Safety Assessment of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 21, 2020
Panel Date: September 14-15, 2020

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst, CIR

Date: August 21, 2020

Subject: Safety Assessment of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside as Used in Cosmetics

Enclosed is a Draft Final Report on the Safety Assessment of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside as Used in Cosmetics (*ascorb092020rep*). Comments on the Tentative Report that were received from the Council have been addressed, and are also enclosed for the Panel's review (*ascorb092020pcpc*).

At the June 2020 Panel meeting, a Tentative Report with the following conclusion was issued: The Expert Panel for Cosmetic Ingredient Safety concluded that Ascorbyl Glucoside and Sodium Ascorbyl Glucoside* are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

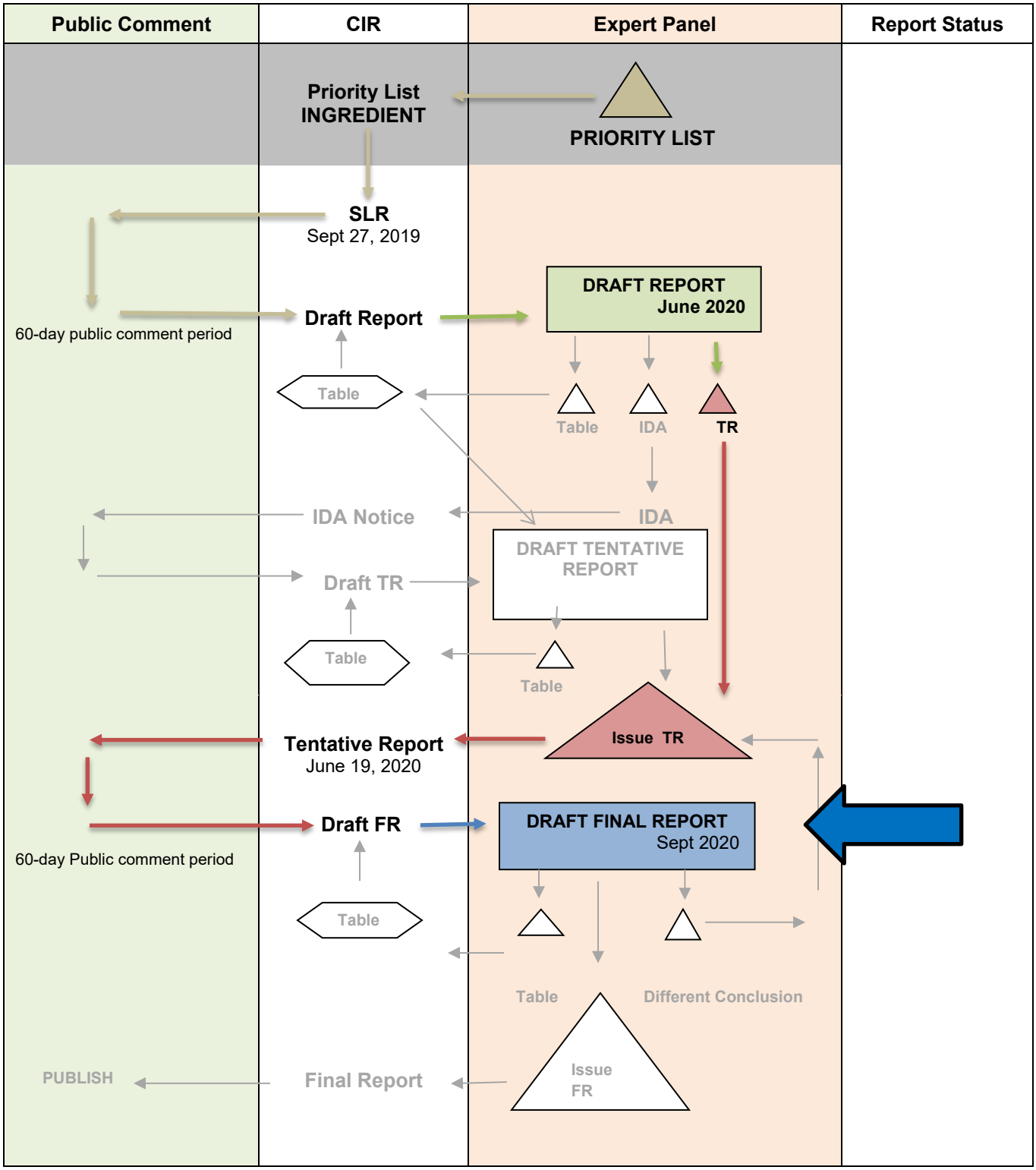
Also included in this package for your review are the report history (*ascorb092020hist*), flow chart (*ascorb092020flow*), literature search strategy (*ascorb092020strat*), ingredient data profile (*ascorb092020prof*), 2020 FDA VCRP data (*ascorb092020FDA*), and transcripts from the June 2020 Panel meetings (*ascorb092020min*).

After reviewing these documents, the Panel should issue a Final Report with the conclusion that is stated in the second paragraph above.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Ascorbyl Glucoside and Sodium Ascorbyl Glucoside

MEETING September 2020



CIR History of:

Ascorbyl Glucoside and Sodium Ascorbyl Glucoside

A Scientific Literature Review (SLR) on Ascorbyl Glucoside and Sodium Ascorbyl Glucoside was issued on September 27, 2019.

Draft Report, Teams/Panel: June 8-9, 2020

The draft report has been revised to include the following unpublished data that were received from the Council:

- HRIPT on a rinse-off product containing 0.1% Ascorbyl Glucoside (diluted prior to testing)
- HRIPT on a leave-on product containing 2% Ascorbyl Glucoside
- HRIPT on a10% solution of Ascorbyl Glucoside (comments on CIR's review of Ascorbyl Glucoside attached)

In addition to the HRIPT data, comments (Nagase Holdings America Corporation, 2019) relating to CIR's review of Ascorbyl Glucoside were received. Comments on the SLR that were received from the Council have been addressed.

The Panel noted the absence of developmental and reproductive toxicity data on Ascorbyl Glucoside and Sodium Ascorbyl Glucoside. However, concern over the lack of these data were mitigated considering that Ascorbyl Glucoside is metabolized to ascorbic acid and glucose in the skin and would not be absorbed in an appreciable quantity. The Panel also noted the potential for skin lightening effects and that skin lightening is considered to be a drug effect, and should not occur during the use of cosmetic products. Furthermore, based on the low current use concentrations in cosmetic products, the results of an in vitro experiment, and clinical experience, concern for this effect in cosmetics was mitigated.

The Panel issued a tentative report with a conclusion stating that Ascorbyl Glucoside and Sodium Ascorbyl Glucoside are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Draft Final Report, Teams/Panel: September 14-15, 2020

Report comments that were received from the Council prior to the June 2020 Panel meeting have been addressed. The same is true for the Council's comments on the tentative report.

Ascorbyl Glucoside and Sodium Ascorbyl Glucoside Data Profile* –September 14-15, 2020 – Wilbur Johnson, Jr.																														
						Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents	Impurities	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Ascorbyl Glucoside	X		X		X	X	X	X	X			X				X	X				X			X	X			X		
Sodium Ascorbyl Glucoside																														

* “X” indicates that data were available in a category for the ingredient

[

Ascorbyl Glucoside – 8/21-22/2019; 9/12/2019;2/4/2020;8/6/2020]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Ascorbyl Glucoside	129499-78-1	Yes		93/25	4/1	No	No	Yes	No	No	No	Yes	No	No	No	No	No	Yes
Sodium Ascorbyl Glucoside		Yes		0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	Yes

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

Qualifiers
Absorption
Acute
Allergy
Allergic
Allergenic
Cancer
Carcinogen
Chronic
Development
Developmental
Excretion
Genotoxic
Irritation
Metabolism
Mutagen
Mutagenic
Penetration
Percutaneous
Pharmacokinetic
Repeated dose
Reproduction
Reproductive
Sensitization
Skin
Subchronic
Teratogen
Teratogenic
Toxic
Toxicity
Toxicokinetic
Toxicology
Tumor

JUNE 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team –June 8, 2020

DR. BELSITO: Okay. Ascorbyl Glucoside. I guess the first question I have to ask, Dan, is are these different from the alkyl glucosides we looked at before; (inaudible)?

DR. LIEBLER: I'm opening this up real quick, Don. They are structurally similar. They're glucosides, just with a different substituent. I mean, ascorbate is the substituent.

DR. BELSITO: Right.

DR. LIEBLER: Does that answer your question? There are a lot of seminaries.

DR. BELSITO: Yeah. I'm just curious why we didn't review them when we reviewed the alkyl glucosides.

DR. LIEBLER: That's a good question. It's not -- I guess chemically speaking it's alkyl -- you know, the bond to the glucoside is an alkyl carbon, but the ascorbate is really distinct from the other alkyl substituents in that report. Nevertheless, from the standpoint of the safety assessment, I think it's more about the glucosides than about the Ascorbyl part. In any case, I don't have concern about this.

DR. BELSITO: Okay.

DR. LIEBLER: If you would throw this ingredient in the other report, I might have paused at least and scratched my head and tried to decide if this really belongs or not.

DR. BELSITO: Okay. The highest leave-on concentration is 5 percent. Do we need DART, or is the ADME we have sufficient? But it's going to basically go to ascorbic acid and glucose.

DR. SNYDER: I think we have some good data there -- that human absorption data to say that it does that. That would help alleviate a lot of (Inaudible).

DR. BELSITO: So basically our systemic profile is not a concern given the metabolisms to vitamin C and glucose.

DR. LIEBLER: Yeah. In fact, I don't even think -- if you're talking about PDF 12 near the bottom, I don't think they actually prove that even ascorbate from this ingredient is absorbed. It's very hard to do this because of the high background level of ascorbate. But it doesn't appear to me that in these data at the bottom of PDF 12 that they really prove absorption through the skin and indirect evidence for ascorbate on the skin. And the problem is the change in the urinary ascorbate we're not sure they derive from the applied material.

And I also would say that it seems to me, just based on the high polarity of the ingredients itself, aside from any hydrolysis, that it's probably unlikely to be absorbed through the epidermis. (Inaudible), excuse me.

DR. SNYDER: Well, that'd be consistent with in vitro that it says it's not absorbed.

DR. LIEBLER: Yeah. I just think this is a tough analytical problem to prove absorption because of the very high background in vivo.

DR. BELSITO: Okay. And here we go again. What is this with all this data on melanin synthesis?

DR. SNYDER: Taiwan.

DR. BELSITO: Yeah. Exactly.

DR. LIEBLER: Same old, same old though -- two millimolar with B16 melanoma cells. Way high.

DR. BELSITO: Okay. Highest leave-on is 5 percent.

DR. SNYDER: Yeah.

MR. JOHNSON: Dr. Belsito, may I call the panel's attention to PDF page 12, at the top.

DR. BELSITO: Sure.

MR. JOHNSON: Yeah. Because there's a statement indicating use of concentrations of 1.89 percent and 2.05 percent in commercial cosmetic bleaching creams in Taiwan.

DR. BELSITO: Right.

DR. LIEBLER: That's our maximum?

MR. JOHNSON: Our maximum is 5 percent in leave-ons.

DR. LIEBLER: Okay. Okay. Oh, I see. Commercial cosmetic bleaching lotion. Do we -- I mean, that doesn't necessarily mean that ascorbyl glucoside bleaches. Do we know what else is in those -- if there's anything else that's possible bleaching ingredient in those commercial cosmetics?

DR. SNYDER: I don't know.

DR. LIEBLER: Yeah. This is not necessarily inconsistent with anything we're saying, and it certainly doesn't provide evidence that we're going to have bleaching at those concentrations or at our highest use concentration. It would be really nice to know what else is in those products that we referred to. We can certainly handle it in the discussion. You know, the panel was aware that commercial bleaching cosmetics sold in Taiwan have comparable levels of ascorbyl glucoside. But the panel is unaware of evidence indicating that this ingredient actually produces bleaching affects at those use concentrations.

DR. BELSITO: Well, the reference is from 2016, and it doesn't even talk about ascorbyl glucoside. It takes about glabridin, bisabolol, and ascorbyl tetraisopalmitate in whitening creams. I don't even know if I can get that reference here -- Columbia's.-- let me see if I can get in on the library. Chromatographia.

DR. LIEBLER: What was the first ingredient you mentioned there in that reference, Don?

DR. BELSITO: Hold on. Glabridin. G-L-A-B-R-I-D-I-N.

DR. LIEBLER: G-L-A-B -- oh, Glabridin. Okay. Oh, Google knows where I'm going. That's a bistonolic compound. So I would be more receptive to the idea that phenolic could product possible bleaching affects. This is actually a -- Glabridin is a meta-substituted phenol. The bisabolol is not a phenol; it's a terpene alcohol. And then the ascorbyl palmitate is not a phenol at all. It is not likely to produce that affect. Ascorbyl palmitate, that is a weak antioxidant.

MR. JOHNSON: I would call the Glabridin. It was one of the components of licorice.

DR. LIEBLER: Interesting.

MR. JOHNSON: Yeah. And I think that it was reported to cause skin depigmentation.

DR. LIEBLER: Yeah. With these phenols, what they can do is basically they have a generic mechanism of action. It would say serve as alternate substrates for tyrosinase and thereby decrease the production of oxidation products of tyrosine, which is the beginning of the melanin biosynthetic pathway. But I don't think -- coming back to this report, I don't see that as a plausible mechanism at all for ascorbyl glucoside.

DR. BELSITO: Let me just see if I can pull up the article. It was Chromatographia? Is that the journal?

MR. JOHNSON: Yes.

DR. BELSITO: I can probably get it. What issue and volume is it?

DR. HELDRETH: 79 and 13-14.

DR. LIEBLER: I can pull it up, Don. I'm logging into the Vanderbilt site for me and --

DR. BELSITO: I've got it now. What are the page numbers on that?

DR. HELDRETH: 851 to 860.

DR. BELSITO: Yeah. Okay. I just got it. Yeah. You're right, Wilbur. Glabridin is an isoflavonoid originally isolated from licorice. Numerous biological properties. And they were specifically looking at Glabridin and bisabolol as depigmenting. Those were the agents of interest.

DR. SNYDER: The reference before that looks at ascorbyl glycoside, kojic acid, and niacinamide in bleaching cosmetics.

DR. BELSITO: And kojic acid is another bleacher.

DR. SNYDER: Yeah.

DR. BELSITO: Honestly, I don't see much about -- maybe that's the wrong word. I see ascorbyl tetraisopalmitate.

DR. SNYDER: I think you might want reference 33 there, Don.

DR. BELSITO: Okay. Which one is that?

DR. SNYDER: That's in Analytica Chimica Acta 2007.

DR. BELSITO: A-N-A-L-Y-T-I-C-A?

DR. SNYDER: Yes.

DR. BELSITO: Anta --

DR. SNYDER: C-H-I-M-I-C-A.

DR. BELSITO: C-H --

DR. SNYDER: I-M-I-C-A.

DR. BELSITO: C-H-I-M-I-C-A.

DR. SNYDER: Acta.

DR. BELSITO: Yeah. I got it. What year?

DR. SNYDER: 2007.

DR. BELSITO: Okay. Just give me the specific volume and issue.

DR. SNYDER: January 2, Volume 581, pages 102 to 107.

DR. BELSITO: 102 to 107?

DR. SNYDER: That's correct.

DR. BELSITO: And it's Volume 581?

DR. SNYDER: January 2nd, 581(1), pages 102 to 107.

DR. BELSITO: It's not -- oh, this is weird. Okay. Well, let me go back to the volume. 581.

DR. SNYDER: (1).

DR. BELSITO: Uh-huh.

DR. SNYDER: Pages 102 to 107.

DR. HELDRETH: I got the abstract here on the screen if you want to see it.

DR. BELSITO: Is this total phenol analysis? No. Let me try -- who are the authors?

DR. LIEBLER: Bart has the abstract up on the screen.

MR. JOHNSON: And I just sent you the publication, Dr. Belsito. Email.

DR. BELSITO: Okay.

DR. LIEBLER: Okay. I think both of these papers -- I just look at the Chromatographia one, which is reference 34. I think that's right. Yeah. 34. And both of these papers are simply analytical method papers that measure these constituents as an example in these products.

DR. SNYDER: Reported to have bleaching affects.

DR. LIEBLER: Right. But they don't measure bleaching affects, per se.

DR. SNYDER: Right. Correct.

DR. LIEBLER: It just measure the molecules. They're just papers -- little one-off papers in analytical journals. They don't really inform our assessment of whether or not ascorbyl glucoside produces any bleaching affect. It's simply present. It's one of the things that they were able to measure in the means of the products .

DR. SNYDER: I think taking the approach Dan presented earlier about the very high concentrations to get in vitro effects on melanogenesis probably is more -- a stronger argument that there's not.

DR. LIEBLER: And with the Korean cosmetic products, this is sort of guilt by association approach. Things labeled as a whitening product or bleaching product and it happens to have this in it, therefore, we have a concern about whether ascorbyl glucoside has bleaching affects, over and above the fact that it doesn't have any of the structural characteristics we typically associate with melanin synthesis inhibitors and the unconvincing in vitro data with ascorbyl glucoside, very high concentrations, and the lack of any corresponding in vivo affect and the fact that this molecule is not really going to be absorbed.

DR. BELSITO: Right. And then on top of that, in this report, it's really kojic acid that you'd expect to be causing the bleaching action.

DR. LIEBLER: Right.

DR. BELSITO: So I would add that as well, Wilbur, as to why we discount this.

MR. JOHNSON: Can you repeat that, Dr. Belsito?

DR. BELSITO: That, as Dan said, there's no structural indications that this should act as a bleaching agent. And on top of that, in this report, the likely agent to cause skin lightening would be kojic acid.

MR. JOHNSON: Okay.

DR. BELSITO: I mean because they're also looking at niacinamide.

DR. LIBELER: Right. Which isn't going to do anything.

DR. BELSITO: Right. I would discount that. But I wouldn't get rid of the reference, but just point out why we think it's not relevant to what we're doing.

DR. LIEBLER: Just to recap, not absorbed, doesn't have the structural features associated with melanin synthesis inhibitors, i.e., phenols.

DR. SNYDER: What about L-ascorbic acid?

DR. LIEBLER: And for context, Paul?

DR. SNYDER: Inhibiting tyrosinase activity.

DR. LIEBLER: No.

MR. JOHNSON: Basically saying that there's no reason to believe that -- at use concentrations that ascorbyl glucoside would cause any depigmentation.

DR. LIEBLER: Correct.

MR. JOHNSON: Okay.

DR. BELSITO: So it's used up to 5 percent. We have HRIPTs with good numbers of patients of 0.1 and 0.2. We do have an HRIPT that was negative at 10 percent, but it was only 51 subjects. Is that an issue for anyone?

DR. LIEBLER: If you're happy, I'm happy.

DR. BELSITO: What do we have from alkyl glucosides? Is that a fair comparison, Dan?

DR. LIEBLER: Well, I take that approach with both ascorbate and alkyl glucosides. If there's no evidence that ascorbate produces any skin depigmentation and there's no evidence that alkyl glucosides produce skin depigmentation, then that's a strong weight-of-evidence argument that could be included against any possibility of skin depigmentation from this.

DR. BELSITO: No, I wasn't talking about depigmentation. I was talking about sensitization.

DR. LIEBLER: I see. Yeah. I don't remember, but I would think alkyl glucosides were pretty clean for skin sensitization. I don't remember specifically.

DR. BELSITO: I just had the CIR up there, and now I lost it. Okay. Alkyl glucoside. We had --

DR. LIEBLER: Safe, nonirritating.

DR. BELSITO: No and formulated to be nonirritating. And maximum leave-on?

DR. LIEBLER: 5 percent.

DR. BELSITO: And then, I don't think -- what's the data we have for irritation with this?

MR. JOHNSON: PDF page 16.

DR. LIEBLER: High concentration, no affect. Half the gram in distilled water.

DR. BELSITO: Okay. Then I'm fine with the 51 having safe as used.

DR. LIEBLER: Yeah.

DR. KLAASEN: Yes.

MR. JOHNSON: And, Dr. Belsito, you want the concerns -- or lack of concerns relating to skin depigmentation included in the discussion section?

DR. BELSITO: Yeah.

MR. JOHNSON: Okay.

DR. LIEBLER: And I did have one other item on this. It's not a big deal, but on PDF page 15 under "Other Relevant Studies, Tumor Promoter Inhibition," this is an in vitro self-transformation assay. So it's not really tumor promotion, even though a tumor promotor was used. It's an in vitro assay, which isn't really promotion. It's transformation. And the test ingredient, ascorbyl glucoside, inhibited that.

I'm not sure what to call that. We might ask Tom Slaga about this tomorrow. I propose changing it to cell-transformation inhibition, but it's not a tumor promotion assay.

MR. JOHNSON: Okay. (Inaudible)?

DR. LIEBLER: No, not really. But it's okay to keep it in if we just change that from tumor promotion to tumor -- sorry, to cell transformation. And I just want to make sure that Tom agrees with that.

MR. JOHNSON: Okay. So cell-transformation or cell-transformation inhibition.

DR. LIEBLER: Yeah. I'd just call it cell-transformation inhibition instead of tumor promotor inhibition.

MR. JOHNSON: Okay. Thank you.

DR. BELSITO: And then later in the discussion also that we weren't concerned about the lack of DART studies given the lack of absorption and the metabolism data that we have. It'll basically go to Vitamin C and glucose.

DR. LIEBLER: Yeah.

MR. JOHNSON: Dr. Belsito, when you say lack of absorption, are you talking about percutaneous absorption?

DR. BELSITO: Yes.

MR. JOHNSON: Okay. Thank you. So Dr. Belsito, so you don't think that it would be metabolized?

DR. BELSITO: Yeah. It is metabolized, and then it's not absorbed.

MR. JOHNSON: Okay.

DR. BELSITO: But it's metabolized to Vitamin C and to glucose.

MR. JOHNSON: Okay. Thank you.

DR. BELSITO: Anything else? Wilbur, you got it?

MR. JOHNSON: Yeah. I have that thought. Thank you.

DR. BELSITO: Okay.

MR. JOHNSON: Save as used.

DR. BELSITO: Yes, safe as used.

Marks Team –June 8, 2020

DR. MARKS: Let me see here. The next ingredient is ascorbyl glucoside, and it's sodium salt. Okay. So there are two ingredients. This is the first review of these ingredients. There were previous reviews of ascorbic acid. Its esters, its ethers, and glucose were all found to be safe.

The function of the ingredients are a bleaching agent, so that to me raised concern, since we're talking about skin lightening and we spent all that time with the last ingredient, the Scutellaria. Is bleaching an issue? And it's actually marketed in Asia, as such -- as a bleaching agent.

So Lisa, Ron, and Tom, the first question is are these two ingredients fine to group together? And I'll start with you, Lisa, now that you're a member of the Grouping/Clustering Committee or subgroup or whatever.

DR. BERGFELD: Work group, it's called. Working Group.

DR. MARKS: Working Group, yeah. And Tom and Ron, I mean, to me, it's pretty straightforward, yes, they are together. But Lisa, you're fine with that?

DR. PETERSON: Yep. Yeah. You get my official okay. And I would not include ascorbate in the report. I just don't think -- I mean you've got the report. You can refer to the report, but I don't think -- I think the skin effects are going to be mostly due to the parent compound, not ascorbate. So I didn't think it needed to be added.

DR. MARKS: Are you addressing Alex's comments from her March 10th memo because she put in her memo --

DR. PETERSON: Yes. Yes, I am.

DR. MARKS: -- should we include ascorbic acid?

DR. PETERSON: I don't think so. I don't think it's --

DR. MARKS: Okay.

DR. PETERSON: I mean, you have that report you can refer to. You know, it sounds like, based on the metabolism, that it is very rapidly hydrolyzed, too. Once it enters the body, it's probably there as ascorbic acid. But I think, from a cosmetic perspective, I would just focus on the parent compounds.

DR. MARKS: Okay. So Wilbur, less issues for you in terms of in the discussions, say, and more work in terms of getting info on ascorbic acid. You don't need to do that. So Lisa, Ron, Tom, your comments, needs? Is there enough to move forward in this? Do we have an insufficient data announcement? Is this safe -- these two ingredients?

DR. SHANK: I think safe as used.

DR. PETERSON: Yeah. I agree with that. My only concern with this skin lightening, especially since it's used up to 5 percent as a leave on, and the information about the skin lightening products indicated that the concentration was about 2 percent. So a lot of the products on the market are actually above that and would be skin lightening. So that was my only concern.

DR. SHANK: Okay. Can we --

DR. MARKS: How would you handle that, Lisa? So would you move onto the safe and then modify? Would you --

DR. PETERSON: No, I felt it needed discussion. I felt that I'd like to hear what the others have to say. It's only -- I did notice that. On one of the pages, there's a description of the concentration in the skin lightening products from Asia, and I just noticed that that concentration was below what the usage in the cosmetics on leave on was up to 5 percent. So I just thought it was worth bringing up for discussion. I don't have experience about how that should be dealt with.

DR. MARKS: So if I heard that correct -- and I think that's going to be very -- in my mind my first reaction, it's difficult. That's why I brought up the issue about the lightening. So in Asia, 2 percent marketed in Asia, and we have use concentrations up to 5 percent on leave ons. To me, that creates a real problem in terms of how do we handle that?

DR. BERGFELD: May I speak? Clinically, ascorbic acid -- and they just converted to ascorbic acid -- does skin lightening, as it has an anti-inflammatory effect. So if you're a red face, it can dampen that. It also builds collagen, such as many of the fruit acids that will do that. It has very active biological behavior. I think we addressed that also with ascorbic acid.

DR. MARKS: In that previous review.

DR. BERGFELD: Yeah.

DR. MARKS: Tom, Ron -- Ron, you made it simple: safe. Can we just deal with the pigmentation in the discussion? But I have some difficulties when it's used in Asia at a concentration less than what we have as our maximum use concentration. And in Asia, it's used for skin lightening, and, of course, we're saying it's safe. So I have a little bit -- I don't know how to handle that in the discussion.

DR. SHANK: I'm looking for the statement in our report where it's used in Asia as a skin lightener. Where is that?

DR. PETERSON: Oh, um.

DR. MARKS: I think that's 10 and 12 is what I have on notes. Let's take a look. 10 or 12, I have two.

MS. FIUME: PDF page 12 on the very top of the page.

DR. MARKS: 12. okay.

DR. SHANK: What page?

DR. PETERSON: 12.

DR. MARKS: 12.

DR. SHANK: 12.

DR. MARKS: And that's where you got the 2 percent, Lisa, huh? Yeah.

DR. PETERSON: Yeah. That's where I got it. And then the table.

DR. SHANK: Well, we have no Keys (phonetic) reports where Ascorbyl Glucoside causes skin pigmentation.

DR. BERGFELD: Also the use concentration is --

DR. SHANK: Could the Asian study be a formulation issue rather than just the ingredient itself because this is fairly widely used?

DR. MARKS: Let me see how many ingredients. It is --

DR. SHANK: 500 products.

DR. MARKS: Yep. 532 products, Ascorbyl Glucoside is used, none for sodium. Yeah. That skin lightening was -- I know, Wilbur, you have in that paragraph right in the beginning on page 12, "Skin bleaching is a drug function, not a cosmetic function, in the U.S." And that's how we started off with the pomegranate. But that's why I was having difficulty reconciling when you say there are no case reports.

It's interesting. Wilma, you can weigh in on this. Clinically, I find it actually very difficult to depigment skin and make a mark lightening, even when we prescribe medicines for that. Usually, it takes a long time. The main condition I prescribe lightening for is Melasma. But I don't know how to reconcile these two concentrations: the 2 percent being marketed in Asia and the 5 percent which we have as a use concentration -- the maximum leave-on use concentration.

DR. BERGFELD: I just know that in the non-prescription physician dispensing ascorbic acid is dispensed in higher values for improving the skin texture, which would include lightening and anti-inflammatory.

DR. MARKS: Hm, I didn't look up -- I should have looked up ascorbic acid. Wilma, did you look up ascorbic acid? Did we deal with the skin lightening with that when we concluded ascorbic acid was safe?

DR. BERGFELD: I did not look it up. Maybe Monice could look it up.

MS. FIUME: I did look it up, and it's not addressed in the discussion of the report.

DR. MARKS: That's not very helpful.

DR. BERGFELD: Were there any tests at all or any mention of it in the body of the --

DR. PETERSON: Actually, in this, page 66 of the report, they say "effects on visual pigment." Would that be --

DR. BERGFELD: Yes, that would be it. That's in the old report. Yeah.

DR. MARKS: Yeah. I find it kind of interesting. So in the cosmetic ingredient handbook where it says its function is skin lightening, that sounds like that's a drug function right off the get-go, not a cosmetic function.

DR. EISENMANN: One thing to note, the dictionary only has one function: skin bleaching agent. They don't have like a skin brightening or a skin lightening function. So anybody could, I mean -- and one of the suppliers claims that it doesn't actually bleach. It's more of a brightening effect. So I don't know how you'd actually draw the line between bleaching and brightening.

MS. KOWCZ: But Carol, skin lightening and skin brightening is a claim that cosmetic companies use. And as Dr. Bergfeld said, the ascorbic acid levels that they use are much higher than what is found in the product that are marketed right now.

DR. MARKS: So Tom, you've been rather quiet. Let's see if your mic works any better. Do you have any -- we need a breakthrough thought of how to deal with this and come to a conclusion?

DR. SLAGA: Well, I suspect we can handle the skin lightening in the discussion like we have before. (Inaudible). As Lisa pointed out, this would be hydrolyzed very quickly into (inaudible) ascorbic acid. (Inaudible). I really don't think that there's the major effect that is related to skin lightening. It would be sensitization.

DR. MARKS: Okay. So Tom, it sounds like you agree with Ron. We move forward with a safe as used --

DR. SLAGA: Safe as used, yeah.

DR. MARKS: -- deal with lightening in the discussion, recognize that it happens but that's a drug function and that we do not expect that would be an effect if it's used as a cosmetic. I don't know. That might be one way to wordsmith it.

DR. BERGFELD: I wonder what Jay would say.

DR. MARKS: Pardon?

DR. BERGFELD: I said I wonder what Jay Ansell would say.

DR. MARKS: Yeah. Lisa, how does that sound to you? And then I'm also -- we're looking at Tom as he's thinking, too. Otherwise, we need an -- I would think we would have to an insufficient data announcement for a NOAEL of skin pigmentation in vitro.

DR. BERGFELD: We have Nakissa from the FDA on.

DR. MARKS: I'm sorry. Oh. We have what, Wilma?

MS. KOWCZ: Nakissa's on from the FDA.

DR. MARKS: Oh, okay. I only get --

MS. KOWCZ: She's here.

DR. MARKS: So if she would like to comment, that would be fine, too. I find it a bit of a conundrum where we're at here and that we pose concentrations used in Asia. For the direct effect we're concerned about is lower than what the maximum use concentration.

DR. SHANK: Did someone say that the cosmetic dictionary says its function is a skin lightener? That's in the dictionary?

DR. MARKS: I think. I can go back -- I have bleaching agent in the dictionary.

MS. KOWCZ: Skin bleaching. You're right, Dr. Marks.

DR. MARKS: So yeah. So skin --

DR. SHANK: It's a cosmetic. That doesn't make sense.

DR. MARKS: Yeah. That's what I said.

DR. SHANK: If its function is -- then it's a drug, not a cosmetic.

DR. MARKS: Ron, that's what I said a bit ago. Why is it considered a cosmetic if its function is bleaching?

DR. SHANK: Right.

DR. EISENMANN: I said there isn't another option in the dictionary for somebody to use. So somebody that wants to use it -- in another country under different regulations where skin bleaching is considered cosmetic, that's why they put it there. We did have a company petition the INCI committee to remove that as the function, and that the INCI committee declined to do so. But they also did not add another function.

DR. SHANK: Well, if you put in the conclusion that it's safe when formulated not to depigment skin and the dictionary says it's a skin lightener, we're building in a conflict. Can this be handled in a discussion some way?

DR. MARKS: Well, I think in the pomegranate discussion, it starts right off by saying -- let me see because I emphasized one sentence -- "that it may have skin lightening effect. The Panel knows that skin lightening is considered to be a drug effect and should not occur during use in cosmetic ingredients." So I really like that, those two sentence, Ron, in the discussion. And we could either -- I think the conclusion could be, as you initially said, safe as used. Or it could have a qualifier, safe as long as it doesn't cause skin depigmentation.

Now, there's technicalities with that because depigment means you go from color to no color, and that, obviously, would be very noticeable like you see in vitiligo patients. If you're talking about skin bleaching or skin lightening, you could take somebody that has a little bit of color and then, say, soften that. So do we want to say safe as used or safe as long as it doesn't cause depigmentation? Because I think that's -- those are important nuances also.

DR. BERGFELD: I think that's a good reasoning, Jim. I think that could be explained in the discussion.

DR. MARKS: Okay. And then would you put in the conclusion, Wilma, safe or safe to not cause depigmentation. To me, that's the real endpoint we're worried about. I don't know.

DR. BERGFELD: I think that I would just say, safe.

DR. MARKS: Safe. Okay.

DR. BERGFELD: I think though with Carol's description that it is a bleaching agent in the dictionary, that one might explain that in the discussion. (Crosstalk) country at a higher concentration for bleaching.

DR. MARKS: Monice, were you going to say --

MS. FIUME: I did just want to give a reminder. So this is only at the draft stage. So if you do need further clarification as to whether there's a true cutoff at the concentration where's it's a bleaching agent versus not -- if that's a concern that is a true drug effect -- that is something you can ask for at this stage because this is the first time you're seeing the document.

DR. BERGFELD: It's a nice way out.

DR. MARKS: I think to me, I don't think it's going to be clarified because we know it's used, as Lisa pointed out from the get-go, with 2 percent for a skin lightening effect in Asia. So I kind of like moving onto a tentative report, and if we could get that, Monice, fine, but I don't think it's not going to change the discussion. But, again, I ask Tom, Ron, and Lisa, for your input and then, Thomas, your input if you want or Carol. I kind of like -- I hear loud and clear safe as used and then handle the skin lightening in the discussion.

MR. GREMILLION: I had a question about -- is there a matter it being claimed to have a skin lightening effect but a lack of data on to what extent it actually has that skin lightening effect? Or is there data demonstrating a skin lightening effect at a given concentration?

DR. MARKS: I think your question, Thomas, goes back to what Monice said. We could ask for more data on skin lightening and issue an insufficient data announcement. Or we could say safe in this tentative report, and we'd like to get more information about the skin lightening. I think that could be handled either way. As Monice said, this is early on, on these two ingredients. So I offered another one, insufficient data announcement and more information on the skin lightening.

So go back to you, Ron, Lisa, and Tom, which way would you want to go? I'm fine with either. I'd like to get as much information as possible on this skin lightening so that the discussion becomes quite robust.

MR. JOHNSON: Dr. Marks? Dr. Marks?

DR. MARKS: Hold on, Wilbur. I want to hear what Ron -- unless you can clarify that, I'd like to hear what Ron and Lisa and Tom think. Still stick with safe?

DR. SHANK: I'm having a very hard time hearing. The speech is all broken up. I think what you're asking is about the conclusion: safe or insufficient with more data on skin lightening.

DR. MARKS: That's correct.

DR. SHANK: Okay. I have a problem if the dictionary says its cosmetic function is a skin lightener. That's a problem because, in this country, that's a drug, not a cosmetic. So I would try to handle this -- poor Wilbur -- I'd try to handle this in the discussion. Good luck, Wilbur.

MR. JOHNSON: Yes.

DR. SHANK: But my feeling is it is safe as used, and in the discussion, we say it is known to have that capability of lightening skin. And if that's not desired, I guess it should be labeled so. If you've asked for more data, what are you going to ask for? Clinical trials? You have in vitro data with melanocytes and two million moles per liter inhibited melanin synthesis. We know it's effective in inhibiting melanin synthesis.

DR. MARKS: Okay. Wilbur, I interrupted you.

MR. JOHNSON: I was going to say that, on PDF page 15, there is a study relating to the effect on melanin synthesis.

DR. SHANK: Yes.

MR. JOHNSON: And I was also going to say that the ingredient is also used as a skin-conditioning agent and antioxidant in addition to the skin bleaching function.

DR. MARKS: Oh, okay.

DR. SHANK: But if we say it shouldn't be used to lighten skin but it says it's okay in the dictionary, that's a conflict.

DR. EISENMANN: The dictionary is an international dictionary, and it also says -- it also notes “for further information regarding functions and cosmetic drugs, see --" you have to go to the more information in the introduction.

DR. SHANK: Okay. Then that could be in the discussion.

DR. EISENMANN: Okay.

DR. SHANK: And handle it that way.

DR. MARKS: Yeah. I like that.

DR. PETERSON: I do, too.

DR. MARKS: Any other comments?

DR. BERGFELD: Yeah. Could you clarify what you're going to put in the discussion because I think I was tuned into that, as well -- to putting that international use in the discussion.

DR. MARKS: I think --

DR. BERGFELD: Wilbur, can you try to do that?

MR. JOHNSON: Yeah. I would like for Carol to repeat that statement.

DR. EISENMANN: For all ingredients for which a supplier claims in a drug effect, there's a default statement in the definition that takes you to the introduction for more information on drug versus cosmetic claims. And because it's an international dictionary, some countries consider skin lightening a cosmetic effect. So that's why --

MS. KOWCZ: I think, Carol, it’s important to state very clearly that the INCI is an international ingredient dictionary. That's pretty much the primary point here. And then you can embellish it with exactly what you just said. That would be my add.

DR. MARKS: So Wilbur, you'll put that in the discussion as such. And, again, I go back to the way the wording with pomegranate, which I thought was very well done. Instead of using pomegranate, we'll substitute this ascorbyl glucoside and sodium ascorbyl glucoside. The report indicates that that may have a skin lightening effect.

You can use skin bleaching. To me, I find that interchangeably. "The Panel noted that skin lightening is considered to be a drug effect and should not occur during the use of cosmetic products." I would say, “The Panel knows that skin lightening is considered to be a drug effect in the United States,” which is what we're saying that the international dictionary has a different use -- but “in the United States and should not occur during the use of cosmetic products.”

So there we're separating out that this refers to the U.S., not international, and that we don't feel that a cosmetic product should have a drug effect, basically skin lightening. That's how I'd handle it in the discussion, Wilbur. Just modify that a little bit, and then, obviously, you'll mention what the studies found.

MR. JOHNSON: Okay. Thank you.

DR. MARKS: Would Ron, Tom, Lisa, Wilma --

MS. SADRIEH: This is Nakissa Sadrieh. Can you hear me? I just wanted to ask a question. Can you hear me?

DR. BERGFELD: Yes.

DR. MARKS: Yes.

MS. SADRIEH: Okay. Good. Yeah. So I was wondering how are sunscreens dealt with in the INCI dictionary because sunscreens are also not cosmetics in certain countries? So are they identified as sunscreens in the INCI dictionary? Like, is there a drug function for them, just like for the skin lighteners and sort of bleaching agents, where there's a drug function associated because of the fact that some countries allow that? I was just wondering about how that's addressed in INCI because you know that a lot of ingredients, some are used as UV filters -- some sunscreen's ingredients are. And I just didn't know really what the definition in INCI was for them. Is the word sunscreen used because that's also a drug claim? Thank you.

DR. BERGFELD: Good point. Monice?

MS. FIUME: I was just going to say I'll defer that to Alex or Carol since we're not involved with the INCI dictionary and function identification.

MR. GREMILLION: CIR report.

DR. EISENMANN: Yes, they are noted. I'm looking up Butyl methoxy dibenzoylmethane which has been on the priority list. And, yes, it says --

MS. KOWCZ: But I think, Carol, to answer Nakissa's point -- which is a good one -- yes, it is determined to be a sunscreen. And because the INCI dictionary is an international one, in many countries, sunscreens are cosmetics, and in the United States, they are drugs. So you're right about the avobenzone example. And Nakissa asks a very good question. Thank you.

MS. SADRIEH: You're welcome. So I just wanted to make sure, you know, that there's consistency in how these are addressed because, you know, it's a similar issue. And I understand, obviously, the sort of dilemma that you're kind of, like, dealing with right now. But I just wanted to make sure that there's another example of this. And so it probably would have to be consistent with how other ingredients that have a drug function are dealt with, hence, to use similar terminology.

MS. KOWCZ: Thank you, Nakissa.

MS. FIUME: Thank you to Nakissa. I would like to point out that CIR does strive in the introduction, when we do list what the reported functions are in the dictionary, that there are others as well such is anti-acne agent that are sometimes reported. And we do include a statement that says, in the U.S., these are referred to as these are drug functions, not cosmetic and, therefore, not under the purview of the Panel. So we try and include that right up front in the introduction that we recognize they're in the dictionary, but it's not the Panel's purview to determine safety for that use because it's a drug use.

MS. SADRIEH: Thank you.

DR. MARKS: Okay. If there are not any further comments, then presumably our team tomorrow will be seconding a motion that says these two -- with a conclusion that these two ingredients are safe as used. And there will be a robust discussion about the skin lightening effect. Okay. If no other comments, we'll move onto the next ingredients, and that's the sulfites.

Full Panel – June 9, 2020

DR. BELSITO: Yes, so this is the first time we're review the Ascorbyl Glucoside and Sodium Ascorbyl Glucoside. And, we really got a very nice package between what was in the literature and what was provided in terms of HRIPTs. And, we felt that, with a lot of discussion, that they were safe as used.

We don't have DART data, but we do have data from Alkyl Glucosides. And we also know the metabolism -- it's metabolized quite quickly in the skin to ascorbyl acid and glucose. And it's really not absorbed to any amount, so we thought we didn't need that data. So we felt we could come to a safe as use conclusion on these two ingredients.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. MARKS: Second.

DR. BERGFELD: Second? Any further discussion?

DR. MARKS: Yeah, this was another one of these botanicals where the issue of skin lightening, bleaching, came up. And, again, we would model our discussion as we have with Pomegranate.

DR. BELSITO: Actually, we looked into those studies and it turned out that the Ascorbyl Glucoside was really not the responsible agent. In one it was kojic acid, and, Dan, I'm blanking on the other. It was (audio skipped).

DR. SNYDER: Ascorbyl Glucoside?

DR. LIEBLER: Yeah, I don't remember myself. But the thing is both of the cited papers were skin lightening products that happened to contain Ascorbyl Glucoside as well as a number of other things. The papers were themselves not about skin lightening, they were simply analytical methods papers that described the measurement of Ascorbyl Glucoside and a couple of other things. So, I don't think it provided any actual evidence to suggest that there's any skin lightening.

The other point I think is relevant here is that, you know, in general, skin lightening agents are usually tyrosinase inhibitors, so they're typically phenols. One of the other one was a phenol, I'm trying to remember, I just don't have it in front of me.

DR. BELSITO: It was a phenol and the other was a kojic acid.

DR. LIEBLER: Yeah.

DR. HELDRETH: And, Claverden was one of them.

DR. LIEBLER: Oh, yeah, Claverden, right. Yeah, okay. So, anyway, I didn't think that there was enough reason to really go down that rabbit hole on skin lightening with Ascorbyl Glucoside. We can mention it in the discussion, so that's the way I think we handle it.

DR. MARKS: Yeah, I agree, we mention it in the discussion, Dan and Don. Actually, Lisa brought up the concern that this is in Asia marketed at the two percent concentration for skin lightening. And the highest use concentration in the cosmetics we're reviewing is five percent. So, there was that disconnect.

And then, Dan, how did you handle the in vitro decrease in melanin pigment, which is on Page 15 of this document? I can understand where you have combination of lighteners, but this has actual data that would support the idea that it decreases melanin pigment.

DR. LIEBLER: Yeah, we've had several reports with experiments like this, so this is basically the data are of B-16 melanoma cells in culture. And, the concentration of the Ascorbyl Glucoside was two millimolar, which is very, very high. And, this is not really -- I don't think this is sufficient evidence of an actually, you know, in vivo lightening effect. I think that this can be, again, handled in the discussion.

DR. MARKS: Yep, concur. I just wanted you to react to it because obviously with things like sensitivity, if we get an in vivo, in vitro alert, then we pay attention to it as far as what potentially could happen in vitro, (inaudible) [02:24:43] use.

How about the marketing in Asia, two percent versus two percent preparation? That, again, will be in the discussion. Is that accurate?

DR. PETERSON: And, you know, I just want to -- when you talk about a two percent solution, it actually is millimolar. So, I think to say that they test it at these high concentrations, but the reality is that the cosmetic has a pretty high concentration in it.

DR. LIEBLER: Yeah, that's a good point. I mean, I tend to look at these subculture studies, I go into them very, very skeptical about their significance, particularly when anything's millimolar. But you're right, if something is millimolar -- I just don't see the chemistry here making any sense for skin lightening, but, it's a fair point. I still think we can handle it in the discussion.

DR. BERGFELD: Dan, if I could just add a clinical experience. We do use ascorbyl acid as a skin lightener and a collagen builder even though it's a skin conditioning rejuvenation-like therapy. And this (audio skip).

DR. LIEBLER: You know the other thing is in this report there are some data that are cited as indicative of the penetration of Ascorbyl Glucoside through the skin. I'm referring to PDF Page 12, at the bottom of the page, under the Toxicokinetic Dermal Penetration.

The problem with that is they apply this and then they look at, I think they look at circulating ascorbate. And the problem is it's almost impossible to do that experiment very well, simply because of the high background level of the ascorbate and the inability to distinguish the effect or the origin of any of that circulating ascorbate. It's such a polar molecule that I would be very skeptical of it being able to penetrate the epidermis. So, I don't think the experiment cited here actually demonstrate that.

So, I think that to actually achieve a skin lightening effect, a chemical would have to penetrate the stratum corneum and get down into, I guess, the epidermis dermis junction, is where the melanocytes are?

DR. BERGFELD: The dermal epidermal.

DR. LIEBLER: Okay. So, but it have to get in there in sufficient concentration to be able to inhibit tyrosinase, for example. And, I just don't think there are, based on the chemical properties of this molecule and the lack of evidence for its actual skin penetration, I don't think there is a case to be made for this as a melanin synthesis inhibitor, or as a skin lightening agent. I think we can handle it, as I said, in the discussion.

DR. BERGFELD: Okay, then? Any other comments before we call the vote on this? It's been moved and seconded, it'll go out as safe, with the expansion of the discussion.

MR. JOHNSON: Dr. Bergfeld?

DR. BERGFELD: Yes?

MR. JOHNSON: Yes, Dr. Bergfeld. It had been mentioned earlier, including information, I guess, sort of like a boilerplate from the Pomegranate report, relating to skin depigmentation. So, given Dr. Liebler's explanation, there's no need to include that boilerplate language, is that true?

DR. BERGFELD: Dr. Marks, what do you think?

DR. MARKS: Wilbur, I think I would modify it. Because I think we should mention in there that skin lightening is a drug effect, and we don't expect that from a cosmetic. I think we also have to elucidate, as you said, Don, right in the beginning that the preparations that were marketed for skin lightening, that contained these Ascorbyl Glucosides also had other skin lighteners in it, and then in addition what Dan had mentioned. So, it's not the same as Pomegranate, but I think that's a framework to use.

MR. JOHNSON: Okay, thank you.

DR. BERGFELD: Don?

DR. BELSITO: Yeah, I agree.

DR. BERGFELD: Okay. All right, then let me ask the question, all those in favor of a safe conclusion, indicate by raising your hand. Looks unanimous, opposed, please be vocal. No one opposing. Unanimous, to move forward with the safe conclusion.

Safety Assessment of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside as Used in Cosmetics

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, CIR.

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ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside in cosmetic products; these ingredients are reported to have the following functions in cosmetics: antioxidant, and skin-conditioning agent - miscellaneous. The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations, and concluded that Ascorbyl Glucoside and Sodium Ascorbyl Glucoside are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The safety of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside, as used in cosmetics, is reviewed in this assessment. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Ascorbyl Glucoside is reported to have the following functions in cosmetics: antioxidant, skin bleaching agent, and skin-conditioning agent – miscellaneous;[1]however, it should be noted that functioning as a skin bleaching agent is not a cosmetic use in the United States (US), and, therefore, the Panel did not evaluate safety for that use. Sodium Ascorbyl Glucoside is reported to function in cosmetics as a skin conditioning agent – humectant.

Because Ascorbyl Glucoside is a derivative of ascorbic acid, it should be noted that the Panel has evaluated the safety of ascorbic acid, and ethers and esters of ascorbic acid. The safety evaluations involve 3 separate ingredient reports, and the Panel's conclusion in each report is that these ingredients are safe in the present practices of use and concentration, as described in the safety assessment. Those 3 final reports are: A final report on the safety assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, and Ascorbyl Stearate was published in 1999.[2] The final report on the safety assessment of *L*-Ascorbic Acid, Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate was published in 2005.[3] Lastly, the final report on ethers and esters of ascorbic acid (Ascorbyl Dipalmitate, Ascorbyl Isostearate, Ascorbyl Linoleate, Ascorbyl Palmitate, Ascorbyl Stearate, Ascorbyl Tetraisopalmitate, and Tetrahexyldecyl Ascorbate) was issued in 2017.[4] The 3 ingredients evaluated in the 1999 published final report were included in the 2017 final report because the safety of these ingredients was reevaluated in 2017 due to the availability of new safety test data. All reports are available on the Cosmetic Ingredient Review (CIR) website. (https://www.cir-safety.org/ingredients)

The Panel has also evaluated the safety of glucose in a published report on monosaccharides, disaccharides, and related ingredients.[5] The conclusion in this report states that glucose and the other ingredients reviewed are safe in the present practices of use and concentration in cosmetics.

The published data in this document were identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that the Panel evaluates, is available on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data may be provided by the cosmetics industry, as well as by other interested parties. Much of the data included in this safety assessment was found at the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) website.[6] Please note that this website provides summaries of information from other studies, and it is those summary data that are reported in this safety assessment when NICNAS is cited.

CHEMISTRY

Definition

Ascorbyl Glucoside (CAS No. 129499-78-1; Figure 1) is defined as the product obtained by the condensation of ascorbic acid with glucose.[1] Sodium Ascorbyl Glucoside (no CAS No.) is defined as the sodium salt of Ascorbyl Glucoside. These 2 ingredients differ in structure only by the replacement of a proton with a sodium cation.

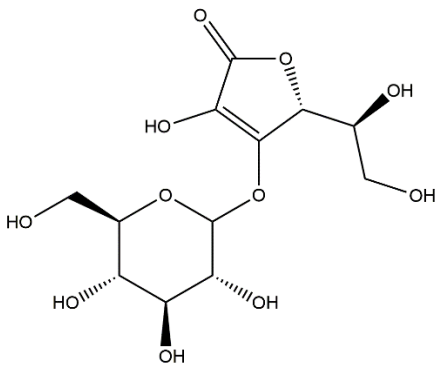

Figure 1. Ascorbyl Glucoside

Chemicals Properties

Ascorbyl Glucoside is a water-soluble compound with a molecular weight of 338.263 Da and an octanol/water partition coefficient (log P_{ow}) of < -2.[6,7] Sodium Ascorbyl Glucoside has a formula weight of 360.25 Da.[8] These and other properties are presented in Table 1.[6-12]

The optimal condition of retaining Ascorbyl Glucoside with the highest stability in cosmetic products has been determined to be 55.3ºC and pH 6.4.[13] It has been noted that, generally, the pH of common cosmetic products is between 5.5 and 7.0.[14]

Method of Manufacture

Ascorbyl Glucoside is synthesized by a biocatalytic transglucosylation in which starch-derived cyclic or linear oligosaccharides are reacted with L-ascorbic acid (aka vitamin C) by a glucanotransferase.[15,16] More specifically, Ascorbyl Glucoside is prepared by transferring a glucosyl residue from α-1,4-glucan to the C-2 position of ascorbic acid and bound with α-1,2-linkage.[9] Enzymatic transglucosylation to synthesize a chemically stable form of L-ascorbic acid has been investigated by using commercially available enzymes.[17] Of the various glycosidases that were used, only rice seed α-glucosidase produced a nonreducing and stable glucoside of L-ascorbic acid, which was identified as Ascorbyl Glucoside.

According to another source, transglycosylation in the presence of the enzyme cyclodextrin glucanotransferase (CGTase, from *Paenibacillus sp.*) was used to produce Ascorbyl Glucoside.[18] The standard reaction mixture contained sodium ascorbate, dextrin or other saccharides, and CGTase. To hydrolyze ascorbic acid-2-oligosaccharides produced by CGTase, glucoamylase (from *Rhizopus* mold) was added to the reaction mixture, yielding Ascorbyl Glucoside.

Composition/Impurities

According to NICNAS, Ascorbyl Glucoside is 99.8% to 100% pure, and contains no hazardous impurities/residual monomers or non-hazardous impurities/residual monomers (> 1% by weight).[6] It is also described as containing no additives/adjuvants.

USE

Cosmetic

The safety of these cosmetic ingredients is evaluated based, in part, on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient 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.[19] Use 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.[20]

According to 2020 VCRP data, Ascorbyl Glucoside is reported to be used in 532 cosmetic products (463 leave-on and 69 rinse-off; Table 2).[19] The results of a concentration of use survey conducted by the Council in 2018 indicate that Ascorbyl Glucoside is used at concentrations up to 5% (in face and neck skin care preparations, not spray), which is the highest reported maximum use concentration for leave-on formulations.[20] In rinse-off products, Ascorbyl Glucoside is reported to be used at concentrations up to 2% (in paste masks and mud packs. According to VCRP and Council survey data, Sodium Ascorbyl Glucoside is not used in cosmetic products.

Cosmetic products containing Ascorbyl Glucoside may be applied to the skin at concentrations up to 5% (in face and neck skin care preparations) and may come in contact with the eyes during use of eye makeup preparations (highest reported maximum use concentration of 2% in eye lotions). Ascorbyl Glucoside also could be incidentally ingested during product use (e.g., use in lipsticks; concentrations not reported). Products containing Ascorbyl Glucoside may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Ascorbyl Glucoside is reported to be used in both pump and aerosol hair sprays at concentrations up to 0.01%.[20] 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.[21-24] 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.[21,22] Ascorbyl Glucoside is reported to be used in face powders at concentrations up to 2%. 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.[25-27]

Ascorbyl Glucoside and Sodium Ascorbyl Glucoside are not restricted from use in any way under the rules governing cosmetic products in the European Union.[28]

Non-Cosmetic

The use of Ascorbyl Glucoside as a vitamin C supplement in foods has been reported.[15] Furthermore, hydrophilic ascorbic acid derivatives such as Ascorbyl Glucoside have been used not only as antioxidants, but also as food and pharmaceutical excipients.[29] However, it is important to note that Ascorbyl Glucoside does not appear on the FDA's list of indirect additives used in food contact substances or in the FDA's substances added to food inventory.[30,31] Ascorbyl Glucoside also does not appear in the FDA's inactive ingredient database for FDA-approved drug products.[32]

Skin bleaching is a drug function, not a cosmetic function, in the US. Ascorbyl Glucoside has been identified as a bleaching agent in commercial bleaching cosmetics in Taiwan.[33] Commercial bleaching cosmetics contained additional ingredients such as kojic acid and niacinamide, which are associated with skin whitening effects. In commercial cosmetic bleaching creams (2 creams) and in a commercial cosmetic bleaching lotion, Ascorbyl Glucoside has been detected at concentrations of 1.89% and 2.05%, respectively, using high-performance liquid chromatography (HPLC). In South Korea, Ascorbyl Glucoside has been identified as one of the main ingredients used in cosmetics that are reported to function as skin whitening agents.[34]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

A three-dimensional cultured human skin model (living skin equivalent) was used to study the percutaneous absorption of Ascorbyl Glucoside in vitro.[35] The skin model consisted of the following: stratum corneum and viable epidermis from human keratinocytes, and a collagen matrix composed of human dermal fibroblasts and a polycarbonate membrane. The skin model was mounted between the donor and receptor compartments of a modified Franz cell (effective area = 1.7 cm^2). The donor compartment contained 1% Ascorbyl Glucoside in phosphate buffer (100 µl), and the receptor compartment contained phosphate buffer only. The donor solution containing the test substance was soaked into a wiping cloth that was set on the stratum corneum. At predetermined times, a 200 µl sample was withdrawn from the receptor solution and the donor was removed using wipes. Both surfaces of the stratum corneum side and the polycarbonate side of the skin model were washed with phosphate buffer, and the model was separated into the skin, collagen matrix, and polycarbonate membrane. The donor (wipes), skin, collagen matrix, and polycarbonate membrane were placed separately into sample vials with phosphate buffer and maintained for 24 h for chemical extraction. Chemical concentration was assayed by HPLC. The recovery rate of Ascorbyl Glucoside was 84.56%. The steady-state penetration flux of Ascorbyl Glucoside, evaluated by the linear portion of the penetration profile, was 0.91 ± 0.15 µg/cm^2/h. Ascorbyl Glucoside only slightly penetrated through the hydrophobic layer stratum corneum, because it is a highly hydrophilic compound. The log P_{ow} was not calculated because Ascorbyl Glucoside does not readily dissolve in octanol. The ratio of Ascorbyl Glucoside in the skin (defined as the percentage of Ascorbyl Glucoside in each section (µg) divided by the total amount of Ascorbyl Glucoside in the skin model) was 7.24%, and more than 90% of the Ascorbyl Glucoside remained in the wipe at 6 h.

The in vitro percutaneous absorption of Ascorbyl Glucoside was evaluated using excised skin (2 cm x 2 cm) from 8 pigs.[36] Each excised skin sample was mounted in a Franz diffusion assembly, with the stratum corneum facing the donor compartment. The donor compartment (0.5 ml) contained Ascorbyl Glucoside in a citrate-phosphate buffer (pH 7.4; quantity of this solution added to the compartment not stated). The receptor compartment (5.5 ml) was filled with citrate-phosphate buffer. The available area of the glass cylinder was 0.7854 cm^2. At appropriate intervals, 300 µl aliquots of receptor medium were withdrawn and immediately replaced with an equal volume of fresh receptor solution. The length of the sampling period was 12 h, and the amount of Ascorbyl Glucoside in the receptor medium was determined using HPLC. Results indicated there was no flux of Ascorbyl Glucoside across the skin samples.

Human

An experiment was performed to evaluate the percutaneous absorption of Ascorbyl Glucoside.[37] To measure percutaneous absorption, a cream containing 2% Ascorbyl Glucoside (7.5 g) was applied to the legs of 5 male subjects. The area to which the test cream was applied was covered for 14 h with cling film and a bandage. Urine samples were taken every 2 h for 26 h. A cream containing no ascorbic acid derivative (placebo) was applied to one other male subject. Though the increase was not a sharp increase, the amount of ascorbic acid excreted in the urine was increased over the amount that was measured prior to cream application. Furthermore, the amount of ascorbic acid excreted into the urine was sustained at virtually the same level for 10 h and peaked at 14 h. Even after the cream was removed at 16 h post-application, the excretion of ascorbic acid into the urine continued up to 26 h. The increase in ascorbic acid concentration in the urine seemed to originate solely from the cream because the subjects were not allowed to take ascorbic acid orally. In the control subject, the amount of ascorbic acid excreted into the urine did not change.

The distribution of Ascorbyl Glucoside in the skin after application of the 2% Ascorbyl Glucoside cream to the forearm was also evaluated. To determine the distribution of ascorbic acid in the skin, the cream was applied to an area on the inside of the forearm. The area was then covered with cling film and a bandage for 12 h. Samples were taken from the area by punch biopsy at 12 h and 3 d after the bandage and cling film had been removed. The skin samples were fixed and prepared

for electron microscopy. In the micrographs of skin treated with the cream, small black silver particles indicated the presence of ascorbic acid in the skin. Silver particles were observed between epidermal cells for as long as 3 d. The authors noted that these results indicate that Ascorbyl Glucoside releases ascorbic acid in the skin, i.e., sustained release. These particles were not observed in micrographs of skin treated with a cream containing no ascorbic acid derivative. The authors noted that the results of the 2 experiments in this study combined indicate that Ascorbyl Glucoside (in cream) was absorbed percutaneously and converted to ascorbic acid through its metabolism in the skin and other parts of the body. It could also be stated that these results indicate that ascorbic acid from dermally applied Ascorbyl Glucoside was absorbed.

Absorption, Distribution, Metabolism, and Excretion (ADME)

In Situ

The intestinal absorption of Ascorbyl Glucoside in fasted Hartley guinea pigs was determined using the perfusion technique.[38,39] Various concentrations of Ascorbyl Glucoside (0.2, 0.5, 1.0, or 5.0 mM) in isotonic phosphate buffer were perfused in the small intestine of the animals. At 2 h after perfusion, blood from the portal vein was collected to determine Ascorbyl Glucoside content, in that compounds absorbed from the small intestine accumulate primarily in the portal vein. Following perfusion, the amount of intact Ascorbyl Glucoside collected in the perfusate was less than the amount perfused, and an increase in ascorbic acid was observed. Intact Ascorbyl Glucoside was not detected in the plasma of the portal vein at 2 h after perfusion. The disappearance of Ascorbyl Glucoside from the perfusate was completely inhibited by the addition of castanospermine, a specific α-glucosidase inhibitor, or by carbohydrates such as maltose. These results indicate that ascorbic acid released from Ascorbyl Glucoside by α-glucosidase on the brush border membrane is effectively taken up across the intestinal ascorbate transport channels, into a serosal site, whereas Ascorbyl Glucoside permeation was poor via the passive transport system. Thus, Ascorbyl Glucoside administered orally could be hydrolyzed to ascorbic acid by α-glucosidase on brush border membranes, and absorbed as ascorbic acid from the small intestine in guinea pigs.

Animal

Oral

The in vivo formation of Ascorbyl Glucoside in guinea pigs and rats given ascorbic acid orally in combination with maltose was examined.[40] A metabolite of ascorbic acid that has the same HPLC retention characteristics as authentic Ascorbyl Glucoside was detected in the blood, urine and liver of guinea pigs 1 to 2 h after their administration. The metabolite was isolated from the urine by chromatographic procedures and identified as Ascorbyl Glucoside by its ultraviolet light (UV) spectrum, non-reducibility, susceptibility to α-glucosidase hydrolysis, HPLC profile, and elementary analysis. The same glucoside was also synthesized by rats and found in the urine, although it could not be determined qualitatively in the blood. The authors concluded that Ascorbyl Glucoside is a possible metabolite produced by enzymatic α-glucosidation after combined administration of ascorbic acid and maltose to guinea pigs and rats.

The ADME of Ascorbyl Glucoside was investigated using groups of male Hartley guinea pigs.[41] (Ascorbic acid activity (i.e., effect on body weight gain and serum alkaline phosphatase activity) was evaluated by comparing the effects of oral dosing with ascorbic acid versus Ascorbyl Glucoside, and these results are presented in the section on Short-Term Toxicity Studies.) Eight groups were fed ascorbic acid-deficient diet supplemented with either 0.96, 1.92, 9.6, or 192 mg/animal/d Ascorbyl Glucoside or 0.5, 1, 5, or 100 mg/animal/d ascorbic acid for 24 d; 5 animals were used per group, with the exception that n = 15 for the 5 mg/animal/d ascorbic acid group. The control group was fed ascorbic acid-deficient diet only, which was defined as follows: casein (20%), sucrose (12%), corn (20%), soybean oil (5%), soybean meal (5%), wheat bran (20%), alfalfa meal (10%), vitamin mixture (ascorbic acid-free, 1%), and mineral mixture (7%). In the Ascorbyl Glucoside dietary groups, Ascorbyl Glucoside was not detected in the liver, adrenal glands, or urine. However, ascorbic acid was detected (in the urine and in these organs), and the ascorbic acid concentration increased with increasing Ascorbyl Glucoside dosage. The ascorbic acid concentration in the tissues of each Ascorbyl Glucoside dose group was higher than that of the control group, and was similar to that of the groups fed ascorbic acid in the diet.

Animal and Human

Oral

A study was performed in which the bioavailability of Ascorbyl Glucoside as ascorbic acid in humans (8 subjects) was compared to that in rats (6 animals).[13,42] The aim of the study was to clarify that Ascorbyl Glucoside is hydrolyzed by human intestinal maltase, and that oral ingestion of Ascorbyl Glucoside is physiologically utilized the same as orally administered ascorbic acid in human subjects. The hydrolyzing activities to Ascorbyl Glucoside by human or rat intestinal homogenates were measured using HPLC. Following an overnight fast, the subjects orally ingested 3.84 g of Ascorbyl Glucoside (2 g of ascorbic acid equivalent) dissolved in 100 ml of water. Venous blood (2 ml quantities) was drawn from the forearms prior to ingestion and at 1, 2, 3, and 4 h after ingestion. At least 1 wk later, ascorbic acid (2 g) was ingested and blood was collected according to the same method. In the rat study, 76.8 mg of Ascorbyl Glucoside (40 mg of ascorbic acid equivalent) were administered by stomach tube. Blood was collected from the tail vein prior to dosing and at 1, 2, and 3 h post-dosing. One week later, ascorbic acid (40 mg) was administered using the same method. Serum concentrations of ascorbic acid between humans and rats were compared.

In humans, Ascorbyl Glucoside was digested by intestinal maltase, and hydrolyzing activity was higher (but not statistically significantly different) when compared to the rat. The average concentration of serum ascorbic acid at basal levels in human subjects was 0.9 mg/100 ml (within normal range). The serum ascorbic acid concentrations increased from 0.9 mg/100 ml to 2.5 mg/100 ml within 2 h and were maintained at these levels until 4 h post-administration of Ascorbyl Glucoside in human subjects. In rats, the serum ascorbic acid concentration increased linearly from 1.1 mg/100 ml to 1.6 mg/100 ml within 3 h after dosing. Thus, the increment of the serum concentration of ascorbic acid in rats was less when compared to humans. These results suggest that the absorption of ascorbic acid in humans occurs at higher levels and at a faster rate when compared to rats. The authors concluded that Ascorbyl Glucoside is hydrolyzed by intestinal maltase and acts as ascorbic acid in humans.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Ascorbyl Glucoside (99.8% to 100% pure) was evaluated using10 Wistar rats, (5 males, 5 females).[6] The study was performed in accordance with Organization for Economic Co-Operation and Development (OECD Test Guideline (TG) 402. Each animal received a single, 2000 mg/kg dose of the test substance in distilled water. The dose was administered under a semi-occlusive dressing. The dressing was removed on day 2. None of the animals died, but the test substance caused yellow discoloration of the skin (initially observed on day 2) at the application sites of all test animals. Skin discoloration was reported until termination of the study; however, the number of animals with skin discoloration at the end of the study was not stated. There were no signs of systemic toxicity or effect on organs. The authors concluded that Ascorbyl Glucoside was of low toxicity (LD_{50} > 2000 mg/kg) when administered dermally.

Oral

The acute oral toxicity of Ascorbyl Glucoside (99.8% to 100% pure) was evaluated using 3 groups of 10 rats (5 males and 5 females per group) of the Crj:CD strain.[6] The study was performed in accordance with OECD TG 401. A single dose of the test substance (in deionized water) was administered, by gavage, at doses of 1000 mg/kg and 2000 mg/kg. The control group received deionized water only. On the day after dosing, soft stool or muddy stool was observed sporadically in test and control groups. None of the animals died, and no effects on the organs (not identified) of test or control animals were observed. The authors concluded that Ascorbyl Glucoside was of low toxicity (LD_{50} > 2000 mg/kg) when administered orally.

Short-Term Toxicity Studies

Oral

As stated in the ADME section, the ascorbic acid activity (i.e., effect on body weight gain and serum alkaline phosphatase activity) of Ascorbyl Glucoside in guinea pigs was investigated using 9 groups of male guinea pigs fed ascorbic acid-deficient diet supplemented with 0- 192 mg/animal/d Ascorbyl Glucoside (5 groups), or fed 0.5 - 100 mg/animal/d ascorbic acid for 24 d (5 animals/group, with the exception that 15 animals were fed 5 mg/animal/d ascorbic acid in diet).[41] Study details are found in the ADME section. The body weight gain, serum alkaline phosphatase activity, and the concentration of ascorbic acid or Ascorbyl Glucoside in the liver, adrenal glands, and urine were measured at the end of the experimental period. Guinea pigs fed diet supplemented with Ascorbyl Glucoside had similar body weight gain when compared to guinea pigs fed diet supplemented with an equimolar amount of ascorbic acid. Serum alkaline phosphatase activity in Ascorbyl Glucoside and ascorbic acid dietary groups was statistically significantly ($p < 0.05$) higher when compared to the control group. However, there was no significant difference in serum alkaline phosphatase activity between the Ascorbyl Glucoside and ascorbic acid dietary groups. The authors concluded that these results, together with the distribution and excretion data in guinea pigs (as described in the ADME section), indicated that Ascorbyl Glucoside has the same vitamin C activity as ascorbic acid on a molar basis.

Groups of 20 Wistar rats (10 males and 10 females per group) were dosed with Ascorbyl Glucoside (in distilled water) daily for 28 d.[6] There were 3 test groups and 1 control group. Ascorbyl Glucoside was administered by gavage at doses of 50 mg/kg, 200 mg/kg, and 1000 mg/kg, 7 d/wk, in accordance with OECD TG 407. The control group was dosed with distilled water. None of the animals died, and there were no clinical signs nor effects on food consumption or body weight gain. Laboratory findings relating to clinical chemistry, hematology, or urinalysis did not reveal any test substance-related changes. There also were no test substance-related changes in organ weights, or any test substance-related macroscopic or microscopic findings. The authors concluded that the no observed adverse effect level (NOAEL) for Ascorbyl Glucoside was 1000 mg/kg/d, the highest dose administered in this study.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

In Vitro

The genotoxicity of Ascorbyl Glucoside (in distilled water) was evaluated in the Ames test using the following bacterial strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 uvrA.[6] The test substance was evaluated at doses up to 5000 µg/plate, with and without metabolic activation. Dose-dependent increases in mutation frequency were not observed in any of the bacterial strains tested with Ascorbyl Glucoside. Both negative (distilled water) and positive controls (not stated) yielded appropriate responses. The authors concluded that Ascorbyl Glucoside was not genotoxic under the conditions of this test.

Ascorbyl Glucoside (in growth medium) was also evaluated for clastogenic potential using Chinese hamster Don cells.[6] The test substance was evaluated with and without metabolic activation at concentrations of 500 µg/ml, 1000 µg/ml, and 2000 µg/ml. The 50% growth inhibitory concentration, with or without metabolic activation, was ~2000 µg/ml. When compared to control (not stated) levels, there was no increase in the frequency of cells with chromosomal aberrations either with or without metabolic activation. The positive controls (not stated) yielded the expected responses. The authors concluded that Ascorbyl Glucoside was not clastogenic to Chinese hamster Don cells under the conditions of this test.

The genotoxicity of Ascorbyl Glucoside (in growth medium) was evaluated in the mammalian chromosome aberration test (OECD TG 473) using Chinese hamster V79 cells.[6] The test substance was evaluated at concentrations up to 3400 µg/ml both with and without metabolic activation. There was no evidence of cytotoxicity over the range of concentrations tested, with or without metabolic activation. When compared to control (not stated) levels, no increase in the frequency of cells with chromosomal aberrations was observed either with or without metabolic activation. The positive controls (not stated) yielded the expected responses. The authors concluded that Ascorbyl Glucoside was not clastogenic to Chinese hamster V79 cells under the conditions of this test.

In Vivo

The genotoxicity of Ascorbyl Glucoside was evaluated in the micronucleus test using groups of 10 mice (5 males and 5 females per group) of the S1c:ICR strain.[6] The test substance (in physiological saline) was injected intraperitoneally (i.p.) at doses of 500 mg/kg, 1000 mg/kg, and 2000 mg/kg. The animals were killed at 24 h post-injection, and bone marrow cells were obtained and prepared for microscopic examination. Physiological saline and mitomycin C served as negative and positive controls, respectively. When compared to control levels, there were no increases in the frequency of micronucleated polychromatic erythrocytes at the administered doses. The authors concluded that Ascorbyl Glucoside was non-clastogenic under the conditions of this test. The positive control was genotoxic.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside were neither found in the published literature, nor were these data submitted.

OTHER RELEVANT STUDIES

Tumor Promoter Inhibition

The effect of Ascorbyl Glucoside (30 µM and 100 µM) at the promotion stage in the two-stage BALB/c 3T3 cell transformation assay was evaluated.[43] When BALB/c 3T3 cells were treated with 0.2 mg/ml 20-methylcholanthrene (MCA) as an initiator, and 100 ng/ml 12-*O*-tetradecanoylphorbol-13-acetate (TPA) as a promoter, the addition at the promotion stage of Ascorbyl Glucoside resulted in inhibition of transformation. When compared to the transformation control (treatment with MCA followed by TPA), the inhibition by 100 µM Ascorbyl Glucoside (31% inhibition) only was statistically significant.

Effect on Melanin Synthesis

The effect of Ascorbyl Glucoside on melanin synthesis was studied using B16 melanoma cells.[37] Cells were cultured in the presence of Ascorbyl Glucoside (2 mmol/l). At 24 h before the cells were harvested, the cells were treated with theophylline and then trypsin. After the cells were harvested, the number of viable cells was determined and the amount of melanin was measured. Melanoma cells to which no ascorbic acid derivative had been added served as the control. Ascorbyl Glucoside inhibited melanin synthesis. It caused a statistically significant ($p < 0.01$) reduction in melanin synthesis when compared to control values (baseline). This reduction was sustained over a period of ≥ 30 h. In another experiment in this study, B16 melanoma cells were cultured with Ascorbyl Glucoside (2 mmol/l) for 48 h, and changes in cell pigmentation were monitored. After 2 d of incubation with Ascorbyl Glucoside, a statistically significant decrease in melanin pigmentation was observed. Decreased melanin pigmentation was observed on days 1 and 2, indicating that Ascorbyl Glucoside had a sustained effect with respect to lightening the color of melanin.

Effect on Collagen Synthesis

The effect of Ascorbyl Glucoside on collagen synthesis was evaluated using cultured human skin fibroblasts.[12,44] Ascorbyl Glucoside effectively stimulated collagen synthesis at concentrations of 0.1 - 0.5 mM. Continuous supplementation

of Ascorbyl Glucoside (0.25 mM) to culture medium for 24 d enhanced cell growth to three-times that of control skin fibroblast cultures.

Cytotoxicity

Cultured human skin (abdominal) fibroblasts at different cell densities were used in a study evaluating the cytotoxicity of Ascorbyl Glucoside and ascorbic acid.[45] The fibroblasts were cultured for 24 h in medium containing Ascorbyl Glucoside (1 mM) or ascorbic acid (1 mM). Cell numbers (estimated by measuring uptake of neutral red) ranged from 0.625 x 10^4 cells per well to 10 x 10^4 cells per well. Results were expressed as the means of duplicate cultures. After 24 h of incubation of fibroblasts (cell density of 0.625 x 10^4 cells/well) with 1 mM Ascorbyl Glucoside, the cell number was 0.37 x 10^4 cells/well; the cell number in the control culture (same cell density) was 0.35 x 10^4 cells/well. After 24 h of incubation of fibroblasts at a higher cell density (cell density of 10 x 10^4 cells/well) with 1 mM Ascorbyl Glucoside, the cell number was 9.6 x 10^4 cells/well; the cell number in the control culture (same cell density) was 6.6 x 10^4 cells/well. These results indicate that Ascorbyl Glucoside was not cytotoxic to cell cultures of different densities. Similarly, Ascorbyl Glucoside was not cytotoxic to cultures at cell densities between 0.625 x 10^4 cells/well and 10 x 10^4 cells/well. However, ascorbic acid (1 mM) was cytotoxic in low density fibroblast cell cultures.

Effect on UVB-induced Cytotoxicity

The inhibitory effect of Ascorbyl Glucoside on mid-wavelength ultraviolet light (UVB)-induced cytotoxicity was evaluated using HaCaT human keratinocytes, used as a skin model in this study.[46] The cytotoxicity assay (WST-1 assay) used is a modified 3-(4,5-dimethylthiazole-2-yl)-2,5-biphenyl tetrazolium bromide assay. After 12 h of incubation with Ascorbyl Glucoside, the cells were exposed to UVB and then cultured for 24 h. UVB irradiation of cell cultures was performed using 2 light sources (range: 280 to 360 nm). Results indicated that that cell viability decreased significantly, when cultures were exposed to UVB at 0.1 to 0.4 J/cm^2, in a dose-dependent manner. Cell viability was ~25% at a UVB dose of 0.4 J/cm^2. Ascorbyl Glucoside dose-dependently (0.5 to 5 mM) suppressed UVB (0.25 J/cm^2)-induced cytotoxicity in HaCaT cells. At a concentration of 5 mM Ascorbyl Glucoside, cell viability was 70.3% when compared to the control cultures.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

The skin irritation/corrosion potential of undiluted Ascorbyl Glucoside was evaluated in accordance with OECD TG 404 using 3 New Zealand White rabbits.[6] The test substance (0.5 g in distilled water) was applied for 4 h under a semi-occlusive dressing, and the test site was observed for 72 h. The area of application was ~ 6 cm^2. Neither erythema nor edema were observed in the animals tested. The authors concluded that Ascorbyl Glucoside was non-irritating to the skin of rabbits.

Sensitization

Animal

The skin sensitization potential of Ascorbyl Glucoside was evaluated in the maximization test (OECD TG 406) using guinea pigs (strain not stated).[6] Groups of 20 and 10 animals served as test and control groups, respectively. The induction phase involved intradermal injection of 1% Ascorbyl Glucoside and topical application of 75% Ascorbyl Glucoside. For topical application, a filter paper (2 cm x 4 cm) was fully-loaded with the test substance in a suitable vehicle (not stated) and applied under an occlusive dressing for 48 h. Control animals received a 48-h application of the vehicle, under an occlusive dressing. All test and control animals were pre-treated with 10% sodium lauryl sulfate (in liquid paraffin) at 1 day prior to topical induction. The challenge phase involved a 24-h topical application of Ascorbyl Glucoside (under occlusive dressing) to the flank at concentrations of 15, 25, 50, and 75%. At topical induction with the test substance for 24 h, slight erythema was observed in 1 animal. However, none of the animals (test or controls) exhibited erythema or edema at the challenge site. The authors concluded that there was no evidence of reactions to Ascorbyl Glucoside that were indicative of skin sensitization.

Human

A human repeated insult patch test (HRIPT) on a rinse-off product containing 0.1% Ascorbyl Glucoside was performed using 103 subjects.[47] Dilution of the product to a 2% aqueous solution (effective Ascorbyl Glucoside test concentration = 0.002%) was performed prior to testing. The diluted product (0.1 ml) was applied, under an occlusive patch, for 48 h and 72 h. The location of the patch test site and the dose per cm^2 were not stated. Patch application was repeated over a 3-wk induction period, which consisted of 9 induction applications. Reactions (induction) were scored according to the following scale: 0 (no evidence of irritation) to 7 (strong reactions spreading beyond test site. The induction phase was followed by a 2-wk non-treatment period. A challenge patch was then applied to a new test site (not identified). Challenge reactions were scored at 48 h and 96 h according to the following scale: 0 (no evidence of erythema) to 3 (severe erythema (very intense

redness)). Reactions with a grade of 0 or 1 were classified as low-level reactions. Reactions with a grade of 2 and above were classified as high-level reactions. One subject had a low-level reaction and 2 subjects had a high-level reaction during induction. Neither low-level nor high-level reactions were observed during challenge. The authors noted that the diluted product did not induce an allergic response, and concluded that it did not induce dermal sensitization in any of the subjects tested.

A second HRIPT was performed on a leave-on product containing 2% Ascorbyl Glucoside (undiluted), and was performed using 113 subjects.[47] The test protocol is the same as that used in the preceding test, except for the following: amount applied (25 µl), only a 48-h patch application period, the scoring of challenge reactions at 30 min, 24 h, and 48 h, and the grading scale used. Locations of patch test sites and the dose per cm^2 were not stated. The following International Contact Dermatitis Research Group (ICDRG) grading scale was used for the evaluation of induction and challenge reactions: 0 (no reaction) to 3 (extreme (bullous or ulcerative). The definitions of low-level and high-level reactions, same as stated in the preceding test, were used. Two subjects had a low-level reaction during induction; there were no high-level induction reactions. One subject had a low-level reaction during challenge; there were no high-level challenge reactions. The authors noted that the undiluted product did not induce an allergic response, and concluded that it did not induce dermal sensitization in any of the subjects tested.

The skin irritation and sensitization (contact allergy) potential of Ascorbyl Glucoside (10% solution) was evaluated in an HRIPT involving 51 subjects.[48] The Fitzpatrick skin types distribution for these subjects was as follows: type 2 (burns easily, tans slightly – 7 subjects), type 3 (burns moderately, tans progressively – 39 subjects), and type 4 (burns a little, always tans – 5 subjects). Occlusive patches containing the test material were affixed to skin of the dorsal intrascapular regions (to right or left of midline). The subjects were instructed to remove the patches 48 h after the first application, and after 24 h for the remainder of the study. Patch application "was repeated until a series of 9 consecutive, 24-h induction exposures had been made 3 times/wk for 3 consecutive weeks." (The report includes scores for 9 induction applications, so it is uncertain if the first patch was actually applied for 24 h or 48 h.) The induction phase was followed by a 10- to 14-d non-treatment period. During the challenge phase, an occlusive patch containing the test material was applied to a new site. Reactions were scored at 48 h and 96 h post-application according to the following scale: 0 (no reaction) to 4 (erythema, induration, and bullae. No adverse reactions of any kind were reported during the course of the study. The authors concluded that, under the conditions of the study, there were no identifiable signs or symptoms of sensitization (contact allergy) after application of the 10% Ascorbyl Glucoside solution.

OCULAR IRRITATION STUDIES

Animal

The ocular irritation potential of undiluted Ascorbyl Glucoside was evaluated in accordance with OECD TG 405 using 3 New Zealand White rabbits.[6] The test substance was instilled into the eye of each animal, and this was followed by a 7-d observation period. A mean ocular irritation score was calculated on the basis of scores at 24, 48, and 72 h for each animal. Discharge and slight effects (not described) on the iris were observed in one animal. The authors concluded that Ascorbyl Glucoside was slightly irritating to the eye.

SUMMARY

The safety of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside, as used in cosmetics, is reviewed in this safety assessment. According to the *Dictionary*, Ascorbyl Glucoside is reported to have the following functions in cosmetics: antioxidant, and skin-conditioning agent - miscellaneous.

Ascorbyl Glucoside is synthesized by a biocatalytic transglucosylation in which starch-derived cyclic or linear oligosaccharides are reacted with L-ascorbic acid by a g. According to another source, transglycosylation in the presence of the enzyme cyclodextrin glucanotransferase (CGTase, from *Paenibacillus sp.*) has been used to produce Ascorbyl Glucoside

According to 2020 VCRP data, Ascorbyl Glucoside is reported to be used in 532 cosmetic products (463 leave-on and 69 rinse-off). The results of a concentration of use survey conducted in 2018 indicate that Ascorbyl Glucoside is used at concentrations up to 5% (in face and neck skin care preparations, not spray), which is the highest reported maximum use concentration for leave-on formulations. In rinse-off products, Ascorbyl Glucoside is reported to be used at concentrations up to 2% (in paste masks and mud packs According to VCRP and Council survey data, Sodium Ascorbyl Glucoside is not being used in cosmetic products.

In vitro skin penetration data indicated slight (human skin) to no (pig skin) percutaneous absorption of Ascorbyl Glucoside. After application of a cream containing 2% Ascorbyl Glucoside to the legs and forearms of 5 male subjects, Ascorbyl Glucoside was absorbed percutaneously and converted to ascorbic acid through its metabolism in the skin and other parts of the body. It could also be stated that the results of this study indicate that ascorbic acid from dermally applied Ascorbyl Glucoside was absorbed.

The in vivo formation of Ascorbyl Glucoside in guinea pigs and rats was observed after oral administration of ascorbic acid in combination with maltose. The authors concluded that Ascorbyl Glucoside is a possible metabolite produced by enzymatic α-glucosidation after combined administration of ascorbic acid and maltose to guinea pigs and rats. In another study, groups of guinea pigs were fed an ascorbic acid-deficient diet supplemented with Ascorbyl Glucoside (0.96 - 192 mg/animal/d) or with equimolar amounts ascorbic acid (0.5 - 100 mg/animal/d. In the Ascorbyl Glucoside dietary groups, Ascorbyl Glucoside was not detected in the liver, adrenals, or urine. However, ascorbic acid was detected in the urine and in these organs, and the ascorbic acid concentration increased with increasing Ascorbyl Glucoside dosage. Thus, it was concluded that Ascorbyl Glucoside was metabolized to ascorbic acid.

Various concentrations of Ascorbyl Glucoside (0.2, 0.5, 1.0, or 5.0 mM) in isotonic phosphate buffer were perfused in the small intestine of fasted guinea pigs, and blood from the portal vein was collected. Following perfusion, the amount of intact Ascorbyl Glucoside collected in the perfusate was less than the amount perfused, and an increase in ascorbic acid was observed. A study was performed that compared the bioavailability of Ascorbyl Glucoside as ascorbic acid between humans and rats. Serum ascorbic acid concentrations increased in both humans and rats after oral dosing, and the results suggested that the absorption of ascorbic acid in humans occurs at higher levels and at a faster rate when compared to rats.

The acute dermal toxicity of Ascorbyl Glucoside (concentration not stated) was evaluated using 10 Wistar rats, and an LD_{50} of > 2000 mg/kg was reported. None of the animals died, and there were no signs of systemic toxicity or effect on organs. An LD_{50} of > 2000 mg/kg was also reported in a study in which 3 groups of 10 rats of the Crj:CD strain were dosed orally with Ascorbyl Glucoside (concentration not stated). There were no animal deaths and no signs of systemic toxicity or organ effects.

Five groups of guinea pigs (mostly groups of 5) were fed an ascorbic acid-deficient diet supplemented with 0 - 192 mg/animal/d Ascorbyl Glucoside, and another 4 groups were fed an ascorbic acid-deficient diet supplemented with equimolar amounts of 0.5 - 100 mg/animal/d ascorbic acid. Guinea pigs fed diet supplemented with Ascorbyl Glucoside had similar body weight gain when compared to guinea pigs fed diet supplemented with an equimolar amount of ascorbic acid. Serum alkaline phosphatase activity in both Ascorbyl Glucoside and ascorbic acid dietary groups was statistically significantly ($p < 0.05$) higher when compared to the control group. However, there was no significant difference in serum alkaline phosphatase activity between the Ascorbyl Glucoside and ascorbic acid dietary groups.

In a study in which groups of 10 male and 10 female Wistar rats were dosed by gavage with up to 1000 mg/kg/d Ascorbyl Glucoside (in distilled water) for 28 d, no adverse effects were reported. The NOAEL was 1000 mg/kg/d.

In the Ames test, Ascorbyl Glucoside (doses up to 5000 µg/plate) was not genotoxic in the following bacterial strains, with and without metabolic activation: *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 uvrA. Ascorbyl Glucoside was not clastogenic to Chinese hamster Don cells (with and without metabolic activation) at concentrations up to 2000 µg/ml. The in vitro genotoxicity of Ascorbyl Glucoside was also evaluated in the mammalian chromosome aberration test using Chinese hamster V79 cells. At concentrations up to 3400 µg/ml, results were negative with and without metabolic activation. The in vivo genotoxicity of Ascorbyl Glucoside was evaluated in the micronucleus test using groups of 10 mice of the Slc:ICR strain injected i.p. with the test substance. The test substance was non-clastogenic at doses up to 2000 mg/kg.

The effect of Ascorbyl Glucoside (30 µM and 100 µM) at the promotion stage in the two-stage BALB/c 3T3 cell transformation assay was evaluated. When compared to the transformation control (treatment with MCA followed by TPA), the inhibition by 100 µM Ascorbyl Glucoside (31% inhibition of transformation) only was statistically significant.

After 2 d of incubation of B16 melanoma cells with Ascorbyl Glucoside (2 mmol/l), a statistically significant decrease in melanin pigmentation was observed.

In an assay using cultured human skin fibroblasts, Ascorbyl Glucoside effectively stimulated collagen synthesis at concentrations of 0.1 - 0.5 mM.

Cultured human skin (abdominal) fibroblasts at different cell densities were used in a study evaluating the cytotoxicity of Ascorbyl Glucoside (1 mM). The test substance was not cytotoxic to cultures at cell densities between 0.625×10^4 cells/well and 10×10^4 cells/well. Ascorbyl Glucoside dose-dependently (0.5 to 5 mM) suppressed UVB-induced cytotoxicity in cultured HaCaT human keratinocytes.

In a study involving 3 New Zealand White rabbits, undiluted Ascorbyl Glucoside was non-irritating to the skin after 4 h of application under a semi-occlusive dressing.

The skin sensitization potential of Ascorbyl Glucoside was evaluated in the maximization test (OECD TG 406) using a group of 20 guinea pigs. The challenge phase involved a 24-h topical application of the test substance (under occlusive dressing) to the flank at concentrations of 15, 25, 50, and 75%. At topical induction, slight erythema was observed in 1 animal after a 24-h application. However, none of the animals (test or controls) exhibited erythema or edema at the challenge site.

An HRIPT on a rinse-off product containing 0.1% Ascorbyl Glucoside was performed using 103 subjects. Dilution of the product to a 2% aqueous solution (effective Ascorbyl Glucoside test concentration = 0.002%) was performed prior to

testing. The diluted product did not induce dermal sensitization in any of the subjects tested. A second HRIPT in the same study was on a leave-on product containing 2% Ascorbyl Glucoside (undiluted), and was performed using 113 subjects. The undiluted product did not induce dermal sensitization in any of the subjects tested. The skin irritation and sensitization (contact allergy) potential of Ascorbyl Glucoside (10% solution) was evaluated in an HRIPT involving 51 subjects. There were no identifiable signs or symptoms of sensitization (contact allergy) after application of the 10% Ascorbyl Glucoside solution.

Undiluted Ascorbyl Glucoside was slightly irritating to the eyes of 3 rabbits.

DISCUSSION

Ascorbyl Glucoside has been identified as a bleaching agent in Asia in commercial bleaching products (that also contain kojic acid), when used at concentrations of ~2%; however, the Panel noted that it is not likely that this chemical would penetrate the stratum corneum at concentrations that would be sufficient for inhibition of the tyrosinase enzyme that catalyzes the synthesis of melanin. This assumption is based on chemical properties of Ascorbyl Glucoside and the understanding that skin penetration would not be likely under cosmetic product use conditions, which takes into consideration the use of Ascorbyl Glucoside in leave-on products at concentrations up to 5%. Additionally, relative to a skin bleaching effect, the Panel determined that the statistically significant decrease in the melanin content of B16 melanoma cells in the presence of Ascorbyl Glucoside (2 mmol/l) in vitro is not sufficient evidence that a similar effect would be observed in vivo. The Panel also acknowledged that skin lightening agents are usually phenolic compounds. Nevertheless, the Panel noted that skin lightening is considered to be a drug effect in the US, and should not occur during the use of cosmetic products, and cosmetic formulators should only use Ascorbyl Glucoside in products in a manner that does not cause depigmentation.

The Panel noted the absence of developmental and reproductive toxicity data on Ascorbyl Glucoside and Sodium Ascorbyl Glucoside. However, concern over the lack of these data were mitigated considering that Ascorbyl Glucoside is metabolized to ascorbic acid and glucose in the skin and would not be absorbed in an appreciable quantity. Additionally, concern was further mitigated because both of these substances are essential constituents of the body, and are not reproductive and developmental toxicants.

Finally, the Panel discussed the issue of incidental inhalation exposure from the use of Ascorbyl Glucoside in pump and aerosol hair spray formulations and in face powers; the maximum reported concentration of use in these types of products is 0.01% in hair sprays and 2% in face powders. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Ascorbyl Glucoside and Sodium Ascorbyl Glucoside* are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

** Not reported to be in current use. Were this ingredient 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 Ascorbyl Glucoside.*

TABLES

Table 1. Properties of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside

Property	Value/Results	Reference
Ascorbyl Glucoside		
Form (at 20 ºC and 101.3 kPa)	White or yellowish white powder or crystalline powder; colorless vitamin C glycosyl derivative with a pillared crystal structure	[6,9]
Molecular weight (Da)	338.263	[7]
Particle size (mass mean aerodynamic diameter, MMAD)	24 µm (approximately 1.5% of particles below 10 µm diameter)	[6]
Density (g/ml at 20.9 ºC)	1.586	[6]
Boiling point (ºC at 101.325 kPa)	188	[10]
Melting point (ºC)	158.5 - 159.5	[9]
Melting/Freezing point (ºC)	152 - 162	[11]
Water solubility (g/l at 19 ±1 ºC)	714	[6]
Solubility (g/100 g water at 25ºC)	125	[12]
Vapor pressure (kPa at 25ºC)	1.1×10^{-13} (estimated)	[6]
log P_{ow} (at 20 ºC)	< -2	[6]
Ultraviolet absorption wavelength λ_{max} (nm)	238 (at pH 2); 260 (at pH 7)	[9]
Sodium Ascorbyl Glucoside		
Formula weight (Da)	360.25	[8]

Table 2. Frequency (2020) and Concentration (2018) of Use According to Duration and Type of Exposure.[19,20]

	Ascorbyl Glucoside	
	# of Uses	Conc. (%)
Totals*/Conc. Range	**532**	**0.00081-5**
Duration of Use		
Leave-On	*463*	*0.001-5*
Rinse off	*69*	*0.00081-2*
Diluted for (bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	61	0.001-2
Incidental Ingestion	1	NR
Incidental Inhalation- Sprays	163[a]; 151[b]	0.01; 0.02[a]
Incidental Inhalation- Powders	10; 151[b]	2; 0.5-5[c]
Dermal Contact	508	0.00081-5
Deodorant (underarm)	1[a]	0.05
Hair - Non-Coloring	6	0.001-0.05
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	8	0.01-0.05
Baby Products	NR	NR

NR = Not Reported

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

[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays

[b]Not specified these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories

[c]It is possible that these products may be powders, but it is not specified whether the reported uses are powders

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2020 VCRP Data

Ascorbyl Glucoside

3C-Eye Shadow	1
3D-Eye Lotion	27
3E-Eye Makeup Remover	3
3F-Mascara	16
3G-Other Eye Makeup Preparations	14
5G-Tonics, Dressings, and Other Hair Grooming Aids	3
5I-Other Hair Preparations	3
7B-Face Powders	10
7C-Foundations	14
7E-Lipstick	1
7F-Makeup Bases	4
7I-Other Makeup Preparations	8
10A-Bath Soaps and Detergents	2
10B-Deodorants (underarm)	1
10E-Other Personal Cleanliness Products	5
11A-Aftershave Lotion	1
11E-Shaving Cream	1
11G-Other Shaving Preparation Products	1
12A-Cleansing	50
12C-Face and Neck (exc shave)	141
12D-Body and Hand (exc shave)	10
12F-Moisturizing	109
12G-Night	42
12H-Paste Masks (mud packs)	7
12I-Skin Fresheners	9
12J-Other Skin Care Preps	49
Total	**532**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: July 10, 2020

SUBJECT: Tentative Report: Safety Assessment of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside as Used in Cosmetics (Release Date: June 19, 2020)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Ascorbyl Glucoside and Sodium Ascorbyl Glucoside as Used in Cosmetics.

Non-Cosmetic Use - In the Non-Cosmetic Use section, it should be noted that the Asian products in which Ascorbyl Glucoside was found also contained additional ingredients such as kojic acid and glabridin which are associated with skin whitening effects.

Genotoxicity, In Vitro - Please correct: “cytotoxicity at over the range of concentrations”

Discussion - In the Discussion, it should be made clear that reproductive and developmental toxicity data are not needed because the metabolites of Ascorbyl Glucoside, ascorbic acid and glucose, are essential constituents of the body and are not reproductive and developmental toxicants.