DR. LIEBLER: Right. I agree with you. I flagged those. I thought that the predictions were nonsensical. The difference between the C-16 and the C-18, one being not, I forget what it said, but I mean, the predictions were useless. And I suggest we delete those. If you want to keep them in the report, I'm okay with that. I just think that we can't draw any conclusions from those. And as far as phototoxicity, this is under the other relevant studies, Promotion of Lipid Peroxidation by UVB. Yeah, I think this is, you know, these activities are an artifact of a very highly, well, of an irrelevant model system for actually predicting phototoxicity as we think of it normally in the skin.

DR. BELSITO: It wasn't phototoxic, it was enhanced sensitization to ultraviolet

B.

DR. LIEBLER: Right

DR. BELSITO: Phototoxicity is marked by a reaction to UVA. So, this, I thought was as dense. More an issue of Lipid Peroxidation and also you need to be very careful when you look. The minute you start moisturizing skin, you will slick down the stratum corneum and absorb ultraviolet B more easily. So I wasn't impressed with these studies.

DR. SHANK: But I think it should be in the discussion.

DR. BELSITO: Yeah, we can, of course.

DR. BERGFELD: Paul, any comment?

DR. SNYDER: Nothing

DR. BERGFELD: Ron Hill, again.

DR. HILL: My take on that one was that it's an interesting piece of science but our ability to further interpret it is highly limited. I also wanted to raise, back to the ether again, I'm picking on the ether I guess. We don't have method of manufacture for that ether. There's a high degree of probability that they're using some kind of reactive to put that ether together. I would like to see either something about method of manufacturer that indicates what kind of residual impurities might be there, or an impurities profile for that which we also do not have. I thought the method of manufacture for the others was, pretty uninformative and not well written. So I had raised that general concern. But at least those are formation of asters, and we have it for one of them. I think I felt reasonably capable of determining the method of manufacture. Inferring methods of manufacture based on the information we did have. And then one other comment about that computational paper. My concern if we leave it in as is. Is that it's presence in those positions in the paper, convey from where I would sit as a naïve reader, that were relying on this much more heavily than I think is reasonable to rely on. Because as far as I can tell, whatever information however valid or invalid is heavily relying on things that are in the black boxes of those computational programs, without knowing the details about how those computer predictions are actually being produced. So I have concerns if we just leave it in the position in the document where it is in all those places. But that's my take on it.

DR BERGFELD: What have you decided to do about that particular document? In the, leave it where it is?

DR. BELSITO: I mean I think that you have as Europe has told us, we can't use animals computational. Data is becoming more and more important. I felt it could be left in.

DR. SHANK: It could be handled in the discussion.

DR. BELSITO: In the discussion, sure.

DR. LIEBLER: Yeah none of the conclusions. There are no important inferences driven by those estimates ya know so. It's one of those things where I suppose. Yeah I can see Ron Hill's point about leaving it in and not implying that we look at it as reliable. But on the other hand, if we go to the trouble of beating up on it in the discussion, maybe we accord it more importance than we need to. I would perhaps at most suggest a sentence to simply say. That computational predictions using older methodology were consistent with the overall safety profile of the ingredients. Something like that, we can damn it with faint praise.

DR. MARKS: And that would only be one sentence, and everything else would be left out so it wouldn't be highlighted?

DR. LIEBLER: Right, yup.

DR MARKS: Yup okay

DR. BERGFELD: So

DR. BELSITO: So more discussion

DR. BERGFELD: Okay

DR. BELSITO: It says Ascorbyl Linoleate can be used as a bleaching agent. So that means we need to in the discussion put that in. That would be inappropriate for a cosmetic. Page 14 we didn't know really how to deal with this, but the title is penetration enhancement, and we look at that. But in fact, it doesn't enhance. It reduces penetration so, you know a reader might just look at this. So I'm not sure if that should be miscellaneous biologic affect. Rather that penetration enhancement just as a title. Again just so that one is. I looked at it, and I go oh my God it's penetration enhancer. So I flagged discussion penetration enhancement and then I write what it does and it doesn't enhance so, just to point that out.

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DR. LIEBLER: I think how we left it yesterday was that. Since penetration enhancement is kind of one of the organizational pieces of our framework. And this was a study to determine if there was. And the answer is no there isn't, actually inhibits slightly. We just need to add a sentence to the end that say's. Ascorbyl Palmitate inhibited penetration.

DR. SNYDER: Right

DR. LIEBLER: Rather than leaving the reader to infer it from the numbers. Just state it plainly, then I think we'd probably okay with that.

DR. BELSITO: And this is a follow up to the question on the computational. So would the developmental and reproductive toxicities, there are none in this report. There are also none in the prior review that we had done. But Dan felt that we could read could read across from mono and Diacyl Glycol's and Saccharides and that read across would, pardon.

DR. LIEBLER: And ascorbic acid

DR. BELSITO: And ascorbic acid, and that read across would also provide support for the safety. So we wanted those summarized in this report.

DR. LIEBLER: So let me just clarify, cause I got curious looks coming from my colleagues across the table here. The idea the read across is that you can think of these as either a fatty sort of a hydrocarbon delivery for ascorbic acid. Or an ascorbic delivery for fatty acids, okay? Is going to tissues where there might be reprotoxicity. And this is a good case where one could use a read across. You've either got the glycol; a simple glycols; or a simple saccharide mono estridge would be or (inaudible -cough), would be very similar to these in terms of overall physical. Being able to deliver the fatty acid with a polar head, that's structurally and chemically similar to an Ascorbic acid. And then you've got the ascorbic acid part of course which we know is safe anyway. But that way we've got something other than, just these lame computational estimates for repro.

DR. HILL: That's where I really wondered, I mean we have statements (inaudible-cough), where they've looked at this. It's the FDA that's looked at the palmitate and approved its safety in several kinds of drug products. I just wondered if we have reference 25, can we mine that data a little better to see what else is actually in there for these esters. Because we do have information that, the palmitate penetrates the skin, hydrolysis there in was likely inefficient. At least that's the statements we have. So they what? I feel like there must be more information there if the EFSA has looked at this; the FDA has looked at this. There's got to be more safety data than what's actually captured in this report somewhere. And if there's not, I'm stunned.

DR. BERGFELD: Can we have a FDA response Dr. Sadrieh?

DR. SADRIEH: I'm not sure what specific data is being referred to, I think it's probably for drugs. Not for, we don't review the safety of anything for cosmetic so I don't know.

DR. HILL: But in the drug use there would be a look in, proof or systatic. Ok I found it, it just flashed by, so on page 12.

Dr. SADRIEH: It's approved only for an indication. So they would have had to evaluate the safety and the efficacy.

DR. HILL: It's approved as a use as an inactive ingredient. Ascorbyl palmitate has been approved by the FDA for use as an inactive ingredient on approved drug products oral; rectal; and dermal. And then the EFSA came to the conclusion. Including some forms including ascorbyl palmitate is safe for all animal species and also stated that setting a maximum contact in feed and water for drinking is not considered necessary. So somebody has more data than what seems to appear in this report. And also reference 23 says. Ascorbyl palmitate is generally recognized as safe as uses for preservative in food and human consumption. So I'm assuming that's an oxidated preservative. In fact up to, it's a low percentage in margarine. So I feel like there ought to be more data out there than what we've actually captured in this report. And maybe we need to work a little harder in mining that.

MR. JOHNSON: One comment ah, doctor Hill. The data from the published report on table one. So those are in addition to.

DR HILL: Yes

MR. JOHNSON: Reports and being before the text.

DR. HILL: You read all through that again. Maybe we need to simply refer to some of that data from that table, and in the main text in some way. Because I think it didn't jump out at me reading it even though it says go see table 1.

DR. BELSITO: We discussed that, with Mike. I mean we understand in the publishing that they need to move that old data into the table. But I think our chief felt it made it hard for all of us to read and know what information we have based upon prior reports. And would like to go back to the old way of having prior reports italicized at the beginning of relevant sections, rather than having to print out table one and keep going back to it every time were on a section. And then if in fact it need to be published such that, that data is moved to a table. You can just pull out all the italicized stuff when it goes in for publication and make a table out of it.

DR. GILL: We discussed it last night and we can go back to including the italicized information from prior reviews in the document.

DR. HILL: That leads to the situation like this where it seems to be critically important to the recent interpretation.

DR. MARKS: Yes

DR. BERGFELD: Any other discussion

MR. JOHNSON: Doctor Hill we only need, method of manufacturing impurities data on Tetrahexyldecyl Ascorbate.

DR. HILL: That's the one

MR. JOHNSON: Just that one okay thank you.

DR. BELSITO: But were going safe as used.

DR. BERGFELD: Correct

DR. BELSITO: So there's never been sufficient data amounts on that number.

DR. BERGFELD: But that's what Ron Hill say's

DR. BELSITO: Right I understand

DR. BERGFELD: Being recorded

DR. BELSITO: I see

DR. BERGFELD: Do you want to restate the motion doctor Belsito?

DR. BELSITO: Yes, safe as used.

DR. BERGFELD: And it was seconded?

DR. MARKS: Correct

DR. BERGFELD: And we've had a lengthy discussion. And any other comments before I call the question? See now I call the question. All those in favor? Thank you. Abstaining, against? One against.

DR. HILL: Opposed

DR. BERGFELD: Opposed, yes. Thank you. Thank you we'll move on then. The Persulfates doctor Marks?

DR. MARKS: So in September of 1998 while I have (inaudible), we should have filed a report with a conclusion in it. Ah these three persulfates ammonia; potassium; and sodium. Are safe as used as oxidizing agents in hair colorance and lightener's, designed for brief discontinuance use. Followed by thorough rinsing from the hair and skin. At the June meeting this year we reopened this report of the persulfates because of other uses of these compounds, such as hair grooming aide; dentifrices; and eye makeup. Our team considered those and decided that. There should be no change in the conclusion therefore we move to close this review.

DR. BERGFELD: Is there a second to that, or additional comments?

DR. MARKS: Yeah we would handle the other uses, in the re-review document as there's insufficient data. But we wouldn't reopen it. I should say we would close it at this point. The conclusion does not include other uses.

DR. BELSITO: Well I mean we certainly agree that the original conclusion can be, sustained. We were asked to review this. It's reported to be used out there in hair tonics and in dentifrices. It certainly is used in a non cosmetic denture cleansers. I actually saw a patient last week who had colitis related to persulfate in his Efferdent. So I thought since it's reported to be used out there, we should go on record that we found it to be insufficient for leave on in dentifrices. For concentration of use which weren't told. And for a no effect level for sensitization and urticaria. Because I copied Lillian when I saw that persulfate on the dentifrices and said. I presume that this is an OTC because it was labeled as antibiotic. Are those the reports? And she came back to me and said no. That's actually used in toothpaste. So I mean if we think it's unsafe, or we don't have the data to support that use. I think we need to review it. We can't just say well you know, we don't want to reopen it.

DR. BERGFELD: Other comments

DR. SNYDER: We also felt this was communicated by The FDA publication knowing the 2008 that there public notification on different issues, at a risk of allergic reactions. So that's out there so it (inaudible)

DR. BELSITO: Yeah if you look at the effort in box, there is a box right on it. Warning about allergic reactions to use of that denture cleanser.

DR. SHANK: So the conclusion has changed?

DR. BELSITO: Well the conclusion changes because we now, say that there are other uses. So it's okay with brief discontinuous use to the hair. Insufficient for leave on cosmetics and dentifrices, and the insufficient data are the concentration of use, which were not being told. And in no effect level for sensitization and urticaria.

DR. SHANK: I think that could be handled in the re-review statement. Without reissuing the report.

DR. BELSITO: Well anyway, I don't know the rules and regs here.

DR. GILL: Yeah I think that's a panel decision on whether or not you (inaudible) use is there, and want to address that.

DR. BELSITO: Well the uses.

DR. GILL: Because it is used.

DR. BELSITO: The use is there. You told me

DR. GILL: That's right

DR. BELSITO: Both FDA and Carol got back to you and said that. They checked again and it was being used.

DR. GILL: It's been used in toothpaste your correct.

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Safety Assessment of Ethers and Esters of Ascorbic Acid as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 19, 2017
Panel Date:	June 12-13, 2017

The 2017 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 report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, Ivan Boyer, Ph.D., Senior Toxicologist, and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 7 ethers and esters of ascorbic acid, which collectively function as antioxidants, skin-conditioning agents, skin protectants, fragrance ingredients, and skin bleaching agents in cosmetic products. The Panel reviewed relevant data relating to the safety of these ingredients, and concluded that the ethers and esters of ascorbic acid are safe in the present practices of use and concentration, as described in this safety assessment

INTRODUCTION

The safety of the following 6 esters and 1ether of ascorbic acid as used in cosmetics is reviewed in this safety assessment:

Tetrahexyldecyl Ascorbate
Ascorbyl Isostearate
Ascorbyl Linoleate
Ascorbyl Tetraisopalmitate
Ascorbyl Palmitate
Ascorbyl Dipalmitate
Ascorbyl Stearate

According to the *International Cosmetic Ingredient Dictionary and Handbook*, the functions of these ingredients in cosmetic products include: antioxidants; skin-conditioning agents; skin protectants; fragrance ingredients; and skin bleaching agents.[1] Ascorbyl Palmitate is the only ingredient with an additional function of fragrance ingredient, and Ascorbyl Linoleate is the only ingredient with an additional function of skin bleaching agent; however, functioning as a skin bleaching agent is not a cosmetic use and, therefore, the Panel did not evaluate safety for that use.

The Panel has evaluated the safety of Ascorbyl Palmitate, Ascorbyl Dipalmitate, and Ascorbyl Stearate in cosmetics, and issued a final report in 1999 with the conclusion that these ingredients are safe in the present practices of use.[2] Safety test data on these ingredients from the original report are included in this safety assessment (in italics) to distinguish these data from more recent data that are summarized. The safety of these 3 ingredients is being reevaluated in the current safety assessment, taking into consideration data that have been identified in the published literature since the original report was published. Additionally, it is possible that data on these 3 ingredients may be useful for evaluating the safety, particularly for certain toxicity endpoints, of one or more of the remaining 4 ingredients in the current safety assessment. These 4 ingredients, Tetrahexyldecyl Ascorbate, Ascorbyl Isostearate, Ascorbyl Linoleate, and Ascorbyl Tetraisopalmitate, are being reviewed for the first time in this safety assessment.

CHEMISTRY

Definition and General Characterization

The ingredients in this report are all alkylated or acylated derivatives of Ascorbic Acid. Ascorbic Acid, also known as Vitamin C (an antioxidant), is a normal constituent of human skin, and is concentrated in the dermis and epidermis.[3,4] Fatty-alkyl and fatty-acyl derivatives thereof are lipophilic ingredients.

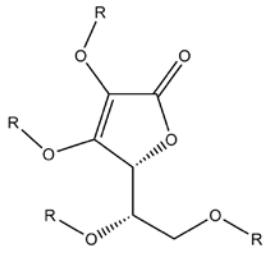


Figure 1. Ascorbate derivatives, wherein R, independently in each case, is hydrogen, fatty-alkyl or fatty-acyl.

The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.

Chemical and Physical Properties

The chemical and physical properties of this group of ascorbic acid derivatives are presented in Table 2.

Method of Manufacture

Fatty acyl ascorbyl derivatives may be synthesized via acylation of vitamin C by direct means (with fatty acids or small chain esters) or enzymatically (e.g., with certain lipases).[5] The enzymatic process may be preferred because it is easier to control regioselectivity. Polar organic solvents, ionic liquids, and supercritical fluids have been successfully used as reaction media.

Ascorbyl Tetraisopalmitate

According to one source, Ascorbyl Tetraisopalmitate (also known as tetra-isopalmitoyl ascorbate or Tetrahexyldecyl Ascorbate) is produced by combining one molecule of vitamin C (ascorbic acid) with 4 molecules of 4 equivalents of tetraisopalmitic acid, a fatty acid that is found in butter.[6]

Ascorbyl Palmitate

Ascorbyl Palmitate is prepared by condensing palmitoyl chloride and ascorbic acid in the presence of a dehydrochlorinating agent such as pyridine.[7]

Ascorbyl Stearate

Ascorbyl Stearate is produced by the reaction of l-ascorbic acid and stearic acid.[8]

Composition/Impurities

Ascorbyl Palmitate and Ascorbyl Stearate

The National Formulary (NF) states that Ascorbyl Palmitate must contain between 95% and 100.5% of $C_{22}H_{38}O_7$, based on the dried weight.[9] Depending on the method of manufacture, Ascorbyl Palmitate could contain stearic acid, because palmitic acid samples contain large quantities of stearic acid. Likewise, Ascorbyl Stearate could contain palmitic acid. When dried, Ascorbyl Stearate contains not less than 93% of *L*-ascorbyl stearate.[10]

The following limits for impurities in Ascorbyl Palmitate are stated in the *Food Chemicals Codex*: lead (no more than 2 mg/kg) and residue on ignition (no more than 0.1% sulfated ash).[11] Additionally, the following limitations have been stated in a cosmetics industry specification for Ascorbyl Palmitate: sulfate ash (0.1% minimum), arsenic (as As) (3 ppm maximum), and lead (as Pb) (20 ppm maximum).[2] Another cosmetics industry specification has indicated a 2 ppm maximum limitation for arsenic (as As) in Ascorbyl Stearate.[2]

According to the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives, 2 mg/kg is the limit for lead in both Ascorbyl Palmitate and Ascorbyl Stearate as food additives.[12]

USE

Cosmetic

The safety of the ethers/esters of ascorbic acid included in this safety assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[13] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[14] Collectively, the use frequency and use concentration data indicate that 6 of the 7 ingredients in this safety assessment are currently being used in cosmetic products; Ascorbyl Isostearate is not reported as being used. (See Table 3).

According to 2017 VCRP data, the greatest reported use frequency is for Ascorbyl Palmitate (2557 formulations, mostly in leave-on products), followed by Tetrahexyldecyl Ascorbate (536 formulations, mostly leave-on products) (Table 3).[13] The results of a concentration of use survey provided in 2016 indicate that Ascorbyl Dipalmitate has the highest maximum concentration of use; it is used at concentrations up to 20% in leave-on products (face powders). The maximum concentration of use in rinse-off products is being reported for Tetrahexyldecyl Ascorbate (concentrations up to 2.5% in shaving cream) (Table 3).[14]

Cosmetic products containing the ethers/esters of ascorbic acid may be applied to the skin and hair or, incidentally, may come in contact with the eyes and mucous membranes (e.g., Tetrahexyldecyl Ascorbate at maximum use concentrations up to 1.5% in eye lotions). Additionally, the following ingredients are being used in lipstick products that may result in incidental ingestion: Tetrahexyldecyl Ascorbate (at maximum use concentrations up to 1%), Ascorbyl Dipalmitate (at maximum use concentrations up to 0.1%), Ascorbyl Palmitate (at maximum use concentrations up to 0.52%), and Ascorbyl Stearate (at maximum use concentrations up to 0.09%). Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

The following ingredients are being used in products that, upon use, may result in incidental ingredient inhalation exposure: Tetrahexyldecyl Ascorbate (in hair sprays [aerosol] at maximum use concentrations up to 000000006% and in tonics, dressings, and other hair grooming aids (aerosol) at maximum use concentrations up to 0.1%), Ascorbyl Dipalmitate (in perfume at maximum use concentrations up to 0.000002% and in hair sprays [pump sprays] at maximum use concentrations up to 0.0000018%), and Ascorbyl Palmitate (in fragrance preparations at maximum use concentrations up to 0.045%, hair sprays [pump sprays] at maximum use concentrations up to 0.048%, body and hand products at maximum use concentrations up to 0.0025%, and in suntan products at maximum use concentrations up to 0.01%). 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 below 10 μm, compared with pump sprays.[15,16,16,17,18] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[15,16,16]

The following ingredients are being used in face powders: Tetrahexyldecyl Ascorbate (at maximum use concentrations up to 0.1%), Ascorbyl Tetraisopalmitate (at maximum use concentrations up to 0.05%), Ascorbyl Dipalmitate (at maximum use concentrations up to 20%), and Ascorbyl Palmitate (at maximum use concentrations up to 0.1%). Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[19,20,21]

Tetrahexyldecyl Ascorbate is included in the Australian Inventory of Chemical Substances (AICS) with the following conditions of use: "(1) for cosmetic use only, (2) for dermal use only, (3) the concentration is not to exceed 1%, and (4) it is not to be included in topical products intended for use in the eye."[22]

The ingredients reviewed in this safety assessment do not appear on the list of substances that are prohibited in cosmetic products that are marketed within the European Union and are not subject to any restrictions relating to their use in these products.[23]

Noncosmetic

Ascorbyl Palmitate and Ascorbyl Stearate

Ascorbyl Palmitate and Ascorbyl Stearate have been approved by FDA as preservatives in margarine, with a concentration limit of 0.02% either individually or in combination.[24] FDA has determined that Ascorbyl Palmitate is generally recognized as safe for use as a preservative in food for human consumption.[25]

The European Food Safety Authority (EFSA) has issued a scientific opinion on the safety and efficacy of vitamin C (ascorbic acid, sodium ascorbate, calcium ascorbate, Ascorbyl Palmitate, sodium calcium ascorbyl phosphate, and sodium ascorbyl phosphate) as a feed additive for all animal species.[26] The EFSA concluded that Vitamin C, in the form of ascorbic acid and its calcium and sodium salts, Ascorbyl Palmitate, sodium calcium ascorbyl phosphate or sodium ascorbyl phosphate, is safe for all animal species. The EFSA also stated that setting a maximum content in feed and water for drinking is not considered necessary.

Ascorbyl Palmitate has been approved by FDA for use as an inactive ingredient in approved drug products (oral, rectal, and dermal).[27]

According to the Environmental Protection Agency (EPA), residues of Ascorbyl Palmitate are exempt from the requirement of a tolerance when used in accordance with good agricultural practice as an inert ingredient in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.[28] The EPA has also determined that Ascorbyl Palmitate is exempt from the requirement of a tolerance when used in accordance with good agricultural practice as an inert ingredient in pesticide formulations that are applied to animals.[29]

Ascorbyl Tetraisopalmitate

In the Republic of Korea, Ascorbyl Tetraisopalmitate, glabridin, (−)-α-bisabolol, arbutin, niacinamide, ascorbyl glucoside, and ethyl ascorbyl ether are the main ingredients used in cosmetics reported to function as whitening agents.[30] Vitamin C, or *L*-ascorbic acid, has the ability to inhibit the activity of tyrosinase.[31,32] Vitamin C is unstable and easily oxidized when exposed to air or light. To overcome this effect, Ascorbyl Tetraisopalmitate and other vitamin C derivatives have been introduced.[32]

TOXICOKINETICS STUDIES

Dermal Penetration

In Vitro

Ascorbyl Palmitate

In a study involving guinea pigs, the topical application of Ascorbyl Palmitate resulted in dermal penetration. Ascorbic acid content in skin, liver, and blood increased 8-, 7-, and 4-fold when compared to control animals.[33] In a study involving guinea pigs with scurvy, ^{14}C-Ascorbyl Palmitate was applied topically. Ascorbic acid concentrations in the skin, liver, kidneys, and blood were 4 to 8 times greater when compared to the control.[8]

According to one source**, "***L*-ascorbic acid is an unstable molecule to formulate for topical use, and more stable derivatives of *L*-ascorbic acid have been utilized in topical formulations." [34] Although esters of ascorbic acid are more stable and readily converted to *L*-ascorbic acid after oral ingestion, it is not clear that derivatives, after topical application, are absorbed into the skin or converted to *L*-ascorbic acid after penetration. With this in mind, the percutaneous absorption of ascorbic acid (15%; pH 3.2) and its derivatives, Ascorbyl Palmitate (10%) and magnesium ascorbyl phosphate (12%), was evaluated using white Yorkshire pig skin positioned in a semi-occlusive chamber. The two ascorbic acid derivatives were described as commercially available high concentration formulations. Each test substance was applied to the skin for 24 h, after which full-thickness 6-mm punch biopsy specimens of skin were analyzed. Skin levels of *L*-ascorbic acid were expressed as the mean ± standard deviation (n = 10). The concentrations of ascorbic acid measured in the skin after exposure to each test substance were compared to baseline skin levels of *L*-ascorbic acid. The ascorbic acid concentrations in the skin after ascorbic acid was applied were statistically significantly elevated when compared to the baseline concentrations, as indicated by a p value equal to 0.0005. The p values for the Ascorbyl Palmitate and magnesium ascorbyl phosphate ester formulations were 0.3176 and 0.9101, respectively, indicating that the differences were not statistically significant. It was noted in earlier publications that although Ascorbyl Palmitate appears to readily enter skin,[35] its conversion to *L*-ascorbic acid may be inefficient. Furthermore, Ascorbyl Palmitate appears to remain on the extracellular surface of cells and may not be readily converted to *L*-ascorbic acid.[36]

A study was performed to examine the suitability of several colloidal systems for Ascorbyl Palmitate skin delivery using pig ear skin and Franz diffusion cells.[37] The receptor fluid consisted of 0.9 % NaCl containing 0.5 % polyoxyethylene (20) oleyl ether and 0.01 M $Na_2S_2O_3$. One gram of a self-microemulsifying system (mixture of oil and surfactants with water), water-in-oil microemulsion, and liquid crystal loaded with Ascorbyl Palmitate (at 1 % or at maximum solubilization concentration) was applied to the skin surface. After 6 h, the formulation was removed and the skin surface was cleaned. The epidermis was separated from the dermis by heat treatment, and Ascorbyl Palmitate was extracted with methanol. The results of Ascorbyl Palmitate skin deposition showed relatively high concentrations of Ascorbyl Palmitate delivered to skin layers, especially to the epidermis, whereas, no Ascorbyl Palmitate was found in receptor fluid. The highest solubilization capacity for Ascorbyl Palmitate was determined for the oil and surfactant mixture alone. The greatest extent of skin permeation was observed for liquid crystal loaded with 1% Ascorbyl Palmitate. Among the phase transition systems tested, liquid crystal was selected as the best potential carrier for Ascorbyl Palmitate. Additionally, the results in a more recent publication suggest that a lecithin-based liquid crystalline system with a lamellar structure could be used as a physiologically acceptable dermal delivery system for Ascorbyl Palmitate.[37]

Animal

Ascorbyl Dipalmitate

The percutaneous absorption of six different oil-in-water cream bases containing 4% Ascorbyl Dipalmitate was studied using rabbits.[38] Details relating to the test protocol and animals tested are not stated in this Korean publication abstract. The concentration of ascorbic acid in the urine varied depending on the characteristics of the cream bases that were tested. The absorption of ascorbic acid was increased and sustained with the cream bases containing branched chain esters of fatty acids instead of natural oils. The level of excretion of ascorbic acid in the urine was high for the cream base with nonionic surfactants and a small quantity of natural oils.

Human

Troxerutin (a flavonol drug), Ascorbyl Palmitate, and alpha-tocopheryl succinate were incorporated in 10 mg of a gel containing hydroxypropylcellulose, butylhydroxytoluene and ethyl alcohol (95%).[39] Alpha-tocopheryl succinate (100 mg) and Ascorbyl Palmitate (10 mg) were previously dissolved in ethyl alcohol, and troxerutin (30 mg) was previously dissolved in distilled water (0.8 ml). The gel (200 mg) was applied to a 25 cm^2 area of the forearm of 5 volunteers (2 women and 3 men) for 45 minutes. The stratum corneum was then removed using 12 strips of transparent adhesive tape. The experiment was repeated 3 times (on same forearm area), and each was carried out after a recovery period of 2 weeks. The gel (200 mg) served as the control, and was tested according to the same procedure. Test results indicated that, at 45 minutes post-application, Ascorbyl Palmitate and the 2 other substances had penetrated into the epidermis, and were found up to the tenth strip. Looking at the cumulated percentage of the 3 substances according to the strips, more than 80% of the total dose of troxerutin and alpha-tocopheryl succinate, and more than 90% of the total dose of Ascorbyl Palmitate was found in the stratum corneum.

Computational Analyses/Predictions

Ascorbyl Tetraisopalmitate

To simulate Ascorbyl Tetraisopalmitate absorption through human skin, Ascorbyl Tetraisopalmitate percutaneous absorption through the hair follicle infundibulum (important route of absorption into the hair follicle of human skin) was modeled and compared with the stratum corneum membrane.[40] This comparative study was performed via computer simulation by molecular dynamics (with Martini force field). The infundibulum membrane model was constructed to reflect the lipid composition of the human epidermis. The composition of the simulated infundibulum membrane was as follows: phosphatidylcholine (17%), phosphatidylserine (17%), phosphatidylethanolamine (18.8%), phosphatidylinositol (6.9%), sphingomyelin (9.8%), cholesterol (24.4%), cholesterol sulfate (1.5%), and ceramide type II (4.6%). The composition of the simulated stratum corneum membrane was: fatty acids with 24 carbons (39%), cholesterol (36%), and ceramide type II (25%).

A single Ascorbyl Tetraisopalmitate molecule penetrated the infundibulum membrane in approximately 320 nanoseconds (ns). In the case of 3 molecules, the first molecule penetrated in the first 10 ns and the other 2 molecules combined with each other and penetrated in 100 ns. When the number of Ascorbyl Tetraisopalmitate molecules was increased to 9, structural changes in the molecule attributed to clustering of groups was observed. Two molecules combined and penetrated the membrane together in the first 10 ns, 4 other molecules grouped together (~ 22 Ångstroms [Å]) and penetrated in 30 ns, and the last 3 molecules (~ 19 Å) penetrated in 110 ns. The authors noted that the structural changes were probably related to the solvent (water) and the hydrophobicity of Ascorbyl Tetraisopalmitate. Another observation was that the Ascorbyl Tetraisopalmitate molecules penetrated the first layer of the bilayer membrane and remained in that position for at least 1000 ns of simulation.[40]

These results suggested that a high concentration of Ascorbyl Tetraisopalmitate molecules accelerated penetration. The Ascorbyl Tetraisopalmitate molecule was found to have more affinity for the stratum corneum than for the infundibulum, and a straight penetration pathway was observed for up to 600 ns in the stratum corneum simulation. Penetration followed a lateral pathway in the infundibulum.[40]

Penetration Enhancement

Ascorbyl Palmitate

Permeation tests of ibuprofen (formulated in Ascorbyl Palmitate coagel (5% w/v) or ascorbyl laurate coagel (5% w/v), or suspended in isopropanol) through excised skin of hairless mice (Strain MF1- hr/hr/Ola, Nossan Srl, Correzzana,

Milano) were performed using Franz-type cells.[41] [At temperatures higher than the critical micellar temperature, 6-*O*-ascorbic acid alkanoate aqueous suspensions turn into either micellar solutions or gel phases, depending on the length of the hydrophobic chain. Upon cooling, coagels (liquid-crystal structures) are formed.[41,42]] Results for the amount of ibuprofen in each vehicle that permeated (mg/cm^2 ± standard error of the mean) the skin after 20 h were: 2.10 ± 0.25 (in isopropanol), 0.83 ± 0.21 (in ascorbyl laurate), and 0.47 ± 0.05 (in Ascorbyl Palmitate). Ascorbyl Palmitate did not enhance the skin penetration of ibuprofen in this study.

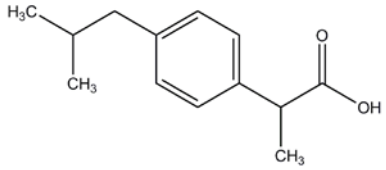


Figure 1. Ibuprofen

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Ascorbyl Palmitate and Ascorbyl Dipalmitate

The enzymatic hydrolysis of Ascorbyl Palmitate and Ascorbyl Dipalmitate was studied using guinea pig tissue homogenates (mixture of small intestine and pancreas homogenates).[43] Details relating to the test protocol were not included in the Japanese publication abstract. The yields of ascorbic acid were 80% with Ascorbyl Palmitate and 20% with Ascorbyl Dipalmitate.

Animal

Oral

Ascorbyl Palmitate and Ascorbyl Dipalmitate

Guinea pigs were dosed orally with Ascorbyl Palmitate (dissolved in sodium taurocholate solution), and hydrolysis by homogenates of the liver, pancreas, and intestines was reported.[44] Approximately 80% of the Ascorbyl Palmitate was hydrolyzed to free ascorbic acid in the small intestines and pancreas. Guinea pigs were also dosed orally with Ascorbyl Dipalmitate (~ 20% in sodium taurocholate solution), and hydrolysis to free ascorbic acid by homogenates of the small intestines and pancreas was reported. In another experiment in this study, guinea pigs were dosed orally with Ascorbyl Palmitate (the equivalent of 20 mg ascorbic acid). Greater amounts of ascorbic acid were excreted at 0 to 24 h than at 24 to48 h. The same results were reported following the oral dosing of guinea pigs with Ascorbyl Dipalmitate (the equivalent of 20 mg ascorbic acid). A difference in body retention or availability of Ascorbyl Palmitate and Ascorbyl Dipalmitate was found, due to differences in the extent and rate of hydrolysis of the 2 esters.[44,45]

Other Routes

Ascorbyl Palmitate

A study was performed to determine the occurrence of Ascorbyl Palmitate hydrolysis in brain tissue using 2 male Wistar rats.[46] Ascorbyl Palmitate (in dimethylsulfoxide (DMSO)) was injected into an internal carotid artery at a dose of 75 mg per rat (dose volume = 0.3 ml). The animals were killed 15 minutes post-injection, and the brain tissue was extracted with chloroform/methanol and chromatographed using thin-layer chromatography.

Spots of Ascorbyl Palmitate were traceable in the hemispheres ipsilateral to the intracarotid Ascorbyl Palmitate injection side and in the contralateral hemispheres. The R_f factor of the spots corresponding to the brain samples of Ascorbyl Palmitate-injected rats was nearly identical to that of the standard spot. R_f was 0.465 for the Ascorbyl Palmitate standard, ipsilateral and contralateral samples in the first rat, and was 0.470 and 0.460 for the ipsilateral and contralateral samples, respectively, in the second rat. These results indicated that Ascorbyl Palmitate resisted hydrolysis in the rat brain, because it penetrated the blood brain barrier and was retained principally in brain tissue as an intact molecule. No conclusion could be

drawn as to the amount of Ascorbyl Palmitate that permeated through the blood brain barrier or the fraction that underwent hydrolysis in the brain.[46]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Ascorbyl Dipalmitate

An LD_{50} of > 5 g/kg was reported for Ascorbyl Dipalmitate (15% suspension) in a study involving rats.[8]

Ascorbyl Palmitate

In an acute oral toxicity study involving rats, the lowest effect level (decreased body weight) for Ascorbyl Palmitate was determined to be 2500 mg/kg.[47] *An LD_{50} of 2000 mg/kg was reported for Ascorbyl Palmitate (33.3% suspension) in an acute oral toxicity study involving mice.*[8]

Ascorbyl Stearate

The acute oral toxicity of Ascorbyl Stearate was evaluated in a study involving rats. Adverse effects were not observed over the range of doses tested, 100 mg/kg to 3000 mg/kg.[8]

Ascorbyl Tetraisopalmitate

The acute oral toxicity of an Ascorbyl Tetraisopalmitate trade name material was evaluated using Wistar rats of the Crl:(WI)BR strain (5 males, 5 females).[48] A single oral dose (2000 mg/kg) of the test substance was administered by gavage to each animal. Dosing was followed by a 15-day observation period and necropsy. There were no clinical signs of toxicity and none of the animals died. Additionally, there was no evidence of organ toxicity at gross necropsy. The reported oral LD_{50} was > 2000 mg/kg.

Computational Analyses/Predictions

The EFSA established a program for the reevaluation of approved antioxidant food additives to help address concerns about the continued safety of food additives.[49] The aim of this research was to predict the toxicity of antioxidant food additives using an in silico methodology for a preliminary evaluation of safety. The in silico prediction was conducted for the following endpoints: acute toxicity (LD_{50}), genotoxicity, carcinogenicity, reproductive toxicity, chronic toxicity (no-observed-effect level (NOEL)), acceptable daily intake (ADI) value, and the toxicity of metabolites. The applied software products used were Toxtree, TEST, Admet Predictor, and the Organization for Economic Co-operation and Development (OECD) QSAR Toolbox. It was noted that many researchers validated the prediction methods used and assessed the accuracy and robustness of each platform. NOEL predictive values were calculated from the predicted value of the ADI, and these NOELs were used to predict long-term toxicity. The antioxidant metabolites were predicted using the Cytochrome P450 method. The in silico method predictions for Ascorbyl Palmitate and Ascorbyl Stearate appear in this section and other sections of the report under this subheading.

Ascorbyl Palmitate

Using the in silico methodology noted above, Ascorbyl Palmitate was predicted to be a moderately toxic compound.[49]

Ascorbyl Stearate

Using the in silico methodology, Ascorbyl Stearate was predicted to be a slightly toxic compound.[49]

Short-Term Toxicity Studies

Ascorbyl Palmitate

In a 63-day oral feeding study involving female mice, signs of toxicity were not observed for Ascorbyl Palmitate at doses up to 3000 mg/kg/day.[50]

Chronic Toxicity Studies

Oral

Ascorbyl Palmitate

Ascorbyl Palmitate (0.25% in diet) was fed to rats in a chronic oral feeding study. The rats received Ascorbyl Palmitate at oral doses of ≤ 2500 mg/kg/day for 728 days. Toxic effects were not observed at doses of 125 or 1000 mg/kg/day, but decreased body weight was observed at doses of 2500 mg/kg/day and greater. Oxalate stones were observed in 2 of 8 rats dosed with 2500 mg/kg/day.[51]

Groups of 10 rats were fed Ascorbyl Palmitate (2% and 5% in feed) for 9 months. Significant growth retardation was observed at a dietary concentration of 5%; also, 2 of 10 rats had bladder stones and hyperplasia of bladder epithelium and 1 rat had nephritis. Slight growth retardationwas observed in the 2% dietary group.[6] *In a 2-year feeding study, groups of 8 rats were fed 2% or 5% Ascorbyl Palmitate(equivalent to 424 mg/kg and 1060 mg/kg, or 0.05% and 0.25% of total diet) in a heat-treated lard diet. Decreased growth rate was reported at the higher dose; also, 2 of 8 rats had oxalate stones after feeding for 9 months.*[8]

Computational Analyses/Predictions

Ascorbyl Palmitate

Using the in silico methodology noted above, the NOEL for long-term toxicity of Ascorbyl Palmitate was calculated to be 916 mg/kg/day.[49]

Ascorbyl Stearate

Using the in silico methodology, the NOEL for long-term (duration not defined) toxicity of Ascorbyl Stearate was calculated to be 834 mg/kg/day.[49]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Computational Analyses/Predictions

Ascorbyl Palmitate

Using the in silico methodology noted above, Ascorbyl Palmitate was predicted not to be a reproductive toxicant.[49]

Ascorbyl Stearate

Using the in silico methodology, Ascorbyl Stearate was predicted not to be a reproductive toxicant.[49]

GENOTOXICITY STUDIES

In Vitro

Ascorbyl Palmitate

The genotoxicity of Ascorbyl Palmitate (dissolved in 0.067 M potassium or sodium sulfate buffer at pH 7) was evaluated in the Ames test at doses of 0.01 to 3.3 mg/plate using the following Salmonella typhimurium strains: TA1535, TA1537, and TA1538. Doses > 3.3 mg/plate were toxic to the bacteria. Test results were negative.[52] *The genotoxicity of Ascorbyl Palmitate (dissolved in 0.067 M potassium or sodium sulfate buffer at pH 7) was also evaluated in the tryptophan reversion assay, and was tested at doses of 0.01 to 3.3 mg/plate. Test results were negative.*[52]

Ascorbyl Tetraisopalmitate

The genotoxicity of an Ascorbyl Tetraisopalmitate trade name material (in ethanol) was evaluated in the Ames test using *Salmonella typhimurium* and *Escherichia coli* (bacterial strains not stated) with and without metabolic activation.[48] Doses of the test substance up to 1000 µg/plate were tested. The positive controls in this study were not stated. The test substance was non-genotoxic, with and without metabolic activation, over the range of doses tested. The negative and strain-specific positive control values were within the background historical ranges associated with the laboratory where the test was performed.

Computational Analyses/Predictions

Ascorbyl Palmitate

Using the in silico methodology noted above, Ascorbyl Palmitate was predicted to be a genotoxic compound.[49]

Ascorbyl Stearate

Using the in silico methodology, Ascorbyl Stearate was predicted to be a non-genotoxic compound.[49] The reason for the difference in the genotoxicity prediction for Ascorbyl Palmitate versus Ascorbyl Stearate was not stated.

CARCINOGENICITY STUDIES

Oral

Ascorbyl Palmitate

The carcinogenicity of Ascorbyl Palmitate (2% in the diet) was evaluated using groups of 12 female CF-1 mice. Mice (6/group) were fed test or control diet for 2 weeks. The remaining 6 mice of one group were injected subcutaneously (s.c.) with 10 mg/kg azoxymethanol (induces focal areas of dysplasia [FADs]) in the colon in saline once weekly for 6 weeks. Six mice of the other group were injected with saline (same procedure). Ascorbyl Palmitate was nontoxic. The administration (s.c.) of azoxymethanol induced proliferation of colonic epithelial cells and the expansion of the proliferative compartment, as well as formation of FADs. There were no FADs in control mice or those fed Ascorbyl Palmitate.[50]

Co-Carcinogenicity

Oral

Ascorbyl Dipalmitate
or Ascorbyl Stearate

The co-carcinogenicity of Ascorbyl Dipalmitate or Ascorbyl Stearate was evaluated using F344 male rats. The rats wee initiated with N-butyl-(4-hydroxybutyl)nitrosamine (BBN) and administered 5% Ascorbyl Dipalmitate or 5% Ascorbyl Stearate. There were no lesions of the liver or kidneys in rats of the test or control group.[53]

ANTI-CARCINOGENICITY STUDIES

In Vitro

Ascorbyl Palmitate

A study was performed to determine whether derivatives of ascorbic acid increase tumor cell death, caused by hyperthermia, to further improve cancer treatment.[54] Hyperthermia is a potent cancer treatment that inhibits the growth of tumor cells. The study was performed using human tongue squamous carcinoma cells (HSC-4). For the examination of carcinostatic activity, cells previously cultured for 24 h were suspended in culture medium. A test solution of Ascorbyl Palmitate (100 µM) was placed in a test tube and the solvent was evaporated by jet flow of nitrogen gas. Culture medium

was then added to the residue and sonicated to become homogenously emulsified. The cell suspensions and test substance were mixed in a glass sample bottle. Hyperthermic treatment involved incubation of the cell suspension for 60 minutes at a temperature of 37°C or 42°C in a water bath. The suspension was then maintained by sequential culture for 24 h (at 37°C). Carcinostatic activity was evaluated using a crystal violet staining assay; cell morphology was observed under a phase-contrast microscope.

The cell viability of control cultures (at 37°C) was considered to be 100%, but was reduced to 57.3 ± 2.7% at 42°C ($p < 0.0001$). Treatment with Ascorbyl Palmitate at 37°C yielded a cell survival rate of 86.8 ± 5.7%. At 42°C, treatment with Ascorbyl Palmitate decreased cell viability to 42.0 ± 2.1% ($p < 0.0001$). The authors noted that the carcinostatic activity of Ascorbyl Palmitate was markedly increased with hyperthermia.[54]

Animal

Dermal

Ascorbyl Palmitate was applied topically to mice at doses of 4 or 5 µmol twice weekly.[55] *Ascorbyl Palmitate (5 µmol) was administered twice weekly to previously initiated mice. Topical application caused inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced tumor production and DNA synthesis in mouse epithelial cells; 60 to 70% inhibition was observed at the 4 µmol dose. Ninety-one percent of tumors were inhibited per mouse at a dose of 5 µmol. When Ascorbyl Palmitate (0.017 mmol) was injected s.c. into mice, the growth of sarcoma 180 was inhibited.*[56]

Inhibition of Tumor Promotion

Dermal

Ascorbyl Palmitate

The effect of Ascorbyl Palmitate (in acetone vehicle) on the induction of epidermal ornithine decarboxylase (ODC) activity, epidermal hyperplasia (epidermal thickness), skin edema, and skin tumor promotion by 1,8-dihydroxy-3-methyl-9-anthrone (chrysarobin, an anthrone tumor promoter) was tested using female SENCAR mice.[57] Many cellular and biochemical changes have been associated with tumor promoters and the process of tumor promotion, such as sustained hyperplasia and the induction of ODC activity. For the analysis of edema and hyperplasia, groups of 4 mice were treated for 4 weeks (once weekly) with acetone, chrysarobin, or chrysarobin plus Ascorbyl Palmitate (4 µmol). After the final treatment with chrysarobin, the mice were killed at 24 h to measure edema, or, at 48 h for histological analysis of hyperplasia. Ascorbyl Palmitate (4 µmol) inhibited (24% inhibition; $p < 0.05$) the induction of edema by chrysarobin (220 nmol). This dose of Ascorbyl Palmitate (4 µmol) also inhibited (26% inhibition; $p < 0.05$) the induction of epidermal hyperplasia by chrysarobin (220 nmol).

In the tumor induction experiment, groups of 30 mice were initiated with dimethylbenzanthracene (DMBA) (25 nmol) and, 2 weeks later, received once weekly treatments of chrysarobin (220 nmol). Ascorbyl Palmitate (0.2 ml in acetone; 1 µmol or 4 µmol doses) was applied to a shaved area of the back 5 minutes before the application of chrysarobin. The number and incidence of papillomas were recorded weekly. Promotion was continued until the average number of papillomas per mouse reached a plateau in all groups. Ascorbyl Palmitate inhibited chrysarobin-induced tumor promotion at 1 µmol and 4 µmol, but the researchers noted that there was no clear dose-response relationship. At 27 weeks of promotion with chrysarobin (220 nmol per mouse), 1 µmol and 4 µmol Ascorbyl Palmitate reduced the average number of papillomas per mouse by 48% and 44%, respectively. Additionally, the number of papillomas per mouse in both groups receiving Ascorbyl Palmitate was significantly lower ($p <0.01$) than the tumor response in the group that was promoted with chrysarobin alone.[57]

Ascorbyl Palmitate was applied topically according to the procedure in the tumor induction experiment (ODC assay). At 60 h after chrysarobin application, mice were killed by cervical dislocation and the dorsal skin was surgically removed. Epidermal scrapings from groups of four mice were pooled, homogenized, and centrifuged. ODC activity in the soluble supernatant was determined by measuring the release of $^{14}CO_2$ from L-(l-^{14}C) ornithine hydrochloride. When applied 5 minutes prior to treatment with chrysarobin (220 nmol), 1 µmol and 4 µmol Ascorbyl Palmitate inhibited the induction of ODC activity by 28% and 59%, respectively. Lower doses of Ascorbyl Palmitate (0.4 µmol) had little or no effect on chrysarobin-induced ODC activity.[57]

The authors concluded that Ascorbyl Palmitate inhibited ODC activity, edema, epidermal hyperplasia, and skin tumor promotion induced by chrysarobin in this study.[57]

Ascorbyl Stearate

Human glioblastomas (gliomas) are characterized as highly invasive and rapidly growing brain tumors.[58] A study was performed to determine the *in vitro* effect of Ascorbyl Stearate on cell proliferation, transformation, apoptosis and modulation of expression of insulin-like growth factor-I receptor (IGF-IR) in human glioblastoma multiforme (T98G) cells. Ascorbyl Stearate showed significant inhibition of fetal bovine serum and human recombinant insulin-like growth factor-I (IGF-I)-dependent cell proliferation in a dose-dependent manner. Treatment of T98G cells with 50, 100 and 150 µM Ascorbyl Stearate for 24 h slowed down the cell multiplication cycle, with significant accumulation of cells at the late S/G2-M phase of the cycle. Ascorbyl Stearate treatment (100 µM) reversed the transformed phenotype, as determined by clonogenicity in soft agar, and also induced apoptosis of T98G cells. These changes were said to have been associated with a significant decrease in IGF-IR expression in a dose- and time-dependent manner when compared to untreated controls. These data clearly demonstrated that Ascorbyl Stearate had antiproliferative and apoptotic effects on T98G cells, probably through modulation of IGF-IR expression and the facilitation of programmed cell death.

Pancreatic cancer is an aggressive tumor with short median survival, and is associated with a high mortality rate.[59] A study was performed to evaluate the effects of Ascorbyl Stearate on pancreatic cancer. The treatment of human pancreatic carcinoma cells with Ascorbyl Stearate (50–200 µM) resulted in a dose-dependent inhibition of cell proliferation. Ascorbyl Stearate slowed down the cell cycle, accumulating human pancreatic carcinoma epithelial-like cells (PANC-1 cells) in late G2-M phase. Furthermore, Ascorbyl Stearate treatment (150 µM) markedly inhibited growth in soft agar and facilitated apoptosis of PANC-1 cells, but not human pancreatic ductal adenocarcinoma cells (Capan-2 cells). These effects were accompanied by a significant reduction in insulin-like growth factor 1 receptor (IGF1-R) expression, when compared to untreated controls. Capan-2 cells, the least responsive to Ascorbyl Stearate treatment, did not overexpress the IGF1-R. These results demonstrated the efficacy of Ascorbyl Stearate in inhibiting the growth of pancreatic cancer cells.

The effect of Ascorbyl Stearate (25 to 150 µM) on human ovarian epithelial cancer cells (OVCAR-3 cells) was studied.[60] Treatment with Ascorbyl Stearate caused a dose-dependent inhibition of cell proliferation. The antiproliferative effect was due to the arrest of cells in the S/G2-M-phase of the cell cycle. Treatment of OVCAR-3 cells with Ascorbyl Stearate also inhibited phosphatidylinositol-3-kinase and protein kinase B (PI3K/AKT) activity. The presence of a constitutively active AKT protected OVCAR-3 cells from the effects of Ascorbyl Stearate, suggesting that this ester targets the PI3K/AKT pathway. The administration of Ascorbyl Stearate by gavage induced involution of human ovarian carcinoma xenografts in nude mice. These studies indicate that the antiproliferative effect of Ascorbyl Stearate on ovarian epithelial cancer cells is associated with decreased PI3K/AKT activity, and point toward the PI3K/AKT signaling pathway as a target for this drug. Data from another study indicated that the anti-proliferative activity of Ascorbyl Stearate on ovarian cancer cells was due in part to G2/M (G2/M phase of the cell cycle) arrest modulated by means of a tumor protein p53-dependent pathway.[61]

OTHER RELEVANT STUDIES

Promotion of Lipid Peroxidation

Ascorbyl Palmitate

A study was performed to determine the antioxidative properties of Ascorbyl Palmitate using human keratinocyte cultures.[62] The fatty acid analog *cis*-parinaric acid (cPA) was used to quantify lipid peroxidation. This fluorescent fatty acid analog integrates into membranes, where it is readily oxidized because of its extensive unsaturation. As oxidized cPA loses fluorescence, relative levels of lipid peroxidation can be determined. Keratinocytes treated with 10 to 100 µM Ascorbyl Palmitate prior to UVB irradiation showed increased loss of fluorescence. At the 100 mM dose, there was significant loss of cPA fluorescence, versus UVB-irradiated cells not exposed to Ascorbyl Palmitate ($p < 0.05$), with little residual fluorescence detectable. UVB-induced increases in lipid peroxidation in the absence of Ascorbyl Palmitate were readily detected ($p < 0.05$ versus nonirradiated cells). Cells pretreated with 100 or 300 mM Ascorbyl Palmitate for 30 minutes prior to irradiation showed dose-dependent increases in mean fluorescence values. At the 300 mM dose, Ascorbyl Palmitate pretreatment resulted in significant increases in lipid peroxidation when compared to UVB irradiation only (no Ascorbyl Palmitate).

Levels of reactive oxygen species were determined using the fluorescent probe dihydrorhodamine (DHR). Keratinocytes were loaded with DHR, pretreated with 1 to 25 µM Ascorbyl Palmitate, and exposed to UVB. Ascorbyl Palmitate effectively inhibited DHR oxidation in a dose-dependent manner, indicating its antioxidant potential. Thus, the authors noted that Ascorbyl Palmitate reduced cellular levels of reactive oxygen species after UVB irradiation.[62]

Furthermore, the treatment of keratinocytes with Ascorbyl Palmitate inhibited UVB-mediated activation of epidermal growth factor receptor, extracellular regulated kinases 1 and 2, and p38 kinase because of its ability to prevent reduced glutathione depletion and scavenge hydrogen peroxide. However, Ascorbyl Palmitate strongly promoted UVB-

induced lipid peroxidation, c-Jun *N*-terminal kinase activation, and cytotoxicity. The authors noted that the lipid component of Ascorbyl Palmitate probably contributes to the generation of oxidized lipid metabolites that are toxic to epidermal cells. They also noted that the data in this study suggest that, despite its antioxidant properties, Ascorbyl Palmitate may intensify skin damage following physiologic doses of UV radiation.[62]

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation

Animal

Ascorbyl Dipalmitate

The skin irritation potential of Ascorbyl Dipalmitate (10% aqueous) was evaluated in a modified Draize test using occlusive patches that were applied for 24 h. The test substance was non-irritating to intact skin of rabbits.[8]

Ascorbyl Palmitate

The skin irritation potential of Ascorbyl Palmitate (10% aqueous) was evaluated in a modified Draize test using occlusive patches that were applied for 24 h. The test substance was non-irritating to intact skin of rabbits.[8]

Ascorbyl Tetraisopalmitate

The skin irritation potential of an Ascorbyl Tetraisopalmitate trade name material was evaluated according to OECD Guideline 404 using 3 New Zealand white rabbits.[48] The test substance (0.5 ml, no vehicle) was applied for 4 h, under a semiocclusive patch, to a 10 x 15 cm^2 area of skin on one flank. Following application, the animals were observed for up to 72 h. Any evidence of skin irritation (reactions not specified) was fully reversible within 2 days. Effects other than irritation were not observed. The test substance was classified as a non-irritant (primary irritation index (PII) = 0.3, classified as negligibly irritating).

Sensitization

Animal

Ascorbyl Tetraisopalmitate

The guinea pig maximization test was used to evaluate the skin sensitization potential of an Ascorbyl Tetraisopalmitate trade name material.[48] The test substance (undiluted) was applied to 10 guinea pigs during induction (epidermal application and intradermal injection) and the challenge phase (epidermal application). Five guinea pigs served as negative controls (substance applied not stated). Following intradermal injection (0.1 ml into scapular region), reactions were assessed 24 h and 48 h later. For the epidermal application, a 2 x 3 cm non-woven patch containing 0.5 ml of the test substance, secured with an elastic bandage, was applied for 24 h to the flank. Again, reactions were assessed at 24 h and 48 h post-administration. There was no evidence of irritation during the induction phase. Skin sensitization was observed in 8 of 10 animals, but not in any of the 5 negative control animals. Scaling (at application site) was observed in one animal. The skin sensitization rate was 80%, and the test substance was considered to have strong sensitization properties.

Human

Ascorbyl Dipalmitate

In another study, the skin sensitization potential of a face powder containing 20% Ascorbyl Dipalmitate (tested at a concentration of 30%; therefore, effective concentration = 6%) was evaluated in the maximization assay using 25 healthy male and female adult volunteers.[63] Patches were applied to the upper outer arm, volar forearm, or the back of each subject. During induction, 0.25% aqueous sodium lauryl sulfate (SLS, 0.1 ml) was applied under an occlusive patch (15 mm disk) for 24 h. After patch removal, the test substance (0.1 ml) was applied to the same site and the site was covered with an occlusive patch for 48 h or 72 h (72 h, when placed over a weekend). This sequence was repeated for a total of 5 induction applications. The challenge phase was initiated after a 10-day non-treatment period. A single 48-h challenge application (occlusive patch) of the test substance was made to a new site on the opposite arm, forearm, or side of the back. The challenge application was preceded (1 h before challenge patch application) by 1 h of pretreatment with 5% aqueous SLS (0.1 ml) under an occlusive patch. Challenge reactions, if observed, were scored at 1 h and 24 h post-removal of the patch. There were no instances of contact allergy either at 48 h or 72 h after challenge patch application in any of the 25 subjects tested. It was concluded that the face powder did not possess detectable contact sensitivity potential.[63]

Ascorbyl Palmitate

The skin sensitization potential of Ascorbyl Palmitate (0.2% in eye cream) was evaluated in the maximization test using 26 male and female subjects. The test substance (0.1 ml) was applied for 48 h to the arm, forearm, or back under occlusive patches during induction (5 applications total). Challenge reactions at a new site were scored at 48 h and 72 h. There were no adverse reactions or signs of sensitization.[64] In another study, the skin sensitization potential of Ascorbyl Palmitate (1%, 3%, and 5% in petrolatum) was evaluated in a modified Draize assay using 106 subjects.[65] Ten induction applications under occlusive patches (in Finn chamber) were made to the scapular back. A challenge patch was applied for 48 h to new site. Reactions were scored at 96 h. Seven 1+ reactions (at 1% concentration) were observed in one subject and five 1+ reactions (at 5% concentration) were observed in one subject. There were no reactions to the 3% concentration. Ascorbyl Palmitate was classified as non-sensitizing at concentrations of 1% to 5%.

Ascorbyl Tetraisopalmitate

The skin irritation and sensitization potential of an Ascorbyl Tetraisopalmitate trade name material was evaluated in a human repeated insult patch test involving 102 male and female subjects.[66] A 2 x 2 cm occlusive patch containing 0.2 ml or 2 g of the test substance (diluted to 10% in silicone) was applied for 24 h to the infrascapular region of the back (to the right orleft of the midline). The procedure was repeated for a total of 9 consecutive 24-h applications. Applications were made on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. Reactions were scored approximately 24 h after patch removal. The challenge phase was initiated following a 10- to 14-day non-treatment period. A challenge patch containing the same amount of the test substance was applied to a previously untreated site. Reactions were scored at 24 h and 48 h post-application. There was no evidence of adverse reactions during the course of the study. The Ascorbyl Tetraisopalmitate trade name material (10% dilution in silicone) was classified as a non-irritant and non-sensitizer.

Phototoxicity

Animal

Ascorbic Acid

Ascorbic Acid (10%) was applied topically to pigs.[67] Treated skin was protected from UVB damage (as measured by erythema and sunburn cell formation) and UVA-mediated phototoxic reactions. The number of sunburn cells reduced by 42% when compared to controls (20% propylene glycol (v/v) with 0.5% hydroxypropylcellulose).

OCULAR IRRITATION STUDIES

Animal

Ascorbyl Dipalmitate

The ocular irritation potential of Ascorbyl Dipalmitate (10% aqueous) was evaluated in a modified Draize test. The test substance was instilled (0.1 ml) into the conjunctival sac. Ocular irritation was not observed.[8]

Ascorbyl Palmitate

The ocular irritation potential of undiluted Ascorbyl Palmitate was evaluated in a modified Draize test. The test substance was instilled (0.1 ml) into the conjunctival sac. The test substance was minimally irritating.[8]

CLINICAL STUDIES

Case Reports

Ascorbyl Tetraisopalmitate

A 54-year-old non-atopic woman presented with a skin reaction 2 days after the initial application of an anti-aging skin care product.[68] The reaction began on the face, and spread to the arms and pre-sternum. Patch testing of the product and ingredients from various test series was performed using patch test chambers, and reactions were scored according to the guidelines of the International Contact Dermatitis Research Group (ICDRG) on days 2, 4, and 7. The patient had positive patch test reactions to methylchloroisothiazolinone (100 ppm), thiomersal, and the product. The results of a repeated open

application test (ROAT) with the product became positive after 3 days. Patch testing with the ingredients of the product revealed a strong positive reaction to Ascorbyl Tetraisopalmitate (20% in liquid paraffin); negative results were reported for the 20 control subjects patch tested with this ingredient.

An 83-year-old man was treated for atopic dermatitis with a non-steroidal over-the-counter (OTC) moisturizer that contained Ascorbyl Tetraisopalmitate.[69] Acute contact dermatitis that spread rapidly to the limbs and trunk was observed on application day 14. Patch tests (chambers) were performed according to ICDRG guidelines; reactions were scored on days 2 and 4. Patch test results for Ascorbyl Tetraisopalmitate (0.05%; dose/cm^2 not stated) were positive (++ reaction) on day 4. The patient refused any additional investigation.

Other Clinical Reports

Tetrahexyldecyl Ascorbate

In a double-blind manner, a newly formulated vitamin C complex containing 10% ascorbic acid (water soluble) and 7% Tetrahexyldecyl Ascorbate (lipid soluble) in an anhydrous polysilicone gel base was applied to one-half of the face of 10 subjects. Polysilicone gel base was applied to the opposite side.[70] Clinical evaluation for inflammation was performed prior to the study and at weeks 4, 8, and 12. Biopsies of both sides of the face, sampling a treated area as well as a control area, were performed at week 12 in four patients. Inflammation of the skin was assessed as present or absent, and the presence or absence of an inflammatory infiltrate in biopsy specimens was evaluated as well. No patients were found to have either clinical or histologic evidence of inflammation on either side of the face. The average epidermal thickness of the treatment side was 51.8 µm, while that of the gel-base side was 48.1 µm. The Grenz zone collagen measurements averaged 52.5 µm on the treatment side and 35.5 µm on the gel-base side, indicating new collagen formation. One patient showed no difference in epidermal thickness between the treatment and gel-base sides, while three patients showed an increase on the treatment side.

A clinical trial on a moisturizer was conducted using 37 female subjects.[71] The composition of the moisturizer was as follows: *Astragalus membranaceus* root extract, a peptide blend including palmitoyl tripeptide-38, standardized rosemary leaf extract (ursolic acid), ubiquinone (coenzyme Q10), and Tetrahexyldecyl Ascorbate. The subjects were instructed to apply the moisturizer twice per day, and were evaluated at baseline and after 4, 8, and 12 weeks of product use. A vehicle control was not used in the study. Digital photography was used to document changes in appearance. At weeks 8 and 12, statistically significant ($p < 0.001$) improvement in the following parameters was reported: fine lines, wrinkles, clarity/brightness, visual roughness, tactile roughness, evenness of skin tone (redness), evenness of skin tone (hyperpigmentation), and overall appearance. Levels of improvement for the parameters evaluated ranged from 89% to 100%, with most of the improvement in the 97% to 100% range. The moisturizer was well-tolerated by the panelists, i.e., there was no statistically significant increase in scores for tolerability parameters at all time points, when compared to baseline scores. Details relating to the tolerability parameters evaluated were not included.

A single-center study was performed to assess the efficacy and tolerance of a dual-product regimen containing a 0.5% retinol treatment and an anti-aging moisturizer containing 30% Tetrahexadecyl Ascorbate.[72] In addition to encapsulated retinol, the 0.5% retinol treatment contained bakuchiol and *Ophiopogon japonicas* root extract. In addition to 30% Tetrahexyldecyl Ascorbate, the anti-aging moisturizer also contained vitamin E and coenzyme Q10. The dual-product regimen was used over a 12-week period by 44 women who had mild-to-moderate facial hyperpigmentation and photodamage. At the baseline visit, the subjects were instructed to apply the anti-aging moisturizer to the entire face once per day in the morning after cleansing. For the first 2 weeks of the study, the subjects were instructed to apply the 0.5% retinol treatment to the entire face every other evening. After the 2-week period, the subjects were instructed to apply the retinol treatment every evening. Tolerability parameters were assessed, at baseline and weeks 4, 8, and 12, and included: erythema, dryness, scaling, burning, stinging, and itching. Use of the dual-product regimen resulted in a statistically significant increase (worsening) in clinical grading scores for dryness on the face at weeks 4 (15% of the subjects) and 8 (13% of the subjects) when compared to baseline scores. However, this change did not persist to the week 12 time point. No statistically significant changes from baseline were detected for the following at weeks 4, 8, and 12: erythema, scaling, burning, stinging, or itching.

Tetraisopalmitoyl Ascorbic Acid

A clinical test was performed to clarify the effect of a tetraisopalmitoyl ascorbic acid cream on UVB-induced skin pigmentation.[73] This study is included because the name tetraisopalmitoyl ascorbic acid is similar to 2 of the synonyms for the cosmetic ingredient Tetrahexyldecyl Ascorbate (other names: vitamin C tetra-isopalmitate and vitamin C-isopalmityl tetraester) that is being reviewed in this safety assessment. Twenty-two males and females with characteristic Japanese photo-skin type II or III were enrolled in the study. The inner side of the upper arm was used for testing as the site of sun-protected skin. The subjects were exposed to 1.5 minimal erythema dose (MED) of solar-simulated light. Following exposure, a cream containing 3% Tetraisopalmitoyl Ascorbic Acid or vehicle only (oil-in-water type cream) was topically

applied to the UV-irradiated area immediately after irradiation. After 1, 2 and 3 weeks, intensities of pigmentation were evaluated with L* value (parameter for lightness of skin; measured with chromameter) measurement. Based on visual scoring, statistically significant differences between vehicle-treated areas and Tetraisopalmitoyl Ascorbic Acid-treated areas were reported 1 week after UVB irradiation ($p < 0.05$). ΔL*-values (L* of each week - L* before UV-irradiation) of Tetraisopalmitoyl Ascorbic Acid-treated areas were significantly lower than those of vehicle-treated areas at 1 week and at 2 weeks after UVB irradiation ($p < 0.05$). It was concluded that the topical application of a 3% Tetraisopalmitoyl Ascorbic Acid cream suppressed pigmentation after UVB irradiation.

Ascorbyl Palmitate

Ascorbyl Palmitate was applied to the skin, damaged by ultraviolet radiation, of 5 subjects.[74] In the first experiment, areas of the skin (forearm) were either left unprotected or had been treated topically with 3% Ascorbyl Palmitate (in a lecithin gel base) prior to UVB exposure (1 to 3 times the MED). When compared to untreated skin, either the absence of erythema or decreased erythema was observed after pretreatment with 3% Ascorbyl Palmitate before UVB exposure. In the second experiment, erythema was produced by UVB exposure in the range of 1 to 2 times the MED and the skin was treated topically with a 5% Ascorbyl Palmitate lotion 3 h later. When compared to untreated skin, the UVB-induced erythema resolved approximately 50% sooner in skin treated with the lotion.

SUMMARY

The safety of the following 7 ingredients, i.e., alkylated or acylated derivatives of ascorbic acid, in cosmetics is being evaluated in this safety assessment: Tetrahexyldecyl Ascorbate, Ascorbyl Isostearate, Ascorbyl Linoleate, Ascorbyl Tetraisostearate, Ascorbyl Palmitate, Ascorbyl Dipalmitate, and Ascorbyl Stearate. The reported functions of these ingredients in cosmetic products include: antioxidants; skin-conditioning agents; skin protectants; fragrance ingredients; and skin bleaching agents. Ascorbyl Palmitate is the only ingredient with an additional function of fragrance ingredient, and Ascorbyl Linoleate is the only ingredient with an additional function of skin bleaching agent; however, functioning as a skin bleaching agent is not a cosmetic use and, therefore, the Panel did not evaluate safety for that use.

According to 2017 VCRP data, the greatest reported use frequency is for Ascorbyl Palmitate (2557 formulations, mostly in leave-on products), followed by Tetrahexyldecyl Ascorbate (536 formulations, mostly leave-on products). The results of a concentration of use survey provided in 2016 indicate that Ascorbyl Dipalmitate has the highest maximum concentration of use; it is used at concentrations up to 20% in leave-on products (face powders). The maximum concentration of use in rinse-off products is being reported for Tetrahexyldecyl Ascorbate (concentrations up to 2.5% in shaving cream).

Skin penetration data from *in vitro* studies indicated that Ascorbyl Palmitate was delivered mainly to the epidermis, but was not found in the receptor fluid. Ascorbic acid levels in pig skin were not significantly increased after Ascorbyl Palmitate was applied to skin positioned in a semi-occlusive chamber. In an *in vivo* percutaneous absorption study involving rabbits, 6 different oil-in-water cream bases containing 4% Ascorbyl Dipalmitate were applied to the skin. The concentration of ascorbic acid in the urine varied depending on the characteristics of the cream bases that were tested.

Ascorbyl Palmitate (10 mg in ethyl alcohol) penetrated into the epidermis after dermal application to human subjects. When the absorption of Ascorbyl Tetraisopalmitate through human skin was simulated using stratum corneum and infundibulum membrane models, the Ascorbyl Tetraisopalmitate molecule was found to have more affinity toward the stratum corneum than toward the infundibulum.

In a skin penetration enhancement study, the amount of ibuprofen that penetrated the skin after 20 h was dependent upon the vehicle that was used. Values for ibuprofen in isopropanol and Ascorbyl Palmitate vehicles were 2.10 ± 0.25 mg/cm^2 and 0.47 ± 0.05 mg/cm^2, respectively.

Ascorbic acid was detected in the urine of guinea pigs at 24 h after oral dosing with Ascorbyl Palmitate or Ascorbyl Dipalmitate. Ascorbyl Palmitate resisted hydrolysis in the brain of rabbits after injection into the internal carotid artery. It penetrated the blood brain barrier and was retained principally in brain tissue as an intact molecule.

An acute oral LD_{50} of > 2000 mg/kg was reported in a study involving rats. There were no clinical signs of toxicity, and none of the animals died. Using in silico methodology, Ascorbyl Palmitate and Ascorbyl Stearate were predicted to be moderately toxic and slightly toxic compounds, respectively.

Using in silico methodology, the NOEL for long-term toxicity was calculated to be 916 mg/kg/day for Ascorbyl Palmitate and 834 mg/kg/day for Ascorbyl Stearate.

Ascorbyl Palmitate and Ascorbyl Stearate were not predicted to be reproductive toxicants using in silico methodology.

Ascorbyl Tetraisopalmitate was non-genotoxic in the Ames test, with and without metabolic activation. Using in silico methodology, Ascorbyl Palmitate was predicted to be a genotoxic compound, whereas Ascorbyl Stearate was not predicted to be a genotoxic compound.

Ascorbyl Palmitate (1 µmol and 4 µmol) inhibited chrysarobin-induced tumor promotion in female SENCAR mice, but the authors noted that there was no good dose-related effect. At concentrations of 1 µmol and 4 µmol, Ascorbyl Palmitate reduced the average number of papillomas per mouse by 48% and 44%, respectively. Furthermore, the number of papillomas per mouse in both groups of 30 mice treated with Ascorbyl Palmitate was significantly lower ($p < 0.01$) than the tumor response in the group that was promoted with chrysarobin alone.

The treatment of HSC-4 cultures with Ascorbyl Palmitate (100 µM) at 37°C yielded a cell survival rate of 86.8 ± 5.7%. At 42°C, cell viability decreased to 42.0 ± 2.1% ($p < 0.0001$). Thus, the carcinostatic activity of Ascorbyl Palmitate was markedly increased with hyperthermia. Ascorbyl Stearate (doses up to 150 µM) had antiproliferative and apoptotic effects on T98G cells, probably through modulation of IGF-IR expression and the facilitation of programmed cell death. The treatment of human pancreatic carcinoma cells with Ascorbyl Stearate (50 - 200 µM) resulted in a dose-dependent inhibition of cell proliferation. Ascorbyl Stearate (25 to 150 µM) also caused a dose-dependent inhibition of cell proliferation in human ovarian epithelial cancer cells.

The pretreatment of human keratinocytes with Ascorbyl Palmitate (300 mM) prior to UVB irradiation resulted in significant increases in lipid peroxidation, when compared to UVB irradiation only. In another experiment in the same study, human keratinocytes were loaded with DHR, pretreated with 1 to 25 µM Ascorbyl Palmitate, and exposed to UVB. Ascorbyl Palmitate effectively inhibited DHR oxidation in a dose-dependent manner, which was indicative of its antioxidant potential. Ascorbyl Palmitate reduced cellular levels of reactive oxygen species after UVB irradiation. Ascorbyl Palmitate also strongly promoted UVB-induced lipid peroxidation, c-Jun N-terminal kinase activation, and cytotoxicity. It was noted that the lipid component of Ascorbyl Palmitate probably contributes to the generation of oxidized lipid metabolites that are toxic to epidermal cells.

An Ascorbyl Tetraisopalmitate trade name material (0.5 ml) was non-irritating to the skin of 3 rabbits. In the maximization test, application of the same material (undiluted) to the skin of 10 guinea pigs resulted in strong sensitization (skin sensitization rate of 80%). In an HRIPT involving 102 subjects, an Ascorbyl Tetraisopalmitate trade name material (10% in silicone) was a non-irritant and non-sensitizer.

The skin sensitization potential of a face powder containing 20% Ascorbyl Dipalmitate (tested at a concentration of 30%; therefore, effective concentration = 6%) was evaluated in the maximization assay using 25 healthy male and female adult volunteers. It was concluded that the face powder did not possess detectable contact sensitivity potential.

In a study involving 5 human subjects, either the absence of erythema or decreased erythema, compared to untreated skin, was observed after pretreatment with 3% Ascorbyl Palmitate before UVB exposure. When the same subjects were exposed to UVB, followed by topical treatment with 5% Ascorbyl Palmitate lotion, the UVB-induced erythema resolved approximately 50% sooner when compared to untreated skin.

When a newly formulated vitamin C complex containing 10% ascorbic acid and 7% Tetrahexyldecyl Ascorbate was applied to the face of 10 patients for 12 weeks, there was neither clinical nor histologic evidence of inflammation; however, there was evidence of new collagen formation. In a clinical trial involving 37 subjects, a moisturizer containing Tetrahexyldecyl Ascorbate (concentration not stated) was said to have been well-tolerated. The moisturizer was applied twice per day for 12 weeks.

A single-center study involving 44 subjects was conducted to assess the efficacy and tolerance of a moisturizer containing 30% Teterahexyldecyl Ascorbate. The product was applied over a 12-week period. No statistically significant changes from baseline were detected for the following tolerability parameters: erythema, scaling, burning, stinging, or itching. A clinical test involving 22 subjects was performed to clarify the effect of a cream containing 3% tetraisopalmitoyl ascorbic acid on UVB-induced skin pigmentation. The cream was applied following UVB irradiation. Pigmentation intensity was evaluated for up to 3 weeks post-application. It was concluded that topical application of the cream after UVB irradiation resulted in the suppression of pigmentation.

DISCUSSION

A study reported that Ascorbyl Palmitate strongly promoted UVB-induced lipid peroxidation in human keratinocyte cultures, and the author suggested that Ascorbyl Palmitate may intensify skin damage by this mechanism following exposures to UV radiation. However, the Panel characterized the results of this study as an artifact of an irrelevant model, and disagreed with the author's interpretation of the results. Furthermore, the results of this study were not consistent with the results of a clinical study in which topical application of Ascorbyl Palmitate prior to UVB exposures resulted in decreased or no erythema (3% Ascorbyl Palmitate cream) or enhanced resolution of UVB-induced erythema (5% Ascorbyl Palmitate cream).

The Panel also reviewed the results of a study in which computational chemistry analyses were conducted to predict the toxicity of some of the esters of ascorbic acid. They agreed that the results of these analyses appeared to be consistent with the safety profile for Ascorbyl Palmitate and Ascorbyl Stearate, although an older methodology was used and few details of the analyses were presented. The Panel found that the information provided was insufficient to explain why the predictions differed for these two ingredients, and determined that the predictions were not very helpful for informing the safety assessment.

The Panel noted the absence of data on developmental and reproductive toxicity, but agreed that pertinent data on ascorbic acid, disaccharides, monosaccharides, mono glycols, and diglycols from prior CIR safety assessments can be used to address these endpoints.

An undiluted Ascorbyl Tetraisopalmitate trade name material was a sensitizer in the guinea pig maximization test. However, the Panel was not concerned about the sensitization potential of the ingredients in this safety assessment, given the negative human skin sensitization data on a 10% dilution of the trade name material and negative results for a face powder tested at a concentration of 6% Ascorbyl Dipalmitate in a human maximization test.

Because the several functions of Ascorbyl Linoleate in cosmetic products include use as a skin bleaching agent, the Panel emphasized that Ascorbyl Linoleate must not have this effect at use concentrations in cosmetic products.

Finally, the Panel discussed the issue of incidental inhalation exposure, as some of the ethers and esters of ascorbic acid are used in cosmetic sprays and could possibly be inhaled. For example, Tetrahexyldecyl Asscorbate is being used in tonics, dressings, and other hair grooming aids (aerosol) at maximum use concentrations up to 0.1%. Additionally, the Panel noted that droplets/particles from spray cosmetic products 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 7 ethers and esters of ascorbic acid are safe in the present practices of use and concentration, as described in this safety assessment:

Tetrahexyldecyl Ascorbate
Ascorbyl Isostearate*
Ascorbyl Linoleate
Ascorbyl Tetraisopalmitate
Ascorbyl Palmitate
Ascorbyl Dipalmitate
Ascorbyl Stearate

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

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.[1] CIR Staff

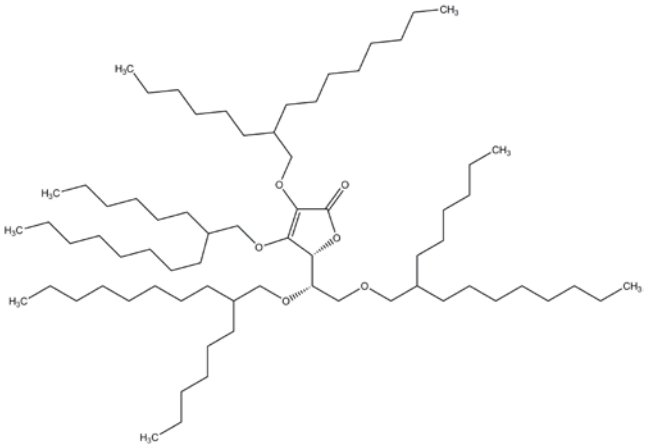
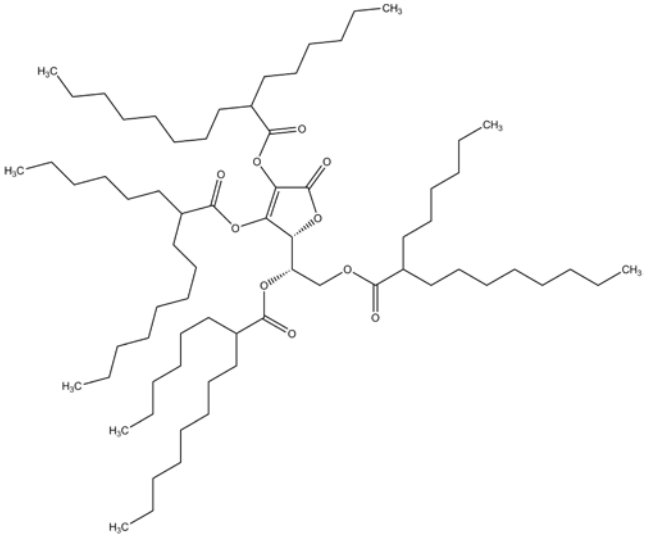
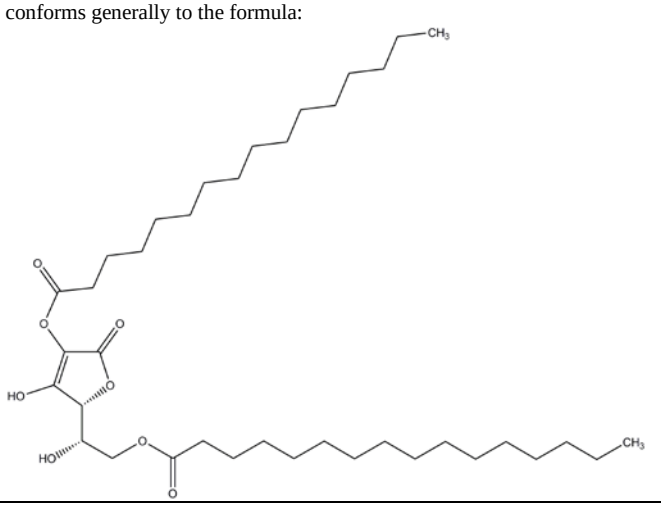
Ingredient CAS No.	Definition & Structure	Function
Tetrahexyldecyl Ascorbate 1445760-15-5	Tetrahexyldecyl Ascorbate is the organic compound that conforms to the formula: 	Antioxidants; Skin-Conditioning Agents - Miscellaneous
Ascorbyl Tetraisopalmitate 161436-56-2 183476-82-6	Ascorbyl Tetraisopalmitate is the tetraester of Ascorbic Acid and isopalmitic acid. It conforms generally to the formula:  one example of an “iso”	Antioxidants; Skin-Conditioning Agents - Emollient
Ascorbyl Dipalmitate 28474-90-0	Ascorbyl Dipalmitate is the diester of Ascorbic Acid and palmitic acid. It conforms generally to the formula: 	Antioxidants

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.[1] CIR Staff

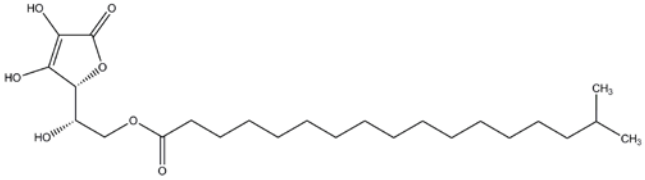
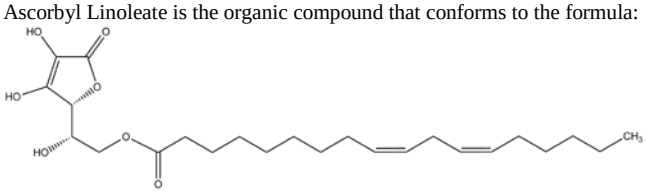
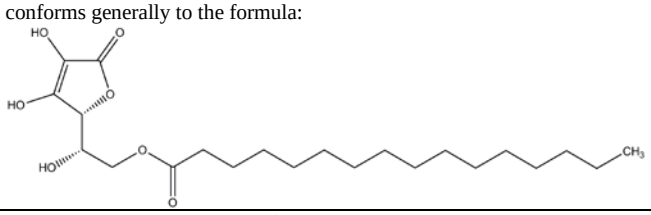
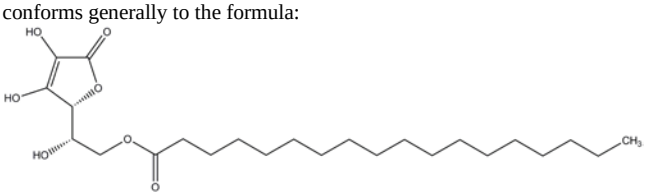
Ingredient CAS No.	Definition & Structure	Function
Ascorbyl Isostearate	Ascorbyl Isostearate is the ester of Ascorbic Acid and isostearic acid. It conforms generally to the formula:  one example of an "iso"	Skin-Conditioning Agents - Miscellaneous
Ascorbyl Linoleate 121869-32-7	Ascorbyl Linoleate is the organic compound that conforms to the formula: 	Antioxidants; Skin Bleaching Agents; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Ascorbyl Palmitate 137-66-6	Ascorbyl Palmitate is the ester of Ascorbic Acid and palmitic acid. It conforms generally to the formula: 	Antioxidants; Fragrance Ingredients
Ascorbyl Stearate 25395-66-8	Ascorbyl Stearate is the ester of Ascorbic Acid and stearic acid. It conforms generally to the formula: 	Antioxidants

Table 2. Properties of Ethers/Esters of Ascorbic Acid

Property	Value	Background Information
	Ascorbyl Tetraisopalmitate	
Form (at 20°C and 1013 hPa)	Liquid.[48]	
Color (at 20°C and 1013 hPa)	Colorless to light yellow.[48]	
Melting Point (°C)	-61 to 60.[48]	
Decomposition (°C)	~ 164.[48]	No boiling was observed below the decomposition temperature.[48]
Density (g/cm^3 at 20°C)	0.94.[48]	
Vapor Pressure (Pa at 20°C)	<0.[48]	
log P_{ow} (at 24°C)	>6.2.[48]	
Water Solubility (at 95°C and pH ~7.5)	<0.09 mg/l.[48]	
	Ascorbyl Palmitate	
Form	White or yellowish-white powder.[2]	Appearance at room temperature.[2]
Molecular Weight	414.54.[2]	
Odor	Citrus-like.[2]	
Solubility	Soluble in alcohol and vegetable oils; slightly soluble in water.[2]	
Melting Point (°C)	107-117°C.[2]	
	Ascorbyl Stearate	
Form	White crystalline powder.[2]	
Melting Point (°C)	115-118°C.[2]	
	Tetrahexyldecyl Ascorbate	
Form	Clear, colorless liquid.[75]	Thermally stable, without change from colorless.
Density (g/cm^3)	0.93.[75]	
Viscosity (cPs, at 20°C)	280.[75]	
Solubility	Almost soluble in oily materials.[75]	

Table 3. Frequency and Concentration of Use According to Duration and Type of Exposure.[13,14]

	Tetrahexyldecyl Ascorbate		Ascorbyl Linoleate		Ascorbyl Tetraisopalmitate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	536	0.000000006-3	3	NR	151	0.00001-4
Duration of Use						
Leave-On	485	0.000000006-3	3	NR	136	0.00001-4
Rinse off	51	0.001-2.5	NR	NR	15	0.0008-0.05
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	46	0.01-1.5	NR	NR	8	0.001-0.04
Incidental Ingestion	140	0.01-1	NR	NR	11	NR
Incidental Inhalation- Sprays	6	0.000000006-0.1	NR	NR	NR	NR
Incidental Inhalation- Powders	16	0.01-0.1	NR	NR	NR	0.05
Dermal Contact	380	0.001-3	3	NR	141	0.00001-4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	10	0.000000006-0.1	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.1	NR	NR	NR	0.2
Mucous Membrane	152	0.01-1	NR	NR	11	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Ascorbyl Dipalmitate		**Ascorbyl Palmitate**		**Ascorbyl Stearate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	6	0.000000002-20	2557	0.000001-2	10	0.09-0.1
Duration of Use						
Leave-On	6	0.0000002-20	2361	0.000001-2	10	0.09-0.1
Rinse off	NR	0.000000002-000002	196	0.000001-2	NR	NR
Diluted for (bath) Use	NR	NR	10	0.00009-0.027	NR	NR
Exposure Type						
Eye Area	NR	0.0000002-0.1	791	0.000028-0.4	NR	NR
Incidental Ingestion	NR	0.02-0.1	510	0.00091-0.52	10	0.09
Incidental Inhalation- Sprays	NR	0.0000018-0.0000020	12	0.02-0.01	NR	NR
Incidental Inhalation- Possible Sprays	NR	NR	NR	0.00001-2*	NR	NR
Incidental Inhalation- Powders	NR	0.1-20	132	0.0075-0.1	NR	NR
Incidemntal Inhalation- Possible Powders	NR	NR	NR	0.00001-2*	NR	NR
Dermal Contact	6	0.000000002-20	1786	0.000001-2	NR	0.09-0.1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.0000002-0.1	62	0.000001-0.05	NR	NR
Hair-Coloring	NR	0.00000018-0.000002	11	0.000002-0.001	NR	NR
Nail	NR	0.0000002-0.000002	20	0.00001-0.05	NR	NR
Mucous Membrane	NR	0.02-0.1	531	0.00009-0.52	10	0.09
Baby Products	NR	NR	9	0.00009-0.01	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Use Product Uses

*Not specified whether a powder or spray, so this information is captured for both categories of incidental inhalation.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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2017 FDA VCRP Data

Tetrahexyldecyl Ascorbate

03B - Eyeliner	1
03C - Eye Shadow	6
03D - Eye Lotion	25
03F - Mascara	6
03G - Other Eye Makeup Preparations	8
04E - Other Fragrance Preparation	4
05A - Hair Conditioner	1
05B - Hair Spray (aerosol fixatives)	2
05F - Shampoos (non-coloring)	5
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
07A - Blushers (all types)	8
07B - Face Powders	16
07C - Foundations	53
07D - Leg and Body Paints	1
07E - Lipstick	140
07F - Makeup Bases	8
07I - Other Makeup Preparations	12
10A - Bath Soaps and Detergents	9
10E - Other Personal Cleanliness Products	7
11G - Other Shaving Preparation Products	1
12A - Cleansing	20
12C - Face and Neck (exc shave)	72
12D - Body and Hand (exc shave)	21
12F - Moisturizing	52
12G - Night	19
12H - Paste Masks (mud packs)	8
12I - Skin Fresheners	5
12J - Other Skin Care Preps	14
13A - Suntan Gels, Creams, and Liquids	3
13B - Indoor Tanning Preparations	6
13C - Other Suntan Preparations	1
Total	**536**

Ascorbyl Isostearate (No VCRP data)

Ascorbyl Linoleate

12F - Moisturizing	1
12J - Other Skin Care Preps	1
13B - Indoor Tanning Preparations	1
Total	**3**

Ascorbyl Tetraisopalmitate

03D - Eye Lotion	5
03G - Other Eye Makeup Preparations	3
07C - Foundations	1

07E - Lipstick	11
07F - Makeup Bases	3
07I - Other Makeup Preparations	1
11E - Shaving Cream	1
12A - Cleansing	7
12C - Face and Neck (exc shave)	56
12D - Body and Hand (exc shave)	5
12F - Moisturizing	33
12G - Night	9
12H - Paste Masks (mud packs)	5
12J - Other Skin Care Preps	9
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	1
Total	**151**

Ascorbyl Dipalmitate

07I - Other Makeup Preparations	2
12C - Face and Neck (exc shave)	3
Total	**5**

Ascorbyl Palmitate

01B - Baby Lotions, Oils, Powders, and Creams	1
01C - Other Baby Products	8
02A - Bath Oils, Tablets, and Salts	7
02B - Bubble Baths	7
02D - Other Bath Preparations	6
03A - Eyebrow Pencil	51
03B - Eyeliner	230
03C - Eye Shadow	372
03D - Eye Lotion	32
03F - Mascara	50
03G - Other Eye Makeup Preparations	56
04C - Powders (dusting and talcum, excluding aftershave talc)	4
04E - Other Fragrance Preparation	5
05A - Hair Conditioner	19
05B - Hair Spray (aerosol fixatives)	7
5E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	17
05G - Tonics, Dressings, and Other Hair Grooming Aids	15
05I - Other Hair Preparations	4
06B - Hair Tints	7
06D - Hair Shampoos (coloring)	1
06H - Other Hair Coloring Preparation	4
07A - Blushers (all types)	91
07B - Face Powders	128
07C - Foundations	101

07D - Leg and Body Paints	1
07E - Lipstick	510
07F - Makeup Bases	18
07G - Rouges	2
07H - Makeup Fixatives	3
07I - Other Makeup Preparations	106
08A - Basecoats and Undercoats	2
08B - Cuticle Softeners	5
08C - Nail Creams and Lotions	1
08E - Nail Polish and Enamel	6
08F - Nail Polish and Enamel Removers	1
08G - Other Manicuring Preparations	5
9A - Dentifrices	6
10A - Bath Soaps and Detergents	33
10E - Other Personal Cleanliness Products	21
11A - Aftershave Lotion	10
11E - Shaving Cream	2
12A - Cleansing	35
12C - Face and Neck (exc shave)	116
12D - Body and Hand (exc shave)	73
12F - Moisturizing	224
12G - Night	50
12H - Paste Masks (mud packs)	18
12I - Skin Fresheners	1
12J - Other Skin Care Preps	59
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	18
13C - Other Suntan Preparations	6
Total	**2557**

Ascorbyl Stearate

07E - Lipstick	10
Total	**10**

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 29, 2016

SUBJECT: Draft Report: Safety Assessment of Ethers and Esters of Ascorbic Acid as Used in Cosmetics (draft prepared for the December 5-6, 2016 CIR Expert Panel Meeting)

Genotoxicity - It would be helpful to state whether or not the authors of reference 42 indicated why the predicted genotoxicity potential of Ascorbyl Palmitate (gentoxic prediction) differed from the genotoxicity potential of Ascorbyl Stearate (not genotoxic prediction).

Summary - It would be helpful to note that this Summary only includes new information. The old report needs to be consulted for additional information on Ascorbyl Palmitate, Ascorbyl Dipalmitate and Ascorbyl Stearate.

Reference 8 - Please use a more recent National Formulary than 1995. The 2009 (NF 27) edition is in John Krowka's office.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 9, 2017

SUBJECT: Comments on the Tentative Report: Safety Assessment of Ethers and Esters of Ascorbic Acid as Used in Cosmetics

Key Issue

In the Introduction and the Discussion, it would be helpful to note that the CIR Expert Panel has reviewed the safety of Ascorbic Acid and concluded that it is "safe as used" in cosmetic products (report published in 2005).

Additional Considerations

Introduction - The functions, fragrance ingredients and skin bleaching agents should be deleted from the first sentence describing functions as the rest of the paragraph states the only ingredients with these functions.

Cosmetic Use - Please state the cosmetic product category in which Tetrahexyldexyl Ascorbate is used at concentrations up to 1.5%.

Dermal Penetration, Ascorbyl Palmitate, original report - Please correct "scurv"

Dermal Penetration and Penetration Enhancement - When describing *in vitro* dermal penetration studies, please state the composition of the receptor fluid as it may influence dermal penetration.

Acute, Ascorbyl Palmitate, original report - Please state the effect (decreased body weight) that was observed in rats treated with 2500 mg/kg (as it was a single dose, "/day" should be deleted).

Acute Toxicity, Computational, Ascorbyl Stearate - It is not clear what is meant by "predicted not to be a slightly toxic compound". If it is not slightly toxic, is it non-toxic, or is it toxic?

Chronic, Oral, Ascorbyl Palmitate, original report - The original report does not mention any studies of Ascorbyl Palmitate that used doses greater than 2500 mg/kg/day. Perhaps "≥ 2500 mg/kg/day" should be "≤ 2500 mg/kg/day". Please correct " concentrarion".

Carcinogenicity, Oral, Ascorbyl Palmitate, original report - In what organ were focal areas of dysplasia observed in mice treated with azoxymethanol?

Distributed for comment only -- do not cite or quote

Inhibition of Tumor Promotion, Summary - It is not clear what is meant by "no good dose-related effect." The Summary states: "no clear dose-response relationship".

Dermal Irritation, original report - Please state the species used in the Draize tests of Ascorbyl Dipalmitate and Ascorbyl Palmitate.

Other Clinical Reports, Tetrahexyldecyl Ascorbate - Please delete the word "Inactive" as it suggests that the formulation with the ascorbate compounds was "active", which was not shown by the results of the study. Please correct: "...detected for in the following at weeks..."

Discussion - Although the CIR Expert Panel agreed to keep the computational predictions in the report, they did not consider the study helpful and they did not understand why predictions were different for Ascorbyl Palmitate compared to Ascorbyl Stearate. The Discussion does not reflect the CIR Expert Panel's concerns regarding this study.

Table 2, Tetrahexyldecyl Ascorbate - The units are missing for the Density row.

Table 3 - Please delete "current" from the title of the table as the information will not be "current" when the report is published or when it is read. The reference dates indicate when the information was obtained.