Safety Assessment of Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	August 20, 2021
Panel Meeting Date:	September 13-14, 2021

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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.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.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. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088
cirinfo@cir-safety.org

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

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

Date: August 20, 2021

Subject: Safety Assessment of Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate as Used in Cosmetics

A Tentative Report with a conclusion stating that the following 7 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment was issued at the March 2021 Panel meeting: Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate. Enclosed is the Draft Final Report on the Safety Assessment of these ingredients as used in cosmetics (*saccha092021rep*). This report has been revised to address comments (*saccha092021pcpc*), received from the Council, on the Tentative Report that was issued at the March 2021 Panel meeting.

Also included in this package for your review are the report history (*saccha092021hist*), flow chart (*saccha092021flow*), literature search strategy (*saccha092021strat*), ingredient data profile (*saccha092021prof*), 2021 FDA VCRP data (*saccha032021FDA*), and minutes from prior Panel meetings (*saccha092021min*).

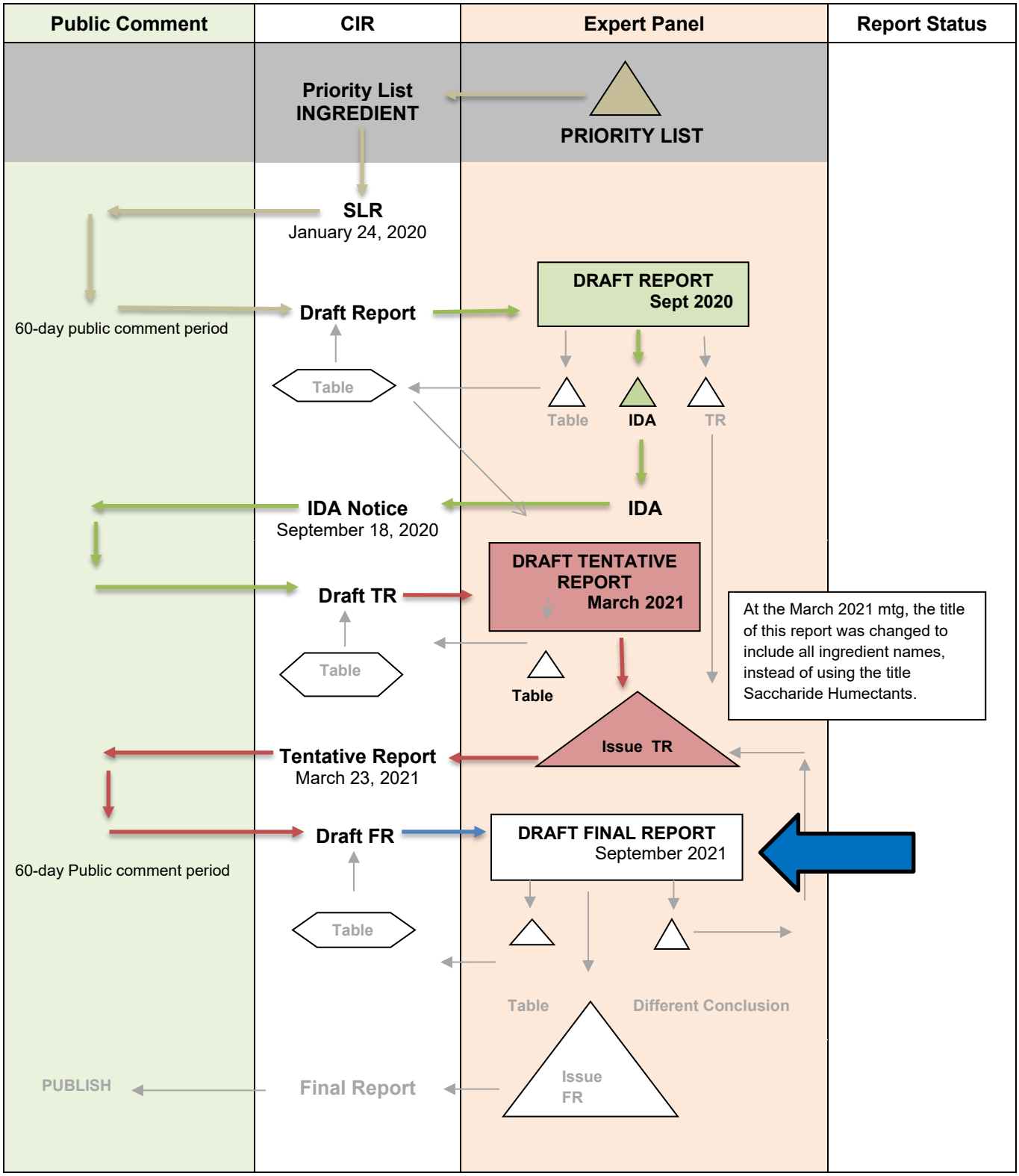
After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Final Report with the conclusion that is stated in the first paragraph above.

1620 L Street, NW Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(email) cirinfo@cir-safety.org (website) www.cir-safety.org

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Saccharide Isomerate, etc

MEETING September 2021



CIR History of:

Saccharide Humectants

A Scientific Literature Review (SLR) on Saccharide Humectants was issued on January 24, 2020.

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

The draft report has been revised to include the Council's comments, and also includes the following unpublished data that were received from the Council:

- Use concentration data
- Human ocular irritation data on an eye cream containing 2.75% Saccharide Isomerate
- Human repeated insult patch test on an eye cream containing 2.75% Saccharide Isomerate

An Insufficient Data Announcement (IDA) with for the following data requests was issued:

- Method of manufacture, impurities, and composition data on all ingredients/ingredient mixtures
- Confirmation of the lack of skin penetration of these ingredients/ingredient mixtures
- Composition of glucose and fructose in the ingredient mixtures; if the 2 monosaccharides are present in sufficient amounts, the available negative data on glucose and fructose skin penetration can be used to evaluate the skin penetration potential of saccharide humectant ingredient mixtures
- 28-day dermal toxicity data on Saccharide Isomerate at cosmetic use concentrations up to 2.8%

The Panel noted the finding of myocarditis (i.e., myopathy described as necrotic inflammatory cell infiltrates) in the 28-day oral toxicity study involving rats, and agreed that this finding should be addressed in the discussion. The Panel also agreed that the anti-melanogenic activity of Anhydrogalactose in B16F10 melanoma cells and human epidermal melanocytes in in vitro experiments should be addressed in the discussion. The discussion will also include inhalation and heavy metals boilerplates, as requested by the Panel.

Draft Tentative Report, Teams/Panel: March 11-12, 2021

The report has been revised to include comments that were received from the Council prior to and after the September 2020 Panel meeting.

The following data, received in response to the IDA, have also been incorporated:

- Chemical properties of Arabinose and Saccharide Isomerate
- Methods of production of Arabinose and Saccharide Isomerate
- Composition/Impurities data on Saccharide Isomerate
- Dermal penetration statement on Saccharide Isomerate
- Acute oral toxicity data on Saccharide Isomerate
- In vitro genotoxicity data on Saccharide Isomerate
- Animal and human skin irritation data on Saccharide Isomerate
- Animal and human skin sensitization data on Saccharide Isomerate
- Animal and human phototoxicity/photosensitization data on Saccharide Isomerate
- Ocular irritation data on Saccharide Isomerate

The Panel issued a tentative report for public comment with the conclusion that the following ingredients are safe in the present practices of use and concentration described in the safety assessment:

Anhydrogalactose
Anhydroglucitol
Anhydroxylitol
Arabinose
Psicose
Saccharide Hydrolysate
Saccharide Isomerate

After consideration of the data received and other data included in the safety assessment, the Panel determined that the available data are sufficient for determining the safety of these ingredients. Specifically, the Panel noted that data on Saccharide Isomerate with varying molecular weights (MW) (lower MW range: 120 to 400 Da; higher MW of 15,000 Da, 20,000 Da, or > 1.4 MDa) are among the data that have been reviewed. The lower molecular weight Saccharide Isomerate consists mostly of

glucose and fructose, and, in the absence of developmental and reproductive toxicity data in the safety assessment, the Panel noted that concerns relating to this toxicity endpoint are mitigated based on this composition. Furthermore, the Panel agreed that concerns relating to this endpoint are also mitigated for the higher MW Saccharide Isomerate, as it would not be percutaneously absorbed.

Draft Final Report, Teams/Panel: September 13-14, 2021

The draft final report has been revised to address comments on the tentative report (issued at March Panel meeting) that were received from the Council.

Saccharide Humectants Data Profile* –September 13-14, 2021 – 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
Saccharide Isomerate	**352**			**X**	**X**	**X**			**X**							**X**					**X**	**X**		**X**	**X**	**X**		**X**		
Saccharide Hydrolysate	**33**	**Yes**		**X**	**X**																								**X**
Anhydrogalactose (is L-Anhydrogalactose)	**0**																												
Anhydroglucitol (is D-Anhydroglucitol)	**0**						**X**					**X**																		
Anhydroxylitol (is D-Anhydroxylitol)	**153**					**X**		**X**	**X**			**X**				**X**	**X**				**X**			**X**				**X**		
Arabinose (is D-Arabinose)	**0**			**X**			**X**		**X**			**X**						**X**												**X**
Psicose (also allulose; Dictionary does not state whether D, L, or DL)	**0**						**X**		**X**			**X**																		**X**

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

Saccharide Humectants – 8/21-22/2019; 9/20/2019;8/7/2020; 1/8/2021;6/6/2021; 7/20/2021

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Saccharide Isomerate	100843-69-4	Yes		0/0	Yes	No	No	No	No	No	No	No	No	No	No	No	No	
Saccharide Hydrolysate	8013-17-0	Yes		89/8	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	
Anhydrogalactose (is L-Anhydrogalactose)	28251-55-0	Yes		86/5	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	
Anhydroglucitol (is D-Anhydroglucitol)	154-58-5	Yes		487/16	1/0	No	No	Yes	No	No	No	No	No	No	No	No	No	
Anhydroxylitol (is D-Anhydroxylitol)	53448-53-6	Yes		5/2	1/0	No	No	Yes	No	No	No	Yes	No	No	No	No	No	
Arabinose (is D-Arabinose)	10323-20-3	Yes		510/6	12/0	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	
Psicose (also allulose; Dictionary does not state whether D, L, or DL)	23140-52-5	Yes		260/11	7/0	No	No	Yes	No	No	No	No	No	No	No	No	No	

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/

SEPTEMBER 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 14, 2020

So this is the first time we're looking at the safety assessment. There are seven ingredients. They are skin conditioning agents and humectants. And anhydrogalactose is also an antioxidant. And anhydroglucitol functions as an oral care agent. And I guess we should look at that as soon as I can find it. Sorry. My computer is really slow today as well. Okay. So I guess the first question I had, Dan, is are you okay with the grouping here?

DR. LIEBLER: Yes. I'm fine with it.

DR. BELSITO: Okay. And just for my information, there had been some talk at the last meeting about you and Lisa getting together and looking at these groupings. Is that happening?

DR. LIEBLER: That didn't happen for this meeting.

DR. BELSITO: Okay.

DR. LIEBLER: I didn't see anything that looked like it would be at all problematic.

DR. BELSITO: Okay.

DR. LIEBLER: In any of the reports.

DR. BELSITO: Okay.

DR. LIEBLER: Not counting out (audio skip).

DR. BELSITO: Okay. And then, again, I guess this goes to the inhalation that we just discussed. So there was possible inhalation but we're not sure of it and so therefore the respiratory boilerplate was not in the conclusion. Is that correct, Monice?

MS. FIUME: Well, actually, this one is used in fragrances so typically we're assuming those are inhaled.

DR. BELSITO: Okay.

MS. FIUME: So that would then be a reason to include the inhalation boilerplate.

DR. BELSITO: Okay. Then just a comment about, there's a whole risk assessment section under use. I didn't think it belonged there at all. Shouldn't that be more under the, I mean, towards the end of the report where we usually include risk assessments or under where we talk about sensitization and irritation but not under use?

DR. KLAASSEN: I agree with that. We have two or three documents here where we talk about risk assessment, a margin of safety early on in the document. It should come in towards the end of the document as far as I'm concerned. Maybe kind of at the end of the animal toxicity studies.

MS. FIUME: So then, can I ask a question about that? Because this is one of those sections that has been being moved around in the report it seems each time. And this one was placed under use because they were looking at it specifically as used in cosmetic products. So even though it was discussing the amounts that could be exposed and the concentration that was found to be somewhat safe based for cosmetic products, it should still get moved to the end of animal tox?

Because you're right we -- this has been coming up more. I mean, typically we didn't include the risk assessments but a lot of times if we have a NICNAS report they have done this type of assessment, or sometimes the SCCS has. So if we could have some guidance on where you really would like to see that that would be helpful.

DR. SNYDER: I think you --

DR. LIEBLER: Well --

DR. SNYDER: I think an easy way to handle this you can, like, at the absorption section you can mention that what study was used, absorption study was used to do the risk assessment and say, refer to the risk assessments at the end of the document or something. So we don't necessarily have to have it -- again, I agree that it should probably be towards the end because it's based upon absorption and NOAEL.

And so I think it should -- it's a little premature to put it up front when you really haven't covered that material yet. But you could mention in it and say with a single sentence and say see the risk assessment this data was used for the risk assessment at the end of the document or something.

DR. LIEBLER: You know, Monice, this is Dan. Maybe the logical place to put these is at the end of the data section of the end-point type they refer to. In this case, it refers to repeated dose dermal and so it could go there at the end of the animal studies on dermal, on a repeated dose tox.

MS. FIUME: Okay.

DR. LIEBLER: Because I agree, this doesn't quite fit here. I understand what you said about the reasoning but it still, I think, just doesn't logically fit here.

MS. FIUME: Okay. Thank you.

DR. BELSITO: So Dan, you're suggesting this be moved to after the repeated dermal?

DR. LIEBLER: Yes. Since it refers to dermal risk assessment.

MS. FIUME: And so even the -- so just -- for total clarification because the name of that section is generally toxicological studies, so that's appropriate to include the risk assessment under the toxicological studies?

DR. LIEBLER: Yeah. I don't see a problem with that.

MS. FIUME: Okay. Thank you.

DR. LIEBLER: I'm only speaking for myself but, guys?

DR. SNYDER: Yeah. I think it should be right at the end. Like, in this case, it should be after carcinogenesis studies. And, I mean, it should be under other relevant studies or evaluations or something. Other relevant studies and evaluations or something.

DR. LIEBLER: Paul, the reason I made my suggestion was because the risk assessment was about repeat dose dermal.

DR. SNYDER: Right. I understand. But it was -- it's kind of a funky thing because we don't have any absorption data on that particular ingredient. We only have absorption data. I mean, we don't have any -- they assumed 100 percent absorption and they used a repeat dose study NOAEL of 1,000 milligrams per kilogram. So it's not, I mean, I don't even think it was -- it didn't impact my decision on the ingredient at all. So….

DR. LIEBLER: Uh-huh. I see. Yeah. You're right. So it is in a way sort of logically disconnected from the repeat dose dermal data that we have.

DR. SNYDER: Right. And it kind of gives -- makes it look like, oh we needed a risk assessment because we had some concern. Even without it, I wouldn't have had any concerns.

DR. LIEBLER: Yeah.

DR. SNYDER: Well, then, I mean, I guess the other all-purpose place to put it is under other relevant studies and evaluations. You might have to just change that heading to, you know, because it's not really a study but give it evaluation or something.

DR. LIEBLER: Or you could put it at the very end after clinical studies. Right before the summary.

DR. SNYDER: Yeah.

MR. JOHNSON: Dr. Liebler, so that means that this would be a major heading after the clinical studies major heading section. Is that correct?

DR. LIEBLER: I think that's correct.

MR. JOHNSON: Okay. Thank you.

DR. BELSITO: Yeah, but haven't we traditionally had a section where we did margins of safety that was entitled margin safety?

DR. SNYDER: I believe so. Risk assessment. Yes.

DR. SNYDER: Or risk assessment.

MS. FIUME: Yes. But a lot of times I think it may have been a secondary heading under something like, if it's the QRA that was with the sensitization data typically I believe because it was specific.

DR. SNYDER: I would just have a separate heading risk assessment and just put it there clear at the end after the clinical reports.

DR. BELSITO: So after or before the clinical studies?

DR. SNYDER: Either one. It doesn't matter to me. But I think we need to do that. We need to be consistent in our reports so that readers get used to where it will be if it's in a report.

DR. KLAASSEN: I will suggest the later the better.

DR. BELSITO: So after clinical studies and before the summary?

DR. KLAASSEN: Yes.

DR. SNYDER: So major heading after clinical studies.

MS. FIUME: Okay. All right. I will make sure that we make that change across the board because as you mentioned this is probably in maybe three reports.

DR. KLAASSEN: Yes. I think there's two or three reports this time that it goes, I didn't like where it was at. It needs to be moved to the end.

MS. FIUME: Okay. Thank you.

DR. KLAASSEN: I think it's most logical to have the risk assessment after you've seen all of the data.

DR. SNYDER: And then, Dan, I had a question. We only had materials and methods on three of the ingredients and composition impurities on one of the ingredients.

DR. LIEBLER: Right.

DR. SNYDER: And then, is there any, the D and the L isomers is that -- does that matter?

DR. LIEBLER: Not really. Not particularly concerned about those from a safety perspective. I think just in terms of documenting materials of the ingredients if we can get that information, we should have it. I felt that representative materials and representative methods for these ingredients would be relevant even if they're not specifically designated for cosmetic ingredients.

So that's under method of manufacture. I think that this saccharide isomerate is the real problem here, is the most type of used ingredient and we have no method of manufacture, no composition, and impurities.

DR. BELSITO: No. So that was my question to you, Dan. Like you said, it's the most frequently used and has the highest concentration of use and we really have no data on it.

DR. LIEBLER: Yeah.

DR. BELSITO: So do you feel we can read across or --

DR. LIEBLER: No.

DR. BELSITO: Okay.

DR. LIEBLER: No. I think, there's no excuse for not having those data on something with that many uses and that high concentration of use. So we simply have to have that.

DR. SNYDER: That's what I was worried about. Thank you.

DR. BELSITO: So we need manufacturing and impurities.

DR. SNYDER: Right.

DR. LIEBLER: I mean, if they have a secret recipe for producing this isomerate that gets a certain amount of this, and a certain amount of that, and a certain amount of the other in terms of the saccharide products that are present, you know, that level of detail isn't quite necessary. But it just says hydrolysis or sorry, actually in Table 1 is the only description we have of it. And it -- I'm going to Table 1 right now. Bottom of Table 1 it says saccharide isomerate is a carbohydrate complex formed from a base-catalyzed rearrangement of a mixture of saccharides.

Now, I don't know if that means polysaccharides, a larger molecular weight mixture of molecules or is this also very low molecular weight like the other ingredients in our report? If it's a high molecular weight and it gives you a high molecular weight product then I have doubts over whether it belongs in the report in the first place. I suspect it's probably not.

In other words, for this humectant function, you probably want a lot of low molecular weight mono, di, trisaccharides. And this is obviously a mix but it just is -- if they only said what they started with or what they finish with, and at least in sufficient terms for us to get an idea, is this a mix of mono, di, trisaccharides maybe or just monosaccharides? That would be sufficient. But right now we don't have anything. So we have to make a lot of assumptions about what this ingredient is. And I think it works against us throughout the report thereafter.

DR. BELSITO: So this is under chemical characterization as well.

DR. LIEBLER: Yes.

DR. BELSITO: In Table 1.

DR. LIEBLER: Right. Well, Table 1 is the only information about this saccharide isomerate. It's just that one entry in the table but maybe describes what it is. So we need method of manufacture, composition, and impurities for that.

DR. BELSITO: Okay. And, Paul, I had a question for you on PDF page 15 on the anhydroxylitol -- droxilytol. This was in the oral toxicity where --

DR. SNYDER: Yeah. That 28-day oral with the myocarditis?

DR. BELSITO: Yeah.

DR. SNYDER: Yeah. That's -- if we use a new terminology for that we better understand that disease. That's a rat specific, rodent specific part of the rat progressive cardiomyopathy. And the incidents and the background finding incidents and the severity can be highly variable. So I was not concerned about that. I had a note that I'm not concerned about that.

DR. BELSITO: Okay.

MR. JOHNSON: Dr. Snyder, will you mention again your lack of concern, the rationale for your lack of concern over that finding?

DR. SNYDER: It's a common background finding in rodents with a highly variable incidence and severity across studies and even within studies.

DR. BELSITO: Yeah. I mean, the next sentence, Wilbur, says it all. That they notice the incidents of these lesions is typical of that observed in rats in this type of study. I just wanted to make sure that Paul was okay with that statement.

DR. SNYDER: Yeah. We got away from using -- it used to be called -- they went through a number of iterations. Myocarditis was initially what it was diagnosed as years ago and because of the concern with risk assessment and myocarditis in people we went away from that. And then we went to progressive cardiomyopathy and now we've gotten away from that because of the myopathy so now we just call it necrosis sliced inflammatory cell infiltrates. Everybody knows that it's just -- it's a rodent specific thing. It has no bearing to risk assessment in people.

DR. BELSITO: Okay. And then, Wilbur, I had a question for you on the chronic tox studies on PDF page 16, just before the DART heading. It says, extensive amyloid doses of liver, spleen, and kidneys occurred frequently in mice. Was this all mice or just those treated with arabinose?

MR. JOHNSON: Which paragraph, Dr. Belsito?

DR. BELSITO: The last paragraph under chronic toxicity. It's on PDF 16.

MR. JOHNSON: Yes.

DR. BELSITO: Subcutaneous arabinose. The last line in that paragraph. It says extensive amyloidosis occurred frequently in the mice. Was that all mice or just mice treated with arabinose?

MR. JOHNSON: It wasn't in all mice. It would have been those just treated with the arabinose.

DR. SNYDER: I'm guessing it was all mice. The same thing with the necrotic change above. I would probably just delete those last two sentences. There was no histologic evidence of an effect on any internal organ because then that's kind of contradictive.

DR. BELSITO: Right. That's what I'm --

DR. SNYDER: If it were me, I would just delete those last two sentences that it only -- once they make a summary statement regarding the test article effect just stop. Don't add anything else because it starts to make it look complicated and it's not. So I would just delete those last two sentences because it already says -- the sentence previous to those two say there was no test article effect.

DR. BELSITO: Yeah. That was my assumption as well, Paul. I just wanted to make sure. So, Wilbur, you have that? You're gonna end it with, "especially, there was no histological evidence of injurious effects on any internal organ especially liver, kidneys in mice or rats," period and that's it. Strike the last two sentences.

MR. JOHNSON: Okay. I'll do that.

DR. BELSITO: Okay. So moving on, we have no DART data. Do we need a 28-day dermal for these?

DR. KLAASSEN: Monice, I have a question for you.

MS. FIUME: Okay.

DR. KLAASSEN: I found this by going on the CIR webpage for the -- this is 155th meeting, except it's been erased this morning.

MS. FIUME: It's been erased?

DR. KLAASSEN: Yeah. We go from 153 to 154 to 156 and this is 155th.

MS. FIUME: Let me take a look.

DR. SNYDER: Don, to your point, since we're gonna go insufficient data announcement I think we should ask for a 28-day dermal because we have no absorption data --

DR. BELSITO: Okay.

DR. SNYDER: -- and we have no regrowth tox data so…

DR. BELSITO: Right. Okay.

MS. FIUME: Curt, on the CIR webpage, are you clicking panel meetings? If you click panel meetings, that brings up today's meeting. It's the third tab from the left.

DR. KLAASSEN: Well, I go to CIR and then I go to the -- okay, on your cosmetic ingredient review page, you know, there's home, about -- oh, panel meetings?

MS. FIUME: Yes. On the top. Do you see?

DR. KLAASSEN: Okay. I go to the events. Okay.

MS. FIUME: For this --

DR. KLAASSEN: If I can find it there it's okay. Okay. It's here. It just wasn't under the -- I go to the events. Fine. Thank you.

MS. FIUME: Mm-hmm.

DR. BELSITO: Okay. So, what did I just do? Moving on, so we need a 28-day dermal because we have no absorption or DART. Then we have, this is the first with a skin lightening discussion because we have anti-melanogenic activity noted. So I basically, it's almost like we should develop a boilerplate for this and use what we've said before that skin lightening would not be a cosmetic effect. And manufacturers should be diligent about assuring that products that they market do not cause this effect or something to that. I mean, we've used this language before.

DR. SNYDER: You know, one of my problems with this is we get these anti-melanogenic activity type reports and they're basically these mouse melanoma cells treated with a high dose of a chemical. And I'm not sure that that's a model that predicts skin lightening in vivo. And if we don't have any indication of skin lightening in vivo like in an animal model, I'm very reluctant to stir the pot on skin lightening with these because I think we don't have sufficient data. So that's my reaction to it. I've said this at other meetings when we've had similar data and I'd just like to hear what you guys think about that.

DR. KLAASSEN: I second that.

DR. LIEBLER: Yeah. I do. I also agree with that. And I had some language, Don, that I've kept on my unique language folder for these reports where you many, many years ago said that in vitro allergy testing can only identify a hazard, you cannot determine the risk. And I think this is the same thing that in vitro may identify a hazard, I mean, I.D. a hazard but you can't determine the risk because you need in vivo data. And I think this is kind of along that same line. So I think in your suggestion for the boilerplate I think we can make a statement similar to that and then follow it by saying that other language that you just used there previously.

DR. BELSITO: So you said in vitro determines a hazard but does not identify a risk? Is that how you put it?

DR. LIEBLER: Well, that's how you used it for in vivo --

DR. BELSITO: Right.

DR. LIEBLER: -- allergy testing. It can only identify a -- I can only I.D. a hazard. It cannot determine the risk. And so yes, so there's a potential because of the in vitro but unless it's supported by in vivo data it's really irrelevant because it can't be translated to the human race.

DR. BELSITO: Okay. So something like that, Monice, in the discussion. I mean, I don't think we can totally ignore it if we're gonna put the data in the paper. You know, I was thinking that the discussion we can say that the in vitro for anti-melanogenic activity identifies the potential hazard for skin depigmentation but does not determine the risk. And it's our assumption that manufacturers will use appropriate practices to prevent this or to minimize the risk, or however you want to word it.

MS. FIUME: Okay. But, Don, you do want the in vitro studies if they're found in the report?

DR. LIEBLER: Yes.

DR. BELSITO: I don't think we can ignore them.

MS. FIUME: Okay.

DR. LIEBLER: Right.

DR. BELSITO: Because then -- yeah.

DR. LIEBLER: I just think we should be careful about overreacting to them. It's certainly not referring to these as having skin depigmenting or a skin lightening activities without any further -- without any data beyond those.

DR. BELSITO: Right. Okay.

MS. FIUME: Okay.

MR. JOHNSON: So, Dr. Belsito, just two data needs. The two that have been identified thus far are the only ones that are needed for the IDA?

DR. BELSITO: I'm just checking. Yeah. So we have appropriate sensitization for the saccharide isomerate. It's 2.75, the reported highest concentration is 2.8. So basically, we have limited mutagenicity but negative carcinogenicity so I'm assuming that that was okay.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay. So we need a 28-day dermal. Well, first of all, we need manufacturing composition and impurities of the isomerate. And then we need a 28-day dermal.

MS. FIUME: Is that on any specific ingredient?

DR. BELSITO: No.

DR. SNYDER: Isomerates.

DR. BELSITO: Isomerate.

MS. FIUME: Okay.

DR. BELSITO: So, I mean, all of our needs are on the isomerate. So we need manufacturing, composition, and impurities, 28-day dermal on the isomerate. And then in the discussion, the skin lightening that we just reviewed, do we need the respiratory boilerplate here? And also, I had a question about heavy metals.

DR. LIEBLER: I think it's reasonable to have the heavy metal boilerplate present because metals are logically, chemically likely to be a contaminant.

DR. BELSITO: Okay. What about the respiratory boilerplate?

MR. JOHNSON: Yeah. We would need it because anhydroxylitol is used in fragrance preparations.

DR. BELSITO: Okay. So in the discussion, we need skin lightening, respiratory boilerplate, and the heavy metal boilerplate. And then we're going to add insufficient for manufacturing composition, impurities, and 28-day dermal tox on the isomerate at concentration of use.

DR. LIEBLER: That's right.

DR. SNYDER: Now the only thing, Don, would be the 28-day dermal might give us some information about the anhydrogalactose with its effect on melanogenesis maybe. Is that a consideration?

DR. BELSITO: I don't understand the mechanism for the melanogenesis, so I'd have to pass that off to Dan and see what he thinks in terms of the chemical structures of these.

DR. LIEBLER: Well, I mean, it's likely that in that melanogenesis effect, let's see, where are we? That's --

DR. SNYDER: Page 17.

DR. LIEBLER: Right. I know. This was kind of an unusual assay. They're basically taking these mouse melanoma cells and then treating them with melanocyte stimulating hormone, MSH, and then they're looking at the effect of the anhydrogalactose on melanin content induced by MSH. And it said that it inhibited melanin secretion at 50 micrograms per mil which is a high exposure. You know, I think the 28-dermal might go away once we know what's in this.

DR. SNYDER: Yeah. I agree.

DR. LIEBLER: So we --

DR. SNYDER: We don't have good data -- the systemic tox data.

DR. LIEBLER: So let's just set aside the whole issue of skin lightening here because I don't think there's any evidence for skin lightening. There's evidence for inhibition of melanin synthesis in an in vitro model of questionable applicability.

DR. BELSITO: So is that -- you're suggesting that in the discussion?

DR. LIEBLER: Well if it comes to that. I want to see method of manufacture or composition impurities for the isomerate and then we can take this up in the discussion once, you know, we can address -- I'm even reluctant to address the skin

lightening in the discussion. But if you want to, we can indicate -- I think that this is -- it's questionable whether or not this is a predictive model for skin lightening.

And we see this enough that, you know, we see this in enough reports of this kind of in vitro model, dump a pile of the chemical on it and then we're forced to talk about skin lightening in vivo. I'd like to get some idea of whether or not these models are actually shown to have real predictive power, predictive utility.

DR. BELSITO: Okay. So --

DR. LIEBLER: We could come up with a boilerplate couple of sentences because it's a very similar situation where, you know, the panel noted inhibition of melanin production by chemical X and chemical Y in an in vitro cell model. Panel noted -- the concern of the panel was mitigated by the high exposure concentration use and the uncertainty as to whether the model actually had any predictive effect, of in vivo -- of predictive in vivo effects.

DR. BELSITO: Okay.

DR. KLAASSEN: That's good. I like that.

DR. BELSITO: I mean, we'll have to re-draft the discussion.

DR. LIEBLER: Oh, yeah.

DR. BELSITO: I mean, clearly, we're insufficient for manufacturing composition, impurities, and 28-day dermal tox on the isomerate.

DR. LIEBLER: Right.

MR. JOHNSON: Dr. Belsito, do you want for the 28-dermal toxicity study, should that be performed at use concentrations?

DR. BELSITO: Yes.

MR. JOHNSON: Yes. Now, it's used in concentrations up to -- the isomerate is used in concentrations up to 4.6 percent in rinse-off products.

DR. BELSITO: No. Leave-ons. It's 2.8 in leave-ons.

MR. JOHNSON: So 2.8 is what you want at that concentration? Okay.

DR. BELSITO: The leave-on concentration, yes.

MR. JOHNSON: Thank you.

DR. BELSITO: Any other issues with this? Okay. Let me just save this. Okay.

Marks Team – September 14, 2020

DR. MARKS: So this is a draft report. It's the first time we've seen these seven cosmetic ingredients. Their monosaccharides and disaccharides and related ingredients were found to be safe in a 2019 report. One of the questions I had is can we use the safety data from that for this report. There's some interesting -- we're back to some anti-effects -- anti-melanogenic, anti-inflammatory, antimicrobial activity of the anhydrogalactose. And we had some irritation, sensitivity data. Lisa, Ron, Tom, ingredients -- first, are the ingredients okay -- these seven ingredients, or should any of them be left out?

DR. SHANK: I think they're all right.

DR. SLAGA: I agree. They're all right.

DR. PETERSON: Yeah. I agree.

DR. MARKS: Okay. Good. And then what are our needs, and what comments do you have?

DR. PETERSON: So my comment is that all of the -- there's no method of -- real method of manufacture and impurities for the things that are used in the cosmetic that you have information about the individual -- some individual chemicals. But my understanding is saccharide hydrolysate is like a conglomeration of a bunch of different things. And there is very little information on that mixture, as I read through it.

I mean, this was a little bit of a hard one for me because I got a little confused about what everything was, and it seemed like most of the detailed information we had was on individual chemicals. But then what is really used outside of the anhydroxylitol -- most of the uses are with this saccharide hydrolysate and saccharide isomerase. And those are mixtures, so that bothered me.

So I would say insufficient and ask for method of manufacturing, composition, and impurity, see what information existed for the -- particularly for the saccharide hydrolysate and saccharide isomerate. And also, there isn't a lot of information for the

anhydroxylitol. That also is missing composition and impurities and method of manufacture. The other ones that aren't really used we have, but there's still some missing information like composition and impurities.

DR. MARKS: So do you think, Lisa, initially just ask for method of manufacturing, composition, and impurities for all of them and see what we get but obviously focus on the ones like you mentioned, the saccharide isomerate, used in almost 500 products and the anhydroxylitol, used in 180?

DR. PETERSON: Right. And then none of the tox data is with the mixture. It's all with the individual chemical. So I'll leave it to the -- I'm an informal toxicologist. I do toxicology, but I'm not as deep into it as the other two. And I'll leave those comments, but that was my reaction was that the -- again, it's a mixture. I don't really expect that anything would be that different, but there's no data on the things that --

DR. MARKS: I thought it was interesting, Wilbur, you began "There was no data on the cosmetic ingredient," but we have all this other stuff. So we want the method of manufacture, composition, impurities. Ron, Tom, what other needs? So insufficient data announcement, that seems a forgoing conclusion at this point. Ron, Tom, your comments and needs?

DR. SLAGA: I have no needs -- other needs if you will.

DR. SHANK: If these are all highly water soluble, are they going to penetrate the skin to an appreciable extent?

DR. BERGFELD: No, epidermis.

DR. MARKS: So your point there, Ron, is if they're water soluble they aren't going to penetrate the skin and we don't need --

DR. SHANK: Well, that would reduce the need for systemic toxicology. We still might need it for sensitization, and can we read across from glucose and fructose to the other ingredients? These mixtures, I agree. We don't know what those really are. I just assumed they were mostly glucose and fructose, but maybe that's wrong.

DR. BERGFELD: There's no information --

DR. SHANK: I don't hear anything, so…

DR. PETERSON: Nobody's saying anything. There's no information, so I think it's worth asking.

DR. MARKS: Yeah. That gets back to your need, Lisa, of what's the composition. Actually, Ron, I have that the irritation and sensitization for the two ingredients that have the most use, the saccharide isomerate -- that that was okay. We have a sensitization and irritation at use concentration, and they were clean. And then the other one I have was the anhydroxylitol, and we have sensitization data on that much above use concentration. And that was okay. So I think --

DR. SHANK: Okay.

DR. MARKS: -- at least for those two ingredients we have sensitization and irritation, which would clear them. I think you're exactly right about can we read across that to the others. Although, with zero uses, we aren't going to get that on that. So that'll come up in the future, but at least I think we have -- two of them we can say are safe from an irritation/sensitization. But obviously, we're going to have an IND for the method of manufacture, composition, and impurities. Did you want to see data on penetration of the skin, Ron?

DR. SHANK: Well, there must be data on glucose or fructose.

DR. MARKS: Mm-hmm.

DR. SHANK: And then I would read across from those. And I think it's negligible penetration.

DR. MARKS: Okay. So we need to confirm. I would put confirm lack of --

DR. SHANK: The concentrations are very low for most of these.

DR. MARKS: Exactly, Ron. 2.8 percent for the saccharide isomerate and for the anhydroxylitol it's 0.88. So yeah. They're small concentrations.

DR. SHANK: Saccharide hydrolysate is 0.002.

DR. BERGFELD: That's a food as well.

DR. MARKS: So it looks like you're using the previous report from last year as a read across possibly once we clarify what the composition of these mixtures are. Is that right?

DR. SHANK: Yes, yes.

DR. MARKS: Oh, okay. Now, if fructose and glucose -- using it as a read across -- would you want them to be a particular concentration in the mixture? How would you want to use that as a read across, Ron? What if they were only 5 percent of the mixture? Would you still be able to read across?

DR. SHANK: Well, that's a good question. If it's just a small amount of the mixture, no, then we'll have to wait until we find out what's in the mixture.

DR. MARKS: Okay. So I'm going to make it --

DR. SHANK: I thought the mixtures were primarily glucose and fructose, but that's not the case, is it? Is that what you're saying?

DR. MARKS: I'm not sure. I think what I'll say tomorrow read across from fructose and glucose if a large portion of the composition of these mixtures.

DR. SHANK: Right.

DR. MARKS: That again will be answered as we delve into it in the future. Any other comments, Lisa, Tom, Ron?

DR. BERGFELD: Who was that?

DR. SLAGA: Who was that?

DR. MARKS: Well, it wasn't one of the team members. Okay. So I'm just --

DR. SLAGA: No, I just yawned.

DR. ANSELL: It wasn't last time either.

DR. MARKS: Okay. So I'm going to move tomorrow an insufficient data announcement be issued. Our primary need is method of manufacture, composition, and impurities of these mixtures. We want to confirm the lack of penetration into the skin. Which then if that's the case, we wouldn't need the systemic tox, and we want to clarify whether we can read across from fructose and glucose if they're a large portion of the composition of these mixtures. Does that sound good?

DR. BERGFELD: Excellent.

DR. SLAGA: Yes.

DR. BERGFELD: Excellent.

DR. MARKS: Okay. Let me go ahead and close this sentence. And then, oh, actually, I almost ignored it. The anti-melanogenic effect, the anti-inflammatory effect, and the antimicrobial effect -- this is on page 17 of anhydrogalactose. And I wasn't -- if it's anti-inflammatory, I like it, same with antimicrobial. I just note those, and perhaps it's --

DR. SLAGA: It's anticarcinogenic.

DR. MARKS: Pardon? Yeah.

DR. SLAGA: Anticarcinogenic. I had no concern with it.

DR. MARKS: Good. How about the anti-melanogenic? Do we handle it like we now are into this semi -- Lisa, whatever paragraph you write for tomorrow, are we going to use the same for this one?

DR. PETERSON: Sure. Yeah. But you don't know what it is for the other -- that chemical. So yeah.

DR. MARKS: It's rather -- if we go to page 17, the last sentence of that section under anhydrogalactose, anti-melanogenic activity, it says anhydrogalactose markedly inhibited melanin secretion.

DR. PETERSON: Excuse me. Does it matter that that is one of the chemicals that's not currently in use and you don't have really any information on the ones that are in use? And knowing -- again, not knowing the composition, it's hard to know whether the ingredients that are actually used have the same property. But I do think we can put in some kind of generic -- based on this, perhaps this class of chemicals can do this. So therefore, it should be -- you know, have the boilerplate language.

DR. MARKS: Ron, Tom?

DR. SHANK: I'm sorry. I missed most of that conversation. I'm having a real problem with the sound.

DR. PETERSON: Have you tried turning up your volume on your end?

[*Discussion regarding resolving reception issues*.]

DR. MARKS: Ron, while you're doing that, I'll go ahead and continue on if that's okay, since you do hear some of what --

DR. SHANK: Please do.

DR. MARKS: So tomorrow I'm going to move again -- I'll repeat insufficient data announcement. We want method of manufacture, composition, and impurities for these mixtures. We want to confirm the lack of penetration to skin. We want to

see whether we can read across from fructose and glucose if a large portion of the composition of these mixtures, and then we'll handle the anti-melanogenic effect in the discussion as we've done with some of these other ingredients that have that same issue. Lisa, Tom, that all sound good?

DR. SLAGA: Sounds good.

DR. MARKS: Okay. I'm going to go ahead and close this set of ingredients.

Full Panel – September 15, 2020

DR. MARKS: Okay, this is a draft report, which means the first time we've seen these seven cosmetic ingredients. Our team, after evaluating them, and also in light of the previous report last year on the monosaccharides, disaccharides and related ingredients, we felt that an insufficient data announcement should be issued.

We wanted to see the method of manufacture and the composition/impurities of these Saccharide Humectants mixtures. We want to confirm the lack of penetration in the skin. We wanted to find out how much of the composition was fructose and glucose, and if it was a large portion of the composition perhaps we could use a read-across to confirm the safety. And then, we wanted the anti-melanogenic effect handled at the discussion as we've done in some recent ingredients. So, the motion is to issue an insufficient data announcement with those needs.

DR. BELSITO: Okay, so, Jim you went through a lot of needs but it sounds to me like most of your needs -- when you were going through the saccharide composition -- essentially were covered by composition and impurities. Is that not correct?

DR. MARKS: Yeah, and we also wanted method of manufacture too.

DR. BELSITO: Yes, okay.

DR. MARKS: Yep, you're absolutely right, Don.

DR. BELSITO: We wanted those, but we also requested a 28-day dermal on the Isomerate at the use concentration. That was the one that had the highest use concentration of 2.8 percent.

DR. MARKS: I think that dovetails in our request as to whether it penetrates the skin.

DR. BERGFELD: So you're agreeable, Jim?

DR. MARKS: Oh, yes.

DR. BERGFELD: Okay. So, there's a second, Don?

DR. BELSITO: Yes, second, with the addition of a 28-day dermal specifically on the Isomerate.

DR. BERGFELD: Okay. Any other suggested changes here?

MR. JOHNSON: Dr. Bergfeld, I have a comment, please.

DR. BERGFELD: Wilbur, go ahead.

MR. JOHNSON: Yes, with respect to the need for method of manufacture, impurities and composition data, are those data needed on all of the ingredients or just on Saccharide Isomerate?

DR. MARKS: Let's ask for all of them, Wilbur, to begin with.

MR. JOHNSON: Okay, thank you.

DR. BERGFELD: Any other comments or needs, or qualifications, clarifications? None? Okay, all those against this moving forward as an insufficient data announcement, please indicate by stating your name. Hearing none, we'll assume unanimous support of this conclusion.

And moving on to the next ingredient in this draft report area, Acetyl Hexapeptide-8, Dr. Belsito.

MARCH 2021 PANEL MEETING – DRAFT TENTATIVE REPORT

Belsito Team – March 11, 2021

DR. BELSITO: Okey-doke. So, then we're moving to Saccharide Humectants, that correct? Okay, so at the September meeting we issued an insufficient data announcement for these seven ingredients with the following request; method of manufacture, impurities, and composition data on all the ingredients and ingredient mixtures; confirmation of lack of skin penetration of these ingredients and ingredient mixtures; composition of glucose and fructose in the ingredient mixtures, and if the two monosaccharides are present in sufficient amounts, the available negative data on glucose and fructose skin penetration could be used to evaluate skin penetration. And, a 28-day dermal tox on Saccharide Isomerate at the cosmetic use concentration of 2.8 percent.

We got a lot of data in response to this IDA. And I won't read it all off; we can look at it in the report. Also, the report's been revised for further information from the FDA VCRP. And, right now it looks like (audio skip) Isomerate is being used in slightly 150 fewer formulations than it was in 2020.

And then we had a comment in this report from the French Societe D'exploitation De Produits Pour Les Industries Chimiques. And, so, the Society for the Exploitation of Products for the Chemical Industry, interesting title. The comment provides the basis for the company's opinion that Anhydroxylitol is not part of the Saccharide Isomerate class, and deserves the panel's consideration. And, is the argument convincing, and should we take out Anhydroxylitol from the review and look at it in a separate review. And that question I'll leave to Dan. So, let's look at this.

I didn't really have a lot of comments on this. The chemical properties -- this is Page 21 -- I just -- the only comment I had was, you say in the last sentence there that "Arabinose reduces both the potential damage to the stratum corneum and epidermis proteins with development of irritation and the formation of covalent bonds with critical components..." And, I wasn't sure of what you meant there, Wilbur? And, I just thought that needed to be rephrased. And I made a suggestion, but I'm not sure it's correct.

And I said both the potential damage to the stratum corneum and epidermal proteins by minimizing the development of covalent bonds with critical components. But, I'm not sure that that's right. Is that what you meant to say that the arabinose protected, or it did not protect?

MR. JOHNSON: The substance of that statement is taken directly from the Industry's submission. But I think that the point that was trying to be made is the formulation of covalent bonds between that ingredient and the proteins, as a property.

DR. BELSITO: Dan, would you --

DR. LIEBLER: Right. So, yeah, I looked at that, and -- the Saccharide Isomerate is a very big molecule. And, so, it's probably -- it's not going to penetrate the stratum corneum anyway. It's possible that the carbonyl group from the Saccharide Isomerate are able to form shift basis with proteins on the stratum corneum. But, I don't know if there's any evidence that that actually happens. I think that that's not an argument that Industry would want to make, because it sort of raises the specter of modification of proteins as a sensitization mechanism.

And, I'm not sure that it's really a concern, because the molecule is so large I don't think it can penetrate the cornified layer and get to the epidermis where modification of proteins would, you know, could be an issue. But the very large molecular weight of these things makes this argument sort of nonsensical or at least not important to us from a safety perspective. It's just --

DR. BELSITO: Right, but, if you look at it, Dan, it says, "arabinose reduces both the potential damage to the stratum corneum and epidermis proteins with development of irritation and the formation of covalent bonds..." That doesn't make any sense.

DR. LIEBLER: Yeah, I know, I'm --

DR. BELSITO: Because if it's causing the development of irritation and formation of covalent bonds with critical components, it's not reducing the potential damage, it's increasing, right?

DR. LIEBLER: That is damage -- yeah, actually, I was conflating two things. The highlighted yellow sentence in the report was on Saccharide Isomerate, and then the next sentence, according to an industry source absence of acid- -- okay, let's see. In Arabinose... Oh, is another molecule. That's a small molecule that maybe it will penetrate the stratum corneum to a limited extent.

DR. BELSITO: But it says that there's absence of acid, basic properties, and strong electrophilic groups in Arabinose reduces the potential of damage. That makes sense?

DR. LIEBLER: No.

DR. BELSITO: But, then to say, development of irritation, I think, I mean, unfortunately that's an unpublished study. I wasn't able to find it. But I suspect --

DR. LIEBLER: I think that's a nonsensical assertion.

DR. BELSITO: Right. I suspect it meant that it reduces both the potential damage to the stratum corneum and epidermal proteins by minimizing the development, or, I mean, because it can't reduce damage and cause irritation in covalent bonds formation.

DR. LIEBLER: Yeah, right.

DR. BELSITO: Right?

DR. LIEBLER: Right. Yes, so modifying proteins is, you know, we think of that as damage.

DR. BELSITO: Wilbur, I think you need to go back and look and see, and I don't know if that paper can be distributed to the panel? But, I mean, that sentence unfortunately just doesn't make sense to me.

DR. LIEBLER: Right, I agree with you.

MR. JOHNSON: Okay, I'll look at that again. But, is there any reason why this sentence should remain, you know, at all? Does it add anything to the safety assessment?

DR. BELSITO: Well, right now it takes away from it.

DR. SNYDER: Right.

DR. LIEBLER: Right. I mean, I think that these molecules are not protein modifiers. In the absence of any evidence to demonstrate otherwise, I don't think that makes sense. I consider that through chemically nonsensical and unless they have data to indicate that, it's just an unsupported assertion.

MR. JOHNSON: Um-hmm.

DR. LIEBLER: And that would raise -- if it were true, that would raise a problem for us. That's not a protective mechanism at all.

MR. JOHNSON: Yeah, I'm sure of the accuracy of that statement, so with that in mind, should it be deleted?

DR. SNYDER: Which page are we on, on that sentence?

DR. BELSITO: It's on Page 21, Chemical Properties, the last sentence.

DR. SNYDER: I mean, the unique thing about this ingredient is that, you know, that we needed -- we were looking for penetration data to clear it so there's no dermal penetration. And I'm hearing in the discussion that we don't get dermal penetration, but it does bind, and according to that new use -- or that new absorption data on Page 23, that it binds to the keratin of the stratum corneum and it stays there, it's not washed off. But, then, we're not worried about that because of the absence of sensitization data at concentrations of use.

So, is this enough information to clear the absorption data, so we don't have that insufficient data announcement? Because if it's bond there and it's not absorbed, but is it modifying the surface such that there could potentially be sensitization issues? But then we have good sensitization data, according to my records.

DR. BELSITO: Right, I mean, and, you know, I mean, that is another... So, if it bonded to corneocytes, you know, those are basically dead cells. I mean, they're like saran wrap over the skin, right?

DR. SNYDER: Right.

DR. BELSITO: So it's not even going to get to the epidermal presenting cells, and you're not going to see sensitization, but, also, you're not going to cause this type of damage that, you know, we're talking about in terms of, you know, PDF Page 23.

DR. LIEBLER: I'm looking at the reference list and Reference 14, which is the source of this --

DR. BELSITO: Right, it's private data. We haven't seen it.

DR. LIEBLER: Well, we don't know if it's even data. It may simply be a sentence that says so. And, so, I mean, I think that unless there are supporting data to support these assertions, it really doesn't belong in the report.

The issue of dermal penetration is really kind of minimally addressed here, but the data that we have in the report -- let's see, where are we? Yeah, PDF Page 23, there's that reference again for Arabinose that says that absorption is limited by its hydrophilicity and ability to form hydrogen bonds. I don't even know if they're conflating hydrogen bonds with covalent bonds for some reason.

And then on Anhydroxylitol and Arabinose from another source, it's simply stated that the hydrophilicity would prevent its -- and low partition coefficient would prevent absorption through the epidermis. I think that's probably correct. And I think along the lines of what Paul was saying, you know, we've got no evidence of penetration and we got good sensitization data, this really kind of goes away.

Wilbur, on PDF Page 23, under Dermal Penetration, you've got two entries for Arabinose here. First paragraph and then the third paragraph, and the first one is that --

DR. BELSITO: They're the same.

MR. JOHNSON: Yeah, that's a duplicate. It should be deleted.

DR. LIEBLER: Yeah, one has the citation, one doesn't. But I think the citation may be problematic.

MR. JOHNSON: Okay.

DR. BELSITO: Well, I guess the question is where are we going? This was an insufficient data, so the next step would be a tentative final, is that not correct?

MR. JOHNSON: It would be a tentative.

DR. BELSITO: Tentative final.

MR. JOHNSON: Yeah.

DR. HELDRETH: A tentative report.

DR. BELSITO: So, do we need Wilbur to send us that Reference 14 so we could review it before tomorrow?

DR. SNYDER: It's critical to clearing Isomerate, because that was the hold up. We have essentially no absorption data on the Isomerate.

DR. BELSITO: Right. That's what I mean.

DR. SNYDER: If we're comfortable with this statement that it's bound on the surface to the keratinocytes and there's no absorption potential, then we just need to make sure that we elaborate on that in the discussion as to why we're, you know, we're clearing the insufficient data announcement for absorption or a 28-day study, dermal (audio skip).

DR. BELSITO: Yeah, but, if in fact, Reference 14, as it seems to be indicating by saying that there are no acidic or basic properties, it's not strongly electrophilic, it reduces both the potential damage to the stratum corneum and epidermal proteins, that make sense with the fact that it's bound to the corneocytes and it's protecting the underlying epidermal tissues. But the way it's written now, it says that it causes irritation. I think that's wrong and because that sentence is contradictory. You know...

DR. LIEBLER: Yeah, I think the issue with the Saccharide Isomerate is that it is a large molecule.

DR. EISENMANN: Can I interrupt for a second?

DR. BELSITO: Yup.

DR. LIEBLER: Yup.

DR. EISENMANN: You've got data on Saccharide Isomerate from two different companies. One company, it's a large molecule. The second company, it's 120 to 400 Daltons; it's essentially glucose and fructose from DSM. The other statement is the Reference 14 that you're looking for is in the panel book on Page 51.

DR. BELSITO: I didn't see it. I tried.

DR. LIEBLER: Well, Carol --

DR. BELSITO: Oh, here it is. Thanks Carol. Go ahead, Dan.

DR. LIEBLER: Carol, Table 2 indicates molecular weight for Saccharide Isomerate as being either 20,000 or 15,000.

DR. EISENMANN: I know, the other materials was --

DR. LIEBLER: That's what I had in the materials I reviewed.

DR. EISENMANN: Right, but if you go look through your panel book and for reference from DSM -- I'll see if I can find the page number -- their material is different.

DR. BELSITO: Okay. Let me -- go to Page 51; I think this is what we need here as it says -- the third sentence at the beginning says, "The dermal/percutaneous absorption of D-Arabinose is limited by its hydrophilicity and ability to form hydrogen bonds. The absence of acidic or basic properties as well as strong electrophilic groups in D-Arabinose reduces both the potential damage to the stratum corneum and epidermis proteins..." And, I mean, that sentence is just -- raise -- I mean, Wilbur is right, he took it directly from there, but it just doesn't makes sense.

Because then after that, I mean, I think they miswrote it, or -- you know, because it already says that it's not going to be absorbed. So, particularly because that sentence makes no sense, I think it should be deleted. But what we should put in from this report is that the dermal/percutaneous absorption of D-Arabinose is limited. Okay, and that there is evidence of human skin compatibility with monosaccharides similar in structure and/or chemical-physical properties such as da, da, da, da. Because, I mean, the sentence is there, you're right Wilbur, but -- and they just give references -- but I think that they did not reference really where they got that information and it's just it doesn't makes sense.

MR. JOHNSON: Yes.

DR. BELSITO: So, we could just, I think, end it, we could say take from that report dermal/percutaneous absorption of D-Arabinose is limited by its hydrophilicity and ability to form hydrogen bonds. The absence of acidic or basic properties, as well as strong electrophilic groups, in D-Arabinose reduces both the potential damage to the stratum corneum and epidermal proteins. You can just say epidermis proteins in quotations, or put sic epidermal period. And then, not include that rest of the sentence, which, again, makes absolutely no sense.

DR. LIEBLER: Don, again, what PDF page are you on again?

DR. BELSITO: 51.

DR. LIEBLER: 51? Okay.

DR. BELSITO: Yeah, it's a very brief summary from Kialab.

DR. LIEBLER: Right, no, I just wanted to get to the right page again. So, I agree with what you said, but there's one thing we need to leave out. So, I agree with the third sentence, the dermal/percutaneous absorption is limited by hydrophilicity and ability to form hydrogen bonds.

The next sentence is really, I think, speculative enough, really correct. Strong electrophilic groups -- Arabinose is like these other molecules, they can exist in a ring open and ring close formed and there's an aldehyde group that reacts, you know, in principle could react with proteins. But those mostly react with the hydroxyl group in the same molecule to form this ring. That's true for most of these small molecules like this.

So, I don't agree with the way that's written, and I don't think we should use that language in our report.

DR. BELSITO: Okay, so just drop that sentence and just use the one before it.

DR. LIEBLER: Yeah, it's just too polar to be absorbed.

DR. BELSITO: Okay. So, Wilbur, you can just put in the first sentence about dermal and percutaneous absorption, and add the references, the SCCS notes and that N'Da study, so References 1 and 2. Or you could just add this, you know, or keep Reference 14. But just delete that and add in the sentence on the percutaneous absorption. Does that sound okay to everyone?

DR. KLAASSEN: Yes.

DR. LIEBLER: Yup.

MR. JOHNSON: I think that sentence is already in the report text, Dr. Belsito.

DR. BELSITO: Where is that, Wilbur?

MR. JOHNSON: Let me see. In the dermal -- one second. It's on PDF Page 23, Arabinose, that sentence.

DR. BELSITO: Oh, okay, perfect. So just leave it there.

MR. JOHNSON: Yeah, um-hmm. But the sentence under the Chemical Properties, that last sentence should be deleted?

DR. BELSITO: Yes.

MR. JOHNSON: Okay.

DR. BELSITO: And I thought based upon all the other information we've got, we could go safe as used for this group. But let me hear from the other members of my team.

DR. SNYDER: I had the same conclusion with the caveat on Page 33. The Draft Discussion is expanded with our reasoning of the absence of absorption data, or the presence of data to assess that it's not absorbed. I'm talking about the physical chemical properties including if they're water soluble, the size, this hydrophilic hydrogen bonding issue. And so I think that needs to be expanded in the Draft Discussion, since it's going to alleviate our initial insufficient data announcement for dermal absorption.

MR. JOHNSON: Dr. Belsito, will someone provide the language, you know, indicating how the Draft Discussion should be modified?

DR. BELSITO: Well, we need to discuss this. Paul is just bringing this up. I'm trying to look and see --

DR. SNYDER: I mean, we went out insufficient data for the method of manufacture, composition, impurities, and then confirmed the lack of skin penetration. If you couldn't do that, then we wanted the 28-day dermal. So we got the method of manufacture. We got composition and impurities on Arabinose and the Isomerate. So it's the one thing that we're lacking or that we need to justify, is the clearing of the dermal absorption -- skin penetration.

DR. KLAASSEN: Can we, you know --

DR. BELSITO: Well, we -- we do have -- we do have this information that Saccharide Isomerate -- this is PDF Page 23 -- is uniquely bound at the corneocytes to the free amino groups of lysine found in the keratin of the stratum corneum. This binding mechanism to the skin and scalp ensures the active ingredient is not washed off, but continues to improve hydration until removed by natural process of desquamation.

Is that sufficient? This is PDF Page 23. And then, we could also bring back in -- well, then we have the statement later on, on Arabinose, but that's not Saccharide Isomerate.

DR. LIEBLER: Yeah, the only problem I have with -- I mean, I suppose this is okay. I'm not sure that they really know that. What they're claiming is the binding -- covalent binding to lysine. It's in the stratum corneum, so it doesn't affect, you know, living cells, so, you know, it's not of any concern with us. I think this won't penetrate simply because it's too polar, not necessarily because it's covalently bound. But that's, you know, like arguing about how many angels can dance on the head of a pin.

The thing that concerns me is that we have two distinctly different chemical characteristics reported for a Saccharide Isomerate. One is from this DSM, I guess it is, in PDF Page 55, that says it's a, you know, low molecular weight, about 150 Daltons. Whereas in the table that we have it says Saccharide Isomerate is a 15,000 to 20,000 molecular weight molecule. And that's a huge difference.

I don't think -- you know, if it's big it won't be absorbed because it's big. And, these differences in the size of the molecules we're talking about doesn't affect our conclusions. I do agree it's safe as used, but, it's just it's these are two totally different description of what these molecules are.

DR. BELSITO: Where are you, Dan, because I didn't pick that up for some reason.

DR. LIEBLER: Okay, on Table 2, which is on -- all right so --

MR. JOHNSON: PDF 34.

DR. LIEBLER: 35, Wilbur, the last --

DR. BELSITO: I got it, 35, yeah.

MR. JOHNSON: 35, yes.

DR. LIEBLER: See where it says molecular weight greater than 1.4 (equivalent dextran), then 20,000, and 15,000. So, these are big, big, big molecules, they're not going to be absorbed simply because they're very large molecules. But, the flyer that we got from the manufacturer, which is on PDF Page 51, tells a different story. It says...

DR. BELSITO: 51?

DR. LIEBLER: Yeah, PDF Page 51. Let's see, where is it? Carol you just pointed me to it and now I can't find it. I thought it was 51.

DR. BELSITO: No, it's not 51, that's the Reference 14.

DR. EISENMANN: 54.

DR. LIEBLER: Oh, 54. Thank you.

DR. EISENMANN: It's right after the next -- 14.

DR. LIEBLER: Yup.

DR. EISENMANN: So there're two different suppliers. One is making a big material, and one is making a small material under the same name. But the small material is essentially glucose and fructose.

DR. LIEBLER: Yeah. So, anyway, that's the issue, it's just inconsistent. There are two of those -- now we can simply say that they're two distinct, you know, chemical substances that are provided under this name, they have very different properties. But, for different reasons they both won't be absorbed.

DR. KLAASSEN: Is it possible that this Saccharide Isomerate is two different things? One is it's an isomerate and the other is the enzyme isomerase.

DR. LIEBLER: I don't think so, but --

DR. SNYDER: So, Dan, I want to bring you back to PDF Page 23, for the Anhydroxylitol?

DR. LIEBLER: Yes.

DR. SNYDER: Because it's down at 134 Dalton range, and it does say there is potential for dermal absorption.

DR. LIEBLER: Across the GI tract.

DR. SNYDER: Well, it says for dermal absorption and passage across the --

DR. LIEBLER: Oh.

DR. SNYDER: -- yeah, so I -- assuming that means for dermal penetration and for GI penetration. But, that kind of goes in the face of those being small, right, also.

DR. LIEBLER: Yeah, looking for Reference 3. That's just the Australian Industrial Chemicals Scheme, a public report on Anhydroxylitol.

DR. SNYDER: And is there -- and that justification to remove this from the report, what was -- that we -- because it -- I thought maybe we'd clear it because of the -- removing this one, because it is smaller and there is this potential. But the other ones are bigger and they don't absorb, according to the information we have, but --

DR. LIEBLER: So, I wasn't justify -- I wasn't suggesting removing anything on Anhydroxylitol.

DR. SNYDER: But we had Wave 2 that's where they asked us to, the SCCS opinion. In Wave 2 they asked us to remove that; they don't consider it to be part of the Saccharide Isomerate class.

DR. LIEBLER: I must've missed that in Wave 2. I mean, I just look at the structures in the tables. I don't see what the issue is.

DR. SNYDER: It was on Page 47 of that Wave 2 data. And then should this report just be Saccharide Isomerate? Instead of -- because there was also that issue about removing the cosmetic function out of the title, Don?

DR. BELSITO: Well, they are humectants. What is the -- what -- let me find the Introduction here and see.

DR. SNYDER: On Page 66 of the PDF, there was a comment about removing the humectant from the title, from Bart, a memo from the Science and Support Committee.

DR. BELSITO: Yeah. Yeah, I mean, that's true. But, are the -- it's only uses as humectants? Right, even if it is I guess you're right.

DR. SNYDER: So I thought about going a roundabout, if we take out the Anhydroxylitol and then the title of it is only the Isomerates, and we're probably for sure safe as used. But, I don't know what to do with that xylitol, where it says that that small size, and then also saying -- that data that Dan raised, a question about saying there's one Isomerate that appears to be small. And, so, I don't understand what the composition of that is that it makes it so much smaller than --

DR. HELDRETH: So, as far as I can tell looking at this, I would understand their objection, if we had thrown in xylitol here, because that's a sugar alcohol and not really a saccharide. But the Anhydroxylitol is a (inaudible) ring, I mean, it's your standard saccharide shape there so I -- it's really, you know, a carbon difference from Anhydroglucitol that's right above it. I don't completely understand their objection of that belonging in the group.

And then, of course, the title is completely up to the panel if you want to change it. I was the one that originally threw humectants in there. The primary reason was they all shared that function in common, and I was trying to separate it from some of the other saccharides the panel has reviewed. But if you want to change the name, that's completely up to you.

DR. LIEBLER: Lisa?

DR. PETERSON: But, Alex, do we normally say a function of -- a function in any of the reports, do we normally highlight a function, that's all. That is I think the reason the CIR SSC really wanted to change the name of the report, because we normally do not put a function in the report title. That's all.

DR. HELDRETH: That's right, we normally do not. I thought it worked here just to differentiate this report from others saccharide reports we've previously done, but, you know, it really doesn't matter to me if you want to change the name, by all means.

DR. BELSITO: Yeah, I mean, I think I would agree with the Council. You know, we've not done it; it would be a break from our sort of standard operating procedures.

DR. SNYDER: And then, are there humectants in any of those other saccharide reports -- reported uses as a humectant? That would be a conflicting thing too.

DR. BELSITO: Right. I see what you mean, Paul, if we're implying all the other saccharides that we've looked at are not humectant -- don't have humectant properties almost.

DR. SNYDER: That's correct.

DR. BELSITO: Yes, I would get rid of humectants. Curt, Dan?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay.

DR. LIEBLER: Lisa Peterson and I emailed back and forth about this and the humectants, you're right that we don't usually use it. The question then would be, so what's the title. Is it just a list of all these molecules?

DR. SNYDER: So, Dan, you're also not buying the logic for removing the Anhydroxylitol?

DR. LIEBLER: I'm trying to read that -- I must've missed this. I apologize, I must've missed this. I'm trying to listen to you guys and read their memo, and I'm not doing too well. So...

DR. BELSITO: So why don't we shut up for a minute and let Dan read the memo.

DR. LIEBLER: Oh, yeah, why don't you play the Double Jeopardy music too? I think the first item in this SSC-PCPC memo is the product that they provide is a mixture. I'm not sure if that's the only provider? And it's a mixture that contains about 24 to 34 percent Anhydroxylitol, because it contains other things, xylitylglucoside and xylitol, etcetera.

And then whether the structure is important, I need to look and think about that.

DR. HELDRETH: From my experience, talking with the folks on the INCI committee, if a particular material was supplied with that high of a concentration of xylitol, or those other quote, unquote, constituents, the INCI committee would suggest that they put those names on the label as additional ingredients because they're not defined as part of the Anhydroxylitol ingredient.

DR. LIEBLER: Yeah. I'm sorry; I'm not going to be able to give you a quick answer to this. I need time to digest it, and think, and I can't really do that right now. Sorry, that's my limitation. And, so, let me get back to you on that. For now I would say let's default to keeping it in.

DR. BELSITO: Okay, and then, so in Wave 3 the Council had a comment on the key issues of the different molecular weights recorded for Saccharide Isomerate. And they said it, first of all, needs to be clearly stated in the CIR report. And then they go on to say the ingredients from two suppliers are very different, the material tested needs to be clearly identified throughout the report.

Is there any way of doing that? Do we know which material was used for the different safety endpoints?

MR. JOHNSON: Yes. So Dr. Belsito, you'll notice that in the report text that the molecular weight of some of the, you know, chemicals tested is stated. And, so, what I have done, and this will appear in the next draft, is just for every occurrence of Saccharide Isomerate, in which there is no molecular weight, I've included the molecular weight range 200 to 400 in there to differentiate the data on the Saccharide Isomerate of one molecular weight versus that of the other Saccharide Isomerate with a different molecular weight.

DR. BELSITO: You have the molecular weights for Saccharide Isomerate for all of the different studies that were done? Is that what I'm understanding?

MR. JOHNSON: Yes. Yes, that's true. And some of the molecular weights are in there, but this submission that we're referring to it also has unpublished data in it, so for those studies that molecular weight range will be stated, you know, for each study's summary.

DR. HELDRETH: I think there's a particularly good example of what the Council was pointing out, if we look at PDF Page 41. We've got the table on Irritation, if you noticed all but for the first entry for Saccharide Isomerate there are weights recited there, 1.4 MDa, or 20,000 Da. But the first one does not have one listed. I believe that's a prime example where Wilbur is suggesting inserting that molecular weight that they've given us.

DR. LIEBLER: So, Bart, can we proceed with a, you know, report on material that so differs, or, you know, divergently classified?

DR. HELDRETH: Yes, we've certainly done that numerous times, I mean, if you look at botanicals we're doing that on a very common bases. If you feel that there are certain, let's say, extremes or outliners constituents or compositions that you don't feel you have enough information on, you can have a conclusion that says -- limiting it to a specific composition.

We did that for some peptides where the definitional allowed it to be, I think, three different possible sequences and the panel cleared on just the one sequence, because they only had data on that one.

DR. LIEBLER: This is different. Yeah, this is kind of different than that. I mean, if the big version and the little version of Saccharide Isomerate are both okay for slightly different reasons, and they both have sufficient data, I think, to clear them.

And, so, I think perhaps we could note it in the discussion. Because I just don't want somebody to read this report and say, man, they don't even notice the difference between, you know, a 20,000 Dalton molecule and a 150 Dalton molecule.

DR. HELDRETH: Right.

DR. BELSITO: But it looks like, I mean, just looking at that table, Bart, all of these studies were done either unknown, or but, if you look under Saccharide Isomerate in humans they were all very large molecules. Right?

DR. HELDRETH: Yes, except for the first one, there's no molecular weight listed. And --

DR. BELSITO: Right.

DR. HELDRETH: -- our understanding is that molecular weight -- that lower molecular weight that the Council has provided belongs with that entry.

DR. BELSITO: Okay. So --

DR. LIEBLER: All right, Don?

DR. BELSITO: Yeah.

DR. LIEBLER: Well, we were talking about the issue of the molecular weight size. I have digested this memo now from SSC-PCPC, and I think that their argument is that the Anhydroxylitol doesn't belongs in this Saccharide Isomerate class largely because the Saccharide Isomerate are big molecules. They also make some other points that I don't think, you know, are particularly relevant.

And, there are other small molecules in this class, in this report that we're reviewing. So I think the Anhydroxylitol is fine to keep in the report.

DR. BELSITO: Okay.

DR. SNYDER: So, Dan, can you go to PDF Page 21?

DR. LIEBLER: Yup.

DR. SNYDER: Under the Chemical Properties, the second (sic) sentence, "...Saccharide Isomerate has the highest molecular weight of greater than 1.4..." And that's not true now, right, because we have one at 134.

DR. LIEBLER: Yeah, so I think that needs to be edited to say that two different descriptions of -- differing descriptions have been provided -- that one of the trade name materials -- and then, that you need to spell out in that sentence -- I'm sorry, I'm looking at the top of PDF Page 22. Let me go up to PDF Page 21.

DR. BELSITO: I'm not seeing that, Paul. Where is that?

DR. SNYDER: Under Chemical Properties on PDF Page 21, the second (sic) sentence says, "Of the ingredients that are being reviewed, Saccharide Isomerate has the highest molecular weight, greater than 1.4."

DR. BELSITO: We struck that. Oh, no, we didn't.

DR. LIEBLER: No, we didn't.

DR. BELSITO: I'm sorry, I struck out too much.

DR. LIEBLER: We struck the following sentence.

DR. KLAASSEN: We need to say that this chemical has two molecular weights. If that isn't the strangest thing I've ever seen.

DR. LIEBLER: Yeah, I think I would edit that, Wilbur, to say Saccharide Isomerate -- instead of, of the ingredients -- I'll edit it on my copy. But, instead of, of the ingredients that are being reviewed, just start with Saccharide Isomerate is reported both in low molecular weight and high molecular weight forms.

MR. JOHNSON: Um-hmm.

DR. SNYDER: So, now, combining that information with the absorption data sentence on Page 23, for the Anhydroxylitol, saying that there's potential at that 134 for dermal absorption, then we can't clear the dermal absorption, right -- or the absorption?

I'm trying to figure out how we can scientifically, logically clear the one data need that I see that we have. We've got material and methods. We've got the composition and impurities. But we wanted to confirm the lack of skin penetration.

DR. BELSITO: What were we concerned about with skin penetration with this molecule?

DR. KLAASSEN: Yeah.

DR. SNYDER: I don't know, because we have some tox data with the NOEL -- or, we don't have a NOAEL because of that myocarditis, which I think is an over interpretation of the data. I think that's just a background rat thing, particularly at that severity of minimal. So, I wasn't concern about that, I had mentioned that at the last time we talked about this.

DR. LIEBLER: Yeah, so, it looks like there are no actual data on dermal penetration for these molecules. Now I haven't read the Australian Industrial Chemical Scheme thing for Anhydroxylitol, but the way it's worded it says, "there is potential for dermal absorption and passage across the gastrointestinal tract." Is that simply -- does that mean they just looked at the structure and said, ah, low molecular weight; that could be absorbed.

DR. SNYDER: My exact comment was, so essentially no absorption data on the Isomerate summary.

DR. LIEBLER: Yup.

DR. BELSITO: But again, I ask, what was the concern? I mean, if absorbed, what would happen? What endpoints are we concerned about, DART?

DR. EISENMANN: The low molecular weight material is essentially glucose and fructose.

DR. LIEBLER: Right, so that's no concern. And then the high molecular weight material cannot be absorbed.

DR. BELSITO: Right. So, that's our discussion.

DR. LIEBLER: Yup.

DR. SNYDER: Yup.

DR. BELSITO: Okay.

DR. SNYDER: And that's my note on the discussion is, we need to expand our justification for the absence of absorption data.

DR. BELSITO: Okay.

DR. SNYDER: We're going to get this back, right, one more time, because -- once those are drafted, the discussion and conclusion. So we can...

DR. BELSITO: Okay. So the conclusion will be safe as used. Where do we put the information about Saccharide Isomerate, after -- at the beginning, or after the anti-melanogenic effects?

DR. LIEBLER: What information are you referring to, Don?

DR. BELSITO: That the low molecular weight is essentially sucrose and fructose? Is that correct, Carol?

DR. LIEBLER: Yeah, I think that should go under Compositions and Impurities.

DR. BELSITO: Right, but then --

DR. SNYDER: I think in the discussion, the most important thing -- I did these kind of backwards, but I had a comment for Amino Acid Diacetates, because that's the number one when we look at tomorrow, but I thought in the discussion we need to have an opening paragraph that says the data was adequate for determining the safety, or the data was inadequate for determining the safety of cosmetic use. And if it's inadequate, and then we follow up by saying specifically a lack of or a concern for.

I don't like these discussions that start off with these -- I don't know why we're starting off with the anti-melanogenic activities, because it's not relevant because at the concentrations they saw that in the models, is not relevant to cosmetics use. I think we need to have opening sentences in these discussions about whether we found the data to be adequate for determining safety. And if it wasn't adequate, what specifically are we lacking for the insufficient data announcement. And if we had a concern, as in this case we had a concern because the absence of absorption data; however, we're going to clear it because of the chemical composition with it being basically largely sugars and large molecules.

DR. LIEBLER: I agree with you, Paul. I think at this stage of the report Wilbur has essentially, you know, labelled this Draft Discussion and thrown in some points that could be included in the discussion. I agree this is not the way that the full discussion would be crafted.

DR. SNYDER: But, most of our discussions are similar to this. Where I think we should have -- all discussions should have that opening paragraph where the panel considers the data were adequate or inadequate for determining safety.

DR. LIEBLER: Oh, yeah, I agree with that.

DR. SNYDER: Yeah. And if it's inadequate then we say why, because there was a concern or because there was an absence of data.

MR. JOHNSON: I would like to call the panel's attention to Page 21, under the Saccharide Isomerate subheading, under Method of Manufacture.

DR. LIEBLER: Yes.

MR. JOHNSON: And, the last sentence indicates that Saccharide Isomerate consists mainly of glucose and fructose. Should that be included in another part of the report other than here?

DR. LIEBLER: Well, I think this need to be rewritten, because one supplier describes this low molecular weight product. And then the other is a high molecular weight product. So, I think this section should start out, there are two described forms of Saccharide Isomerate.

MR. JOHNSON: Um-hmm. Should that be in the Chemical Properties section initially, or should it just be in this section, Dr. Liebler?

DR. LIEBLER: Yeah, I think it should be in the Chemical Properties, and should just be briefly mentioned.

MR. JOHNSON: Okay.

DR. LIEBLER: And I've made an edit to my copy to indicate -- let's see -- yeah, Saccharide Isomerate is reported in both low and high molecular weight forms

MR. JOHNSON: And that's in the Chemical Properties section.

DR. LIEBLER: Correct.

MR. JOHNSON: Okay.

DR. LIEBLER: And then under Method of Manufacture, it should also be addressed, there's a low molecular weight and a high molecular weight. And you've kind of got that already in that description, but you just need to start -- under Saccharide Isomerate, need to be able to start by saying there are both low molecular weight and high molecular weight forms.

MR. JOHNSON: Okay.

DR. LIEBLER: One is this base-catalyzed isomerization of plant-derived d-glucose. And that gives you mainly glucose and fructose. And then the next paragraph is for three other trade name materials, you have high molecular weight products.

And then under Composition and Impurities you need to basically state it again under Saccharide Isomerate. So you drive this point home in the three sections on the chemical properties, method of manufacture, and composition.

MR. JOHNSON: Okay. Now, regarding the discussion, I know you stated that there is no concern about skin penetration with respect to both molecular weight chemical -- referring to Saccharide Isomerate. So, what other information should be included other than that?

DR. LIEBLER: Well, I think -- I don't want to speak for Paul, but maybe Paul can restate what he wanted up front in these discussions, some broader statement about the adequacy of the data to assess their safety.

DR. SNYDER: Yeah, I just felt that there should be -- the opening paragraph of all reports should say that with information about the use, the concentration of use, and the data related to safety for cosmetic as being adequate or inadequate. And if it's inadequate, then we can make a determination as to why. I mean, it may be an absence of something, or it could be a concern. So then in this case we have a concern for -- because they don't have absorption data, but we can have a discussion and clear it because we're going to talk about the properties, if that's the path we take.

And if it's adequate, then we can just add in the inhalation or the boilerplate and things like that and we're done. And then come up with our conclusion. But I just think that we need to -- we should just make a clear statement saying that the, you know, the information on use, concentration of use and data related safety for cosmetic use as being adequate or inadequate.

Because I find myself putting a lot of sticky notes saying well we need to move this up here because this is what we were concerned about. Or, we didn't have any concerns, so why are we highlighting this, etcetera, etcetera.

MR. JOHNSON: So, has it been determined, you know, exactly which category, are they adequate or inadequate and the rationale for stating either?

DR. SNYDER: Well, I think this case we're going to go down the path where it's adequate. However, the panel had a concern in the absence of the absorption data for Isomerate. However, the chemical properties, etcetera, etcetera. And give that discussion as to why we're not concerned, same thing with the anti- melanogenic activity.

DR. BELSITO: So then the three concerns that we would address, the first, Paul, would be something like --

DR. SNYDER: Most important, absorption.

DR. BELSITO: Right, so, the first would be the panel was concerned about the potential for Saccharide Isomerate to be absorbed. It's aware that it's available both in a low molecular weight that could be absorbed, but this consist of sucrose and fructose, and a higher molecular weight that would not be absorbed, something to that effect?

DR. SNYDER: Absolutely. Perfect. Just like that.

MR. JOHNSON: Um-hmm.

DR. SNYDER: And then the other one would be the panel also noted the anti- melanogenic activity -- and that paragraph can stay. And the issue of incidental inhalation -- that could stay -- and the heavy metals. And then we're done.

MR. JOHNSON: Um-hmm. Now, Dr. Snyder, should anything be stated about the other ingredients that are reviewed in the safety assessment, because we're just talking about Saccharide Isomerate, so far?

DR. SNYDER: That was the only one we had a concern about. The other ones we said they -- everything was adequate, I guess, if that's what we believe. I mean, there was that one, that xylitol, on Page 23, where I asked what about that statement

saying a dermal absorption and GI absorption. But we have systemic data that clears it, I think, because we had some tox data. Yeah, we had some tox data on the xylitol. We had LD50, and we had --

DR. BELSITO: This is the Anhydroxylitol, right?

DR. SNYDER: Correct. We had -- and we also had a short-term study. Now, we didn't have any developmental reproductive, but, if...

MR. JOHNSON: I know the panel had requested the 28-day dermal toxicity data, but those data are no longer needed?

DR. BELSITO: That -- yeah, we had requested it on the Saccharide Isomerate, and we're clearing it by the fact that it's sucrose, fructose in the Saccharide Isomerate low molecular weight.

MR. JOHNSON: Okay.

DR. BELSITO: And, we also said that if we had clarification on that, it wouldn't be a concern.

DR. SNYDER: That's correct, we said we need to confirm the lack of skin penetration, otherwise a 28-day dermal.

MR. JOHNSON: Okay, um-hmm.

DR. BELSITO: But we also said if it was primarily composed of sucrose and fructose, we weren't concerned.

DR. SNYDER: Correct.

MR. JOHNSON: Um-hmm.

DR. BELSITO: And, you know, I mean, it says here of humans -- if this helps at all -- oh, that's Anhydroglucitol. Arabinose, Arabinose, short-term -- all Arabinose. I don't see any short-term or chronic on Anhydroxylitol. Where did you see that, Paul?

DR. SNYDER: On the bottom of Page 25, Don, that first one. An experiment involving 12 rats -- oh, that's glucitol. I'm sorry, I misread that.

DR. BELSITO: Oh.

DR. SNYDER: Yeah, I'm sorry.

DR. BELSITO: So, where does that leave us?

DR. SNYDER: Is that a good read-across for the xylitol, Dan, Anhydroxylitol, Anhydroglucitol?

Now, Don, go to the next page on the top of Page 26, now it switches over to a 28-day oral toxicity study on Anhydroxylitol. See that?

DR. BELSITO: Yeah, yeah, so that needs to be --

DR. SNYDER: Split out of there.

DR. BELSITO: Yeah. Not counted as the same -- yeah.

DR. SNYDER: Yeah, I thought I read it. I thought I read it in there. Because my notes have that we had it.

DR. BELSITO: Up to 1,000 mg/kg a day.

DR. SNYDER: Yeah.

DR. BELSITO: And that was for how long?

DR. SNYDER: 28 days, a 28-day oral toxicity study.

DR. BELSITO: Yeah. So, I mean, I think that clears it. So, Wilbur, are you seeing where Paul is on Page 26 of the PDF?

MR. JOHNSON: Yes.

DR. BELSITO: He ran in the oral tox study of Anhydroglucitol with Anhydroxylitol, so that should be a separate paragraph.

MR. JOHNSON: Okay.

DR. BELSITO: And, probably, I mean, should -- don't we usually put the material, or do we just run everything in. I mean, because it would be nice to separate this out. So, the first would be short-term and chronic toxicity studies and --

DR. SNYDER: And, a specific ingredient just like up above with Oral and Parenteral, yeah.

DR. BELSITO: Right. Yeah, so, break them out by specific ingredient. So this should be subtitled -- the first one -- Anhydroglucitol, then the next one, Anhydroxylitol.

MR. JOHNSON: Um-hmm. So you want separate ingredient heading in this section.

DR. BELSITO: Yeah, so we know, you know, it becomes immediately clear where, you know, what chemicals we're looking at. Or at least separate the paragraphs.

MR. JOHNSON: Okay.

DR. SNYDER: Yeah, I had it in my notes, but then I -- when you pointed it out, Don, I thought I put it down wrong, so.

DR. BELSITO: Yeah, because it's easily missed. Because it all looks like it's the same paragraph, so you assume it's the same material.

MR. JOHNSON: Um-hmm. So, and so basically for each ingredient that's mentioned, there should be a separate paragraph and the appropriate subheading for each.

DR. BELSITO: I would like that.

MR. JOHNSON: Okay.

DR. BELSITO: What about Curt, Dan, Paul?

DR. KLAASSEN: Yeah.

DR. SNYDER: Yeah. Wilbur, for under acute, just have acute and then say whether -- if it's a dermal, then just like you did above this, tox study, there on Page 25. You have Oral, Arabinose, Parenteral, Arabinose.

MR. JOHNSON: Yes.

DR. SNYDER: So in this case you would have Acute under that Dermal, and then the specific ingredient. And then you can have an Acute, Oral, and then under the Acute, Oral also, and then you can have the specific ingredient. And just do that so it's easy to follow the flow.

MR. JOHNSON: Yeah.

DR. SNYDER: That's how I put it in my notes when I review the report.

MR. JOHNSON: Yeah. Okay. One other question about the short-term and the chronic toxicity studies, do you want further breakdown into short-term and chronic, so that you have the short-term subheading and then you have the chronic subheading.

DR. BELSITO: Yes.

DR. SNYDER: Yes.

MR. JOHNSON: Okay. Thank you.

DR. KLAASSEN: I would actually like the title, Short-Term Repeat Studies. You know, that you're (audio skip).

DR. SNYDER: Repeat dose studies, yeah.

DR. KLAASSEN: But, not a big deal.

MR. JOHNSON: Okay.

DR. SNYDER: Well, lucky you, Don, you get to report on this tomorrow.

DR. BELSITO: Yeah, so, let me get this clear. We're okay with the short-term and chronic tox studies being all under the same section, but we want a separate heading for the route of administration. And then under that, a subheading for each of the different ingredients that are studied in those -- is that right?

DR. SNYDER: Well, if you go to Table 5, he actually has it done. Table 4, are acute toxicity studies; and then Table 5 is repeat dose toxicity studies with short-term, and he's got short-term oral, and then the chronic oral and chronic parenteral. So, basically we just need to have the narrative follow the way that the table is, Don.

MR. JOHNSON: Okay, thank you.

DR. BELSITO: And we want a term, short-term repeat dose, or just short-term?

DR. KLAASSEN: Yes.

DR. SNYDER: Well, there's that -- the main heading is Acute Toxicity Studies, which are almost always the LD50's; they just did a large dose. And then there's the repeat dose, which then can be short-term, generally, you know, days; and then, the sub-chronic, which are 90-day; and then the chronic, more than 90 days total.

DR. BELSITO: (Phone ringing.) I just have to take this, excuse me one minute.

DR. SNYDER: So, Wilbur, I think if you just follow the way you have it in Table 4 and 5 you'll be fine.

MR. JOHNSON: Okay.

DR. SNYDER: The big heading will be Acute Toxicity Studies, and then the next big heading will be Repeat Dose Toxicity Studies, and under there you'll have short-term, sub-chronic, chronic.

MR. JOHNSON: Okay.

DR. SNYDER: And then, of course, the route of administration, dermal, oral, subcutaneous, whatever.

MR. JOHNSON: Okay. Okay, thank you.

DR. BELSITO: So, let me get this. So, we want headings for the route of administration, and then subheadings for the ingredients, and -- but, overriding all of that we want separate sections for acute --

DR. SNYDER: Don, go to Page 37, Table 4.

DR. BELSITO: Yeah, but I want to put this where we need it tomorrow to discuss. So separate sections for acute --

DR. SNYDER: And then under acute would be the route -- the route, dermal and oral.

DR. BELSITO: Right. Right, and then the ingredient.

DR. SNYDER: Correct.

DR. BELSITO: So acute, short-term, repeat dose and chronic.

DR. SNYDER: And under the repeat dose, there'll be short-term, sub-chronic --

DR. BELSITO: Oh.

DR. SNYDER: Yeah.

DR. BELSITO: Okay.

DR. SNYDER: And, the route.

DR. BELSITO: So, acute and repeat dose would be the major subheadings.

DR. SNYDER: Correct.

DR. BELSITO: Okay. Short-term, chronic -- okay.

MR. JOHNSON: And also, I think you said that you'd like for the ingredient name to appear as a subheading as well.

DR. BELSITO: Yes.

MR. JOHNSON: Okay.

DR. BELSITO: And where was that table, Paul, I'm sorry.

DR. SNYDER: Page 37, Table 4 and Table 5.

DR. BELSITO: Yeah. Okay, great, yeah exactly. So the narrative has to follow the tables.

DR. SNYDER: Correct.

DR. BELSITO: Right. And then just break it out. I mean, the tables obviously have all of them, but we would have Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose -- or however you pronounce it -- Psicose, interesting. Yeah, perfect. Yeah, okay.

Anything else? Dan, Curt, Paul are we satisfied with those suggested edits to the text and the safe as used conclusion?

DR. LIEBLER: Yeah, I am.

DR. SNYDER: I agree.

DR. LIEBLER: Where are we on the title?

DR. BELSITO: We're getting rid of humectants.

DR. LIEBLER: So it's just says, Safety Assessment of Saccharides?

DR. BELSITO: I don't know, Paul -- I think we sort of agreed to get rid of humectants, but we also didn't agree whether to list all the things we're looking at, which is also a break from tradition.

DR. LIEBLER: So, I had emailed back and forth with Lisa Peterson about this the other day and we didn't come to a conclusion. If we take out humectants, one possibility is, Safety Assessment of Saccharide Isomerate and Related Saccharides as Used in Cosmetics. The only other thing is to, you know, name the ingredients. I don't have other alternative to that.

DR. SNYDER: Bart, where are we at on the re-review of the Saccharide report?

DR. HELDRETH: Let me take a look.

DR. SNYDER: Because one thing would be to reopen that and then put this one in there, if there's no reason not to, right? Put these in there, add them in.

DR. HELDRETH: So, the safety assessment on Mono-Saccharides and Di-Saccharides and Related Ingredients as Used in Cosmetic, was published in 2019.

DR. BELSITO: Awhile.

DR. HELDRETH: So, we're only three years in on that, another 12 years.

DR. SNYDER: How did we miss these? Is there a reason why we didn't include these? I mean, I have a little bit of a problem having two different saccharide reports out there that... Hmm.

DR. LIEBLER: Well, that's why I came back to Saccharide Humectants after all.

DR. BELSITO: But were any of the saccharides we previously used had a listed function as humectant?

DR. EISENMANN: Yes.

DR. SNYDER: Yeah, that's not going to work.

DR. KLAASSEN: That's what I thought.

DR. SNYDER: That's what I thought too. I suspected that, because it would be weird that these would be so different from the others.

DR. BELSITO: So I think we have no option but to say the Safety Assessment of, and list the ingredients. Long title, but, I mean, it's the only way to go, right?

DR. LIEBLER: I have no objection to that.

DR. SNYDER: I think so, Don. I think that it's just otherwise it's too confusing.

DR. BELSITO: Yeah. And then, in 2019 plus 15 years, which will get us out to -- I'm 84. Someone else can incorporate all of the saccharides together. Okay.

DR. HELDRETH: That works.

DR. KLAASSEN: Could have Part A and Part B.

DR. BELSITO: Okay.

MR. JOHNSON: I have another question relating to the discussion. That 28-day oral toxicity study on Anhydroxylitol, is that just basically addressing the safety --

DR. BELSITO: What page are you on Wilbur?

MR. JOHNSON: The discussion.

DR. BELSITO: What page number?

MR. JOHNSON: Okay, one second. It's on Page 33.

DR. BELSITO: Discussion, yes.

MR. JOHNSON: Yes, now you mentioned adding the results of the 28-day oral toxicity study on Anhydroxylitol. Is that meant to just support the safety of that ingredient, or other ingredients as well?

DR. BELSITO: I don't remem- -- who mentioned that again, a 28-day on Anhydroxylitol?

DR. SNYDER: No, nothing went in discussion, Wilbur.

MR. JOHNSON: Repeat that, please.

DR. SNYDER: I don't think we talked about having that in the discussion. In the summary we have a paragraph on it.

MR. JOHNSON: Okay, but it doesn't belong in the discussion. Okay.

DR. BELSITO: Yeah, no, the discussion -- the only thing we're adding is the first paragraph that the panel was concerned about the absence of DART data and requested a 28-day dermal absorption study on Saccharide Isomerate, period. We were aware that it was available both in a low molecular weight form that could be absorbed and a higher molecular weight form that would not be absorbed. We're now aware that the low molecular weight is composed of sucrose and fructose, and the concern for absorption is therefore mitigated.

MR. JOHNSON: Okay, thank you.

DR. BELSITO: Is that fair, Dan, Curt, Paul?

DR. LIEBLER: Yeah.

DR. SNYDER: Fine.

DR. KLAASSEN: Yeah.

DR. BELSITO: Okay, anything else? No? We've beaten this horse to death. Okay, it's 10:17, do we need a short break?

DR. LIEBLER: Sure.

DR. BELSITO: Why don't we come back at 10:30, is that good?

DR. LIEBLER: Sounds good.

DR. BELSITO: Okay. See you then.

DR. KLAASSEN: That's an hour and 15 minutes.

DR. BELSITO: No, for you, Curt, 9:30.

DR. KLAASSEN: All right. See you in 13 minutes.

Cohen Team – March 11, 2021

DR. COHEN: Okay. If we can, we'll move on to saccharide humectants. Wilbur, this is yours. This is a draft tentative report. In September of 2020, the panel issued an insufficient data announcement for the seven ingredients.

We asked for method of manufacturing, impurities, composition data. We wanted confirmation of lack of skin penetration. We wanted information about glucose and fructose concentrations and 28-day dermal tox on the isomerate at 2.8 percent.

We received method of manufacturing in the report, but a March 8th memo from Bart suggested that we don't have method of manufacturing for the isomerate. We have impurities on the isomerate, and it's further elaborated on in a recent memo. What are the comments from the group?

DR. PETERSON: So there was a question about whether -- about the title. And I think I want to start here because it does get to a bunch of chemistry questions. I don't know what the title should be --

DR. COHEN: Is this regarding the anhydroxylitol?

DR. PETERSON: Well --

DR. COHEN: That it wasn't supposed to be part of the isomerate class? Is that the issue that you're talking about?

DR. PETERSON: Right now, I'm talking about the issue about the title of this report being saccharide humectants because we don't typically title a report based on its use -- application, I guess, or whatever you -- and it's used as a humectant. And I actually -- my question was why these -- there's several of these that probably should have been in the report with glucose and fructose, and just curious why that didn't happen because there's basically two -- you know, to come up with a title and to think about how you classify these, there's the polyols, which are the anhydroxylitol, anhydroglucitol, and anhydrogalactose. And then this -- and it's a product that has the anhydroxylitol in it.

But then when you're looking at the arabinose and glucose, they're reducing sugars that are like fructose or glucose. And then the saccharide hydrolysates and isomerases, which are really sugars -- I mean, they're -- they would have belonged -- I would have put them in the other group. So I'm just curious about how the grouping gets decided.

And, I mean, actually -- and I did think this report kind of needed a major revision about how things are presented and put based on chemistry. But, I mean, that's going to take a long time, and I will make recommendations in the document. So I'm not sure if that helps anything at all. I don't know what the title -- to change the title to if they don't want to have the humectant in the title because it's a mixture of polyols and then saccharides, monosaccharides, polysaccharides.

DR. COHEN: Can you go out on a limb with a suggestion on a title for this grouping?

DR. PETERSON: Dan and I talked about it. Neither one of us could come up with a different one than what was already there.

DR. BERGFELD: Just saccharides would not be good enough -- just saccharides?

DR. PETERSON: You could say saccharides because they're all -- I mean, if you could -- yeah. And, again, the -- I think the polyols are part of saccharides so, you know, yeah, I think you could do that. That would work.

DR. ANSELL: Yeah. And we netted out pretty much in the same place that it was odd to have humectant in the title, which is a functional description as opposed to a chemical description. And a producer also felt that those two materials, the xylitol and the anhydroxylitol, were not members of this particular family and should be removed.

DR. PETERSON: Say that again.

DR. ANSELL: We basically ended up agreeing with you.

DR. PETERSON: But what should be removed?

DR. ANSELL: The xylitol --

DR. SLAGA: Xylitol and --

DR. COHEN: And the anhydroxylitol. Xylitol and anhydroxylitol. It was in the late-breaking material that came.

DR. ANSELL: Yeah. Mm-hmm.

DR. PETERSON: And you'll do those as a separate report? But if you're going to remove anhydroxylitol, why not also remove the other two polyols? I guess I'm very confused this morning. I mean --

DR. COHEN: So do you agree with removing the xylitol and the anhydroxylitol? Do you agree with removing those? We can start with that.

DR. PETERSON: I don't know if I -- again, it depends on -- there's -- I never wake up until, like, 11:00 in the morning. It's just like, really -- this was a complicated one.

DR. COHEN: Do you want -- you know, I had some other comments and questions. Do you want me to come back to you on it?

DR. PETERSON: So I missed the information. Where did it propose that the one be removed from the group because I didn't suggest anything should be removed from the group?

DR. COHEN: It was in --

MR. JOHNSON: Wave 2.

DR. COHEN: It was in, right, Wave 2. Yeah. There was a -- it was memo dated March 8th from Bart.

DR. PETERSON: So I read that, but I didn't see the -- can you give me the page number for that?

MR. JOHNSON: Sure. PDF page 49 in the data supplement.

DR. COHEN: That was in the data supplement. Right. I'm sorry.

MR. JOHNSON: Yeah. Uh-huh.

DR. COHEN: It was in the data supplement.

MR. JOHNSON: Mm-hmm.

DR. PETERSON: Right. But where is the proposal that it be removed from this report? Because page 49 of the Wave -- of the data supplement is -- oh --

MR. JOHNSON: Okay.

DR. PETERSON: Oh --

MR. JOHNSON: It's actually on PDF page 51, the second paragraph there.

DR. PETERSON: Well, I agree. Okay. So I read this differently. I agreed with the issue that it was an isomerase, but it -- how did I read this? It's not part of that class, but, you know, the other chemicals on this report are not part of that class either. So I don't -- I didn't see this as a proposal to remove the anhydroxylitol from the report. Because I actually think it belongs in the -- you know, that you can group these together. I just --

DR. COHEN: Jay, is there an objection to keeping it in, particularly if it's moving along?

DR. ANSELL: No. I think I agree with Lisa's characterization to begin with. The idea of forming a family is that the data on any material should be relevant to assessing all of the materials, and we don't believe that these fit within the family. Whether we reorder it or remove it, I guess, is a really a second question.

DR. PETERSON: So what does anhydroxylitol -- and I agree that this -- there's a xylitol glucoside that they're talking about in this Wave 2, and I thought that that should be added because this -- the product that they have -- and a lot of the data -- the toxicity data and all this is -- with this anhydroxylitol is actually done with the cosmetic ingredient, which is called the -- I spent a long time on this report trying to go through all the chemistry.

But the (inaudible) is actually a mixture of this xylitylglucoside and anhydroxylitol. And it is not a saccharide hydrolysate or isomerate. It's a separate entity. And so I think that if you're going to use all the data from the -- I cannot say this -- cosmetic ingredient, which is actually a mixture of the xylitol glucoside and anhydroxylitol and has a trace amount of glucose in it and some xylitol, you know, that's a mixture that has these different components, and it should stand by itself.

It doesn't fit as it was originally classified, which is a saccharide isomerate. It's really something different than that. So I'm seeing adding things, not taking things out. But removing this -- and all the -- when you look at the data for anhydroxylitol, it's actually done with this cosmetic ingredient mixture which has the glucoside in it and some glucose in it. So I agree that it's separated but not removed from the report.

It belongs in the report. You just have to reframe it. So I actually felt this report needed completely to be rewritten and then we should talk about insufficiencies/sufficiencies because it was confusing to me actually. I mean, we could talk about what's needed or not needed, but a lot of the data that's given from saccharide isomerate is actually for -- I mean, so the -- yeah.

DR. COHEN: Lisa, it sounds like you at one point you were -- it seemed like you were arguing to separate them and remove them, and then you concluded that we should keep them together.

DR. PETERSON: Well, I think, you know -- so my -- you know, one is a -- one question I have is about process because I was curious why, for example, arabinose and Psicose, and then the saccharide hydrolysate, which is a mixture of glucose and fructose, were not included in the fructose/glucose report. I'm just asking. That's just a process question. And if it's just how life rolled, that's fine.

And then they do all -- you can make them all fit in this report. So that's one question. And then, I agree with the comment that this saccharide isomerase that refers to this product that has the xylitol and anhydroxylitol is not a saccharide isomerate. It's something completely different, and it's a different item. And it becomes adding xylitol glucoside to the report. But that's not confusing. So I probably confused the two issues. There's title and who's in the report, and then it's the misclassification of this one thing in the report that really needs to be put out as a separate thing.

DR. COHEN: So what are we --

MR. JOHNSON: Dr. Cohen?

DR. COHEN: Yes.

MR. JOHNSON: I'm sorry. You can continue. I'll speak later.

DR. COHEN: No. If you have something that can help clarify it, we'll take it.

MR. JOHNSON: Yes. I'd like to call the panel's attention to PDF page 21.

DR. COHEN: In the report?

MR. JOHNSON: Yes. PDF page 21 and under the saccharide isomerate subheading right before composition and impurities.

DR. COHEN: Okay.

MR. JOHNSON: Yeah. I'd like to point out that we received data on saccharide isomerate from two different chemical suppliers. And the saccharide isomerate in the first paragraph under that subheading has a molecular weight range of 120 to 400 Dalton. And in certain parts of the report, the molecular weight of the chemical that's being tested is stated, but it isn't stated for the saccharide isomerate in the first paragraph. But the molecular weight range for all of the data that relate to this particular saccharide isomerate will be added to the safety assessment. So I'm just pointing out that there are two different molecular weights stated for saccharide isomerate.

DR. COHEN: And there's some mention of some greater than 1.4 megadaltons?

MR. JOHNSON: Well, this is under -- this is 120 to 400 Daltons, which is a lower molecular weight range.

DR. COHEN: Yeah.

MR. JOHNSON: Mm-hmm. And that will be added to the chemistry table to indicate that, for another saccharide isomerate, there's different molecular weight range.

DR. PETERSON: Okay. So, Wilbur, this gets to a really big confusion I had reading this report because there's basically -- for this saccharide isomerate, there's basically two different kinds of products with four different -- with different trade names. And I was wondering if it would be possible to define early on, you know, the compound and products in paragraph one of the -- of that method of manufacturing on page 21 --

MR. JOHNSON: Yes.

DR. PETERSON: -- is really trade name -- it's really -- its trade name is Pentavitin. But you can't use the name in the report, so I would call it Trade Product 1. And then the other one is Trade Product 2, of which I think there's multiple versions of it that get tested if I'm remembering right -- and to just number them Trade Product 1, Trade Product 2 -- that they represent this group which are the -- actually are chemically distinct from one another. The Trade Product 1 is small molecular weight. The Trade Product 2 is large molecular weight, so they have different --

MR. JOHNSON: Yes.

DR. PETERSON: -- compositions chemistry. So put them under the same thing because the process of making them is similar. But I think it would help in the report if you define -- this would have helped me is to have --

MR. JOHNSON: Yes.

DR. PETERSON: -- Trade Product 1 -- Isomerate Trade Product 1 and then Isomerate Trade Product 2. And there might have even been more than one that are used throughout the thing, but you know that you can read-across. But it certainly would -- I found this a very complicated report to read in part because -- and then for this report to come in in a second wave on the -- I mean, maybe that's how I got confused because there's saccharide isomerase in that title of that memo. And --

MR. JOHNSON: Yes.

DR. PETERSON: -- you know, the -- actually, the anhydroxylitol is not an isomerase. But that's probably where my confusion came in because I thought that they were equating the two.

MR. JOHNSON: Yes. But -- well to --

DR. PETERSON: They're different.

MR. JOHNSON: -- make it a little bit --

DR. PETERSON: They're different. They're different. They're very different.

MR. JOHNSON: Yeah. But to make it, you know, easy to differentiate one saccharide isomerate from the other, all the data that relate to the saccharide isomerate with a molecular weight range of 120 to 400, the molecular weight will be stated by that saccharide isomerate. Now, the other --

DR. COHEN: I think that makes sense.

MR. JOHNSON: -- saccharide isomerates, that information is already included in the report.

DR. PETERSON: Yeah. Okay. I just thought maybe I had a simpler thing for it, but I understand there's a protocol you have to follow so --

DR. COHEN: And I think if we do Trade 1 and Trade 2, it'll be easy to forget which one you're talking about if you go further down in the report.

DR. PETERSON: Okay.

DR. SLAGA: Yeah.

DR. PETERSON: Okay. That's fine. I think it's just different minds work different ways, and for me, it would have been --

DR. COHEN: All right. A couple of other things and then we'll just articulate what we're going to say. Bless you, Ron.

DR. SHANK: Thank you.

DR. COHEN: So we'll go through them. For the saccharide isomerate, we have irritation and sensitization at 20 percent, but we don't have the number of subjects or the test methodology. It would be nice to see that -- that was. I mean, is it five or 100 subjects because it's at a high concentration?

The other irritancy studies were up to 1.5 percent below the maximum leave-on concentration of the isomerate of 2.8 percent. But I'd like to see what that 20 shows. And we do have a human HRIPT at 2.75 percent, which is pretty close. I think it would help.

I needed the group's advice on the issue of the anhydrogalactose demonstrated inhibition of melanin secretion. How do deal with that finally? Is there some kind of disclaimer or macro that we use for that in these reports?

DR. PETERSON: You know, I read in -- I don't know if it was for this one but for another report where there was a similar kind of thing where you saw some evidence that it could be -- that these in vitro tests are sort of a --

DR. COHEN: What's that Wilma?

DR. BERGFELD: A de-pigmentor. That's what your word is.

DR. PETERSON: Right. And so these in vitro tests are a signal that maybe they could be but until you do a test in real skin and show that it -- you know, you need an in vivo model to show depigmentation. So this is a signal, and I think in another report there was sort of a statement about how it indicates the potential but doesn't necessarily mean that it does that. And there was some kind of -- I remember some kind of boilerplate statement about how the, you know, cosmetics are not meant to be --

DR. COHEN: Right. So do we have --

DR. BERGFELD: Biologically active.

DR. PETERSON: Yeah.

DR. COHEN: Right. So do we have --

DR. BERGFELD: I think Monice might be looking that up. Monice?

MS. FIUME: I'm sorry.

DR. BERGFELD: Do you -- I don't think we have a specific boilerplate for depigmentation, but we have dealt with it.

MS. FIUME: We've discussed several times that we need one. I think there's been difficulty in crafting the exact wording. But there are reports, and again -- and it was just within the last two meetings, but again it's escaping me exactly which report it was that we had that issue where it was seen in vitro. And then in vivo was needed. And then often in the discussion, the gist of what is said is that these are not expected to depigment because they're cosmetics.

DR. PETERSON: Yeah. That's what I'm remembering. And it was another chemical that we've dealt with. This time because it's in the --

DR. COHEN: Right. So I think if we just say -- we cover that in the discussion would it be?

DR. BERGFELD: Right.

MS. FIUME: Right.

DR. COHEN: I think it's fine. I wasn't going out and asking for in vivo data or human data on that. I just -- but that would not be a function of a cosmetic. So if the warning is there, we can just address it that way, I suspect.

MR. JOHNSON: Dr. Cohen, excuse me.

DR. COHEN: Yes.

MR. JOHNSON: That's stated in the first paragraph of the draft discussion on PDF page 32.

DR. COHEN: All right. Let me just go there so I can just -- in the discussion.

DR. PETERSON: Which was this one?

DR. COHEN: Draft discussion. Ah, yes.

DR. PETERSON: Great.

DR. COHEN: It's perfect. Okay. Thank you.

DR. PETERSON: Yeah. That's what I remember. Maybe it's exactly what I'm remembering.

DR. COHEN: This might be the one we were thinking of.

DR. PETERSON: Yeah.

DR. COHEN: Yeah.

DR. PETERSON: I like the statement actually because it is -- the in vitro tests are always just showing the potential, but it doesn't mean anything until you can see something in vivo.

DR. COHEN: Okay. So again, in some of that late-breaking information, it's seen that the method of manufacturing of the isomerate we don't have, Wilbur? Right? We had it originally in the report, but we should be --

MR. JOHNSON: We do have it, Dr. Cohen.

DR. COHEN: We do?

MR. JOHNSON: It's on PDF page 21 under the saccharide isomerate subheading.

DR. PETERSON: So what I think is we need to add, you know, the Wave 2 information where they clarify the difference between the isomerate and just base catalyzed and the acid catalyzed formation of the anhydroxylitol -- that we need to add the method of manufacturing for the anhydroxylitol and also indicate that it includes, you know, the xylitol glucoside, which is actually the major component of that reaction.

DR. COHEN: Wilbur, I think I was thrown a little by the memo of March 8th from Bart where it says, "The following is not correct as DSM did not provide a method of manufacture, which is presented under saccharide isomerate, nor were such methods submitted as unpublished data." So --

MR. JOHNSON: Well, actually the first paragraph under saccharide isomerate is from DSM, and that is for the 120 to 400 Dalton molecular weight chemical.

MS. FIUME: I think I can clarify. I think the issue was with the introductory paragraph under method of manufacture where it says that the methods are not specific to the cosmetics industry. And what they're saying is that actually the saccharide isomerate information is from a supplier and is specific to cosmetics. That's how I read that comment.

MR. JOHNSON: So, Monice, should that be deleted?

MS. FIUME: Deleted or adjusted, Wilbur. I mean, because it's making it sound like all of this information is generic, and that's not the case. To me, that's how I read the comment --

MR. JOHNSON: Oh.

MS. FIUME: -- that the concern was that the saccharide isomerate was specific to cosmetics.

MR. JOHNSON: Okay. Thank you.

DR. BERGFELD: You can say that right in that paragraph, "except for …"

MS. FIUME: Yes.

DR. COHEN: That's right. That's perfect. Yes. Okay. I think, you know, we have to bring this one in for a landing on what we're going to say tomorrow on this. And so we're going to have an IDA on this for --

MS. FIUME: Well, so you did have one IDA already. And I don't -- I just wanted to offer some historical perspective for Lisa. As far as the groupings from when we did the monosaccharides and disaccharides, generally, Bart would create those groups based on the tools that he had. So if some were missed, I'm just guessing it was just part of that process.

But as far as the reorganization, we do have reports where, within the report, we've done subcategories of ingredients and given them, you know, subtitles. I mean, simple would be this is an acid, this an ester, this is salt. I mean, obviously, that wouldn't apply here, but if you have subheadings for the ingredients that you would prefer and that would help organize the report, that is something that could be suggested.

DR. PETERSON: Okay. And I also think a piece of it is that there are some of these ingredients that if we don't have the data for the -- for example, the saccharide isomerase one, the first paragraph is primarily glucose and fructose. So if we're missing information for those in terms of toxicity or sensitization or irritation, I feel -- and I don't, you know, that and the group can discuss this -- that you could read-across from the glucose/fructose report. You know, you could pull in information from that because it's primarily glucose and fructose according to what the industry told us, right?

So, I mean, this is part -- this -- I know I maybe come across as a bit confused because there's multiple different things here, but some of it was trying to get to the point is -- okay. If we can understand this then, we can read-across -- some of these we can actually pull safety information from the previous reports because they're structurally similar and their composition is similar. So if we're missing information at least we can pull it from the (audio skip). That is what I'm proposing.

MS. FIUME: So would it be sufficient -- again, this is something we've done in the past, but you're more than welcome to say you would want it presented differently. When there is information in existing reports that would be very relevant to the report you're doing now and provide read-across, often we've done it in a summary table of information. Would that be sufficient if it was put into a table -- all of the relevant ingredient that have been reviewed in the past?

And we would break it down. It would be the same thing, we would tell you what sensitization information was there, you know, what tox information had been included, what ADME. And then it -- we would present that as a table, or do you actually want to see it in the text?

DR. PETERSON: For me, a table would be fine, but I -- you know, and I need to defer to my colleagues here what their thoughts are about being comfortable using glucose and fructose for at least the isomerase number one. There's that, yeah. So I --

DR. COHEN: Ron, Tom, do you want to comment on that? You're on mute, Ron.

DR. SLAGA: In a table would be fine for me.

DR. BERGFELD: Don't you think a little summary in the text --

DR. SLAGA: Yeah.

DR. BERGFELD: -- referring to the table?

DR. PETERSON: Yeah.

DR. SLAGA: Yeah. A little summary in the text and then would be fine.

DR. PETERSON: Yeah. I think it always needs a little summary in the text (audio skip).

DR. COHEN: Ron?

DR. SHANK: Yeah. Adding glucose and fructose as a table would be fine. I thought the data on the isomerate was sufficient. These are unlikely to penetrate the skin -- the epidermis to any great extent, so I don't think any more toxicological data are necessary.

DR. COHEN: Great.

DR. BERGFELD: I think that should go in the discussion because of all the things Lisa has said about the differences in these different chemical ingredients.

DR. SHANK: Uh-huh.

DR. PETERSON: I mean, they're different and they're not different. You know, it gets to, you know, the fructose, the --

DR. COHEN: Okay. So, Monice, appropriately pointed out we have an IDA. We already sent an IDA out on this. Ron, you were satisfied with the tox.

DR. SHANK: Yes.

DR. COHEN: Is there anything we need to move -- anything else we need to move this along? I mean, it was a good conversation, but I think it's coming back down to moving this along. I'd like to see the method and then the number of subjects in the 20 percent isomerate, but is there anything else we need to move this report along?

DR. SHANK: Not for me.

DR. SLAGA: I agree. I'd -- initially, I had what Ron had and suggested last time the 28-day dermal, but I don't think that we need that because of lack of penetration. So I would go along with being safe.

DR. BERGFELD: I think because of all of the discussion on the chemistry that we need to do something in the text regarding the chemistry, whether it be the separation or whatever. Looking at the Table 1, which shows the chemical formulation, they are different. The first three are different than the last three.

MR. JOHNSON: And Dr. Bergfeld, you know, I had mentioned that the saccharide isomerate with the molecular weight 120 to 400 --

DR. BERGFELD: Yeah.

MR. JOHNSON: -- those data will be added to Table 2.

DR. BERGFELD: Right. Okay.

DR. COHEN: Table 2. Okay.

DR. PETERSON: And I think you can add the method of manufacturing for the --

MR. JOHNSON: Anhydroxylitol?

DR. PETERSON: Yeah, xylitol. And I actually think that, you know, the glucoside that is in that method of manufacturing -- so you have the composition of that solution, which is basically the trade product that's used as the xylitol glucoside, and I think that structure could be added. And then you've got all -- you've actually got a lot of the safety information because it's all the safety information for anhydroxylitol because it -- they're always -- when you use a trade product that they talk -- and it's the same -- if you look at all the things, the chemical is in all that -- those same solutions and tests.

I was going to -- I have a number of edits, and I'll just -- and some of it will address, like, the chemistry part and how they should be grouped. And when I update the -- when I put in my report with my comments, I'll make some suggestions.

MR. JOHNSON: Yes.

DR. COHEN: So we're going to do edits to the chemistry description --

DR. BERGFELD: And organization.

DR. PETERSON: Yeah. I have some suggestions for that.

DR. COHEN: Lisa, you said you needed method of manufacturing for xylitol?

DR. PETERSON: No. Anhydro. We have it. We don't need it. We have it. It just needs to be -- it was in Wave 2. It needs to be added to --

DR. COHEN: Ah, yeah. Okay.

DR. BERGFELD: We have to assume that all Wave 2 will automatically go into the text.

DR. PETERSON: Oh. Okay.

DR. COHEN: Okay.

DR. PETERSON: I didn't want to make that assumption.

DR. BERGFELD: Mm-hmm. And the writers do that.

DR. PETERSON: Okay.

DR. COHEN: So it's okay moving this along and just asking for some additional data on the irritation and sensitization data when we talk about it tomorrow, right?

DR. BERGFELD: Well, then it doesn't -- then it goes on a different way if you're asking for something. It's insufficient.

MS. FIUME: It's been handled several ways through the years. If you are comfortable with that information whether or not you get the details, it could just move ahead, and we could include a comment in our post-meeting announcement saying that this information is wanted. But recently in the past, there've been, for a number of reports where only summary data were submitted -- and there were times where there were signals that something might be going on, and the panel has rejected that information and said, "No, we need this." And it could be reason for insufficiency in the report.

DR. COHEN: I didn't have that -- based on this particular group of chemicals, I didn't have that very high level of suspicion. But I just felt that at the 20 percent I just wanted a little more information understanding that they reported this out as okay at that concentration. I don't think I would hold it up for that.

MS. FIUME: Okay. We can include it in our post-meeting announcement that clarification and more details for that study would be beneficial for the document.

DR. SHANK: Do you want more sensitization data?

DR. COHEN: No. I wanted just to -- we didn't know how many subjects or methodology at the 20 percent isomerate irritation and sensitization study. I didn't know if it was five people or 100 people -- how they did that.

DR. SHANK: Okay. We could ask for that to be clarified.

MR. JOHNSON: That --

DR. SHANK: It's probably in some report.

DR. COHEN: What was that last bit, Ron?

DR. PETERSON: Yeah. That was my comment is that there was data for the skin sensitization, but they're not really showing you any data. They're just summarizing --

MR. JOHNSON: Right.

DR. PETERSON: -- the outcome, and I thought we should push for -- I mean, they're --

DR. SHANK: Okay.

DR. PETERSON: -- acceptable. We've had this discussion in other situations --

DR. COHEN: So --

DR. PETERSON: -- where they've given us that it's been done. And this is the outcome, but there's no data. And we've gone back to see if they'll share the data because they, you know --

DR. COHEN: Well, it's tentative report. Monice, any other advice, or Wilma, on --

DR. BERGFELD: No. I did want to make sure you put the statement that Ron made about penetration. It would not penetrate.

DR. COHEN: About what?

DR. BERGFELD: The penetration. That you put that in --

DR. SHANK: These are unlikely to penetrate the epidermis.

DR. COHEN: Got it.

MR. JOHNSON: So that's the only additional statement that should be added to the discussion?

DR. BERGFELD: Could I just ask a question? I have a note here in mine that some of this is GRAS. I'm just going back to clarify that. Do you know that right off hand if any of these particular ingredients have a GRAS category?

DR. SHANK: I don't.

MS. FIUME: PDF page --

DR. SHANK: I would assume they do.

MS. FIUME: -- 22.

DR. BERGFELD: I think that could go in the discussion.

MR. JOHNSON: Okay. The GRAS --

DR. COHEN: It look like (audio skip).

DR. BERGFELD: Yeah. Because then it makes it sort of a food.

DR. SHANK: Right.

DR. BERGFELD: That helps with the safety.

MS. FIUME: Saccharide --

DR. COHEN: Hydroxate.

MS. FIUME: -- hydrolysate is the one. And then, David, I don't know if it gives you any reassurance with not having that number. That 20 percent seems to be much higher than the actual use concentration. I think you do have --

DR. COHEN: That's right.

MS. FIUME: -- numbers, right, for the ones that are close to actual concentration of use?

DR. COHEN: We have it for 2.75 percent, which, I think is -- that's why I was reassured and didn't want to hold it up for that. I wanted procedurally to understand, you know, can we get this because it would be even more bolstered data? But yes. The 2.75 percent on 213 was good.

MS. FIUME: Okay.

DR. COHEN: All right. So we're finished with that. Does the group want to break now or do one more and then break?

DR. SHANK: Let's break now. It's noon there, right?

DR. BERGFELD: Right.

DR. COHEN: It's noon, yeah. It's noon here in New York. I think the --

DR. SLAGA: Ron's going to have breakfast.

DR. SHANK: That's right. Breakfast time for me.

DR. COHEN: The saccharides got to us today.

DR. SHANK: Yes.

DR. COHEN: All of us. All of us.

DR. BERGFELD: So you're going to reassemble --

DR. COHEN: How long --

DR. BERGFELD: An hour, 45 minutes?

DR. SHANK: 1:00?

DR. BERGFELD: 1:00? 45 minutes?

DR. COHEN: 45 minutes would be -- I think that's good. 12:45, is that okay with everybody?

DR. SHANK: Yes.

DR. ANSELL: 12:45.

DR. SLAGA: Yeah.

DR. COHEN: Okay. We'll see you. We only have one, two, three, four -- we have six left. So we've really put a big dent on it. We're getting there.

DR. BERGFELD: Well, more than a big dent. You did a lot of the botanicals.

DR. COHEN: Oh, my god, yes. And, yeah, we only have one botanical left. And I don't think it'll be quite as --

DR. BERGFELD: Oh. Arduous.

DR. SHANK: Yeah.

DR. COHEN: -- highly discussed. Okay. See you in 45 minutes.

DR. PETERSON: Okay.

DR. SHANK: Okay.

DR. BERGFELD: Okay.

DR. COHEN: Take care.

DR. BERGFELD: I'm going to leave myself on, so I don't come out. Should we come out Monice and come back in or what?

MS. FIUME: You can do it either way, Wilma. I just usually just shut off my camera and mute my mic.

DR. BERGFELD: Okay. I'll do that.

MS. FIUME: I mute my mic, but you can do it either way.

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DR. BELSITO: Yeah, so, these were formerly known as Saccharide Humectants, and I'll get to the title in a moment. At the September meeting for seven ingredients we asked for manufacturing, impurities, composition, confirmation of the lack of skin penetration, composition of glucose and fructose in ingredient mixtures and if the two monosaccharides are present in sufficient amounts, the available negative data on glucose and fructose skin penetration could be used. Then 28-day dermal tox on Saccharide Isomerate at cosmetic use concentrations up to 2.8 percent.

We received an amazing amount of data on these, including a Wave 3 letter indicating that these were fructose and sucrose. And, based on all that data we felt that these ingredients, all of the saccharide "humectants" were safe as used in the present concentrations and practices of use.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: David, is there a second or a discussion?

DR. COHEN: There's a second on that.

DR. BERGFELD: Okay. Any discussion regarding the motion? I want to call for the vote, and then discuss, unless you have something that relates to the motion itself. Okay?

DR. COHEN: I guess one question, did anyone on your team, Don, feel the need for method of manufacturing for the Anhydroxylitol? That came up in our discussion.

DR. BELSITO: Not that I recall. Dan, Paul, Curt did you have concerns with that?

DR. LIEBLER: I don't remember being concerned about that. I'm going back to look.

DR. PETERSON: I think my suggestion was it needed to be added to the report.

DR. LIEBLER: Yeah, it's not specifically present, is it?

DR. BELSITO: Is it in Wave 2?

DR. PETERSON: Yeah, it's in Wave 2, it's in that whole discussion about how the Anhydroxylitol is not Saccharide Isomerate.

DR. BELSITO: Right. Yeah, Lisa, anything that was in Wave 2 that we looked at will be added into the document.

DR. PETERSON: Yeah, and I actually thought that the xylitylglucoside should be added as an ingredient, because it's actually my understanding of that Wave 2. And then looking at what was the cosmetic ingredient that was actually tested is a composition of the -- it's primarily the xylitylglucoside. And then it also has some of the Anhydroxylitol in it.

So, if I read the document right, the testing for the Anhydroxylitol also has this xylitylglucoside in it too. So I thought that there should be as another structure that is added to the list of chemicals. Because they always exist together, based on my understanding of the reading of all the material that came.

DR. BERGFELD: Dan, do you want to respond?

DR. LIEBLER: If I understand correctly, Lisa, you're suggesting adding another ingredient? I mean, it's only eligible for the report if it's in the dictionary, and --

DR. PETERSON: Okay, okay, okay. So, that's fine. I'm forgetting those things because if the one isn't in the dictionary. But the reality is, is that the company that provided a lot of the data has this other chemical in it. So, that's fine, that's my learning the process and (audio skip).

DR. LIEBLER: Yeah, that's okay. And, actually, getting back to the question -- oh, well, actually maybe Carol -- Carol's about to comment, she's got her hand up. Maybe she could shed some light on this. And I do want to come back to the point that Don raised.

DR. EISENMANN: All I want to say it is in the dictionary.

DR. LIEBLER: The glucoside?

DR. EISENMANN: Yes, it's one word, xylitylglucoside. It's there.

DR. LIEBLER: So, I don't know why it's not in the report. I mean, if it's related function, structure.

DR. PETERSON: Well, the thing is that for the one trade compound or mixture -- it's a mixture. That's what Wave 2 is all about. I mean, that's my reading of the information that came about this, you know, the synthesis of Anhydroxylitol. And, when they described in, you know, wanting -- I think the company didn't want us to think that it was the isomerate. They wanted to explain the difference between an isomerate and the method of manufacturing for the Anhydroxylitol. And when you read that then, you know, the primary product of that Anhydroxylitol synthesis is the xylitylglucoside.

DR. LIEBLER: Yeah, so, well, actually I didn't realize that that was in the dictionary. I'm not sure what we do at this point, Bart?

DR. BERGFELD: Bart?

DR. SNYDER: Bart, was that in the previous saccharide report? Is that covered in the previous saccharide report?

DR. HELDRETH: It is not. So, a couple things I want to point out here. One, the xylitylglucoside is a glucoside. It's different than these other ingredients. I can show you exactly what it looks like. Right here is the xylitylglucoside. So it's a little bit different than these other saccharides that we're looking at.

The other thing I will point out, based on my experience working with the Nomenclature Committee, is that they wouldn't consider all of these other constituents as part of that ingredient. If a supplier submitted an application for a name for Anhydroxylitol and showed all of these other constituents, they would write back to the supplier and say, okay, you can have your name for the Anhydroxylitol but you need to list xylitylglucoside on the label, you need to list the water on the label. They're not part of the ingredient itself.

So, I feel like what the supplier has given us in this case is actually a tradename mixture. It wouldn't really fit within the definition to be the ingredient xylitylglucoside.

DR. PETERSON: Okay, and so a lot of the toxicity testing was done with that mixture, so we just --

DR. LIEBLER: Have to take that into consideration.

DR. PETERSON: Okay, awesome.

DR. LIEBLER: So, yeah, we often have the ingredient we're reviewing is in the dictionary and (audio distorted), but it's applied as a mixture, or it's got impurities (audio skip).

But the other point I wanted to come back to about method of manufacture, I don't have that document in front of me, but I think that had sufficient information, even if it wasn't detailed and precise, to allow us to put that into the report. Lisa, I think (audio skip) memo where they described briefly how it was produced, I think.

DR. PETERSON: Yeah, I actually agreed with that and I thought that we now have some version of a method of manufacturing for the Anhydroxylitol.

DR. LIEBLER: Right. Okay.

DR. BERGFELD: So, have we clarified this? We clarified?

DR. BELSITO: We sort of clarified it, but I think I heard Dan and Lisa say they would want it added into the report even though it's structurally dissimilar. Is that what you said?

DR. LIEBLER: No, no. I don't mean that. I meant that the information in the letter about the Anhydroxylitol contained enough information about method of manufacture and we can take that text and put it into our report.

MR. JOHNSON: Dr. Bergfeld, I have a question.

DR. BERGFELD: Certainly.

MR. JOHNSON: Yes, there is information, other than the method of manufacture, for Anhydroxylitol in that submission, do you basically want all the information included in that submission or just the information relating to method of manufacture?

DR. BERGFELD: I'll have to ask Dan to answer that, Dan?

DR. LIEBLER: Can you just say that one more time, Wilbur? I'm sorry.

MR. JOHNSON: There's information other than the method of manufacture in that industry's submission. Since it seems that you're singling out the method of manufacture, is that the only information from that submission that should be added to the report?

DR. LIEBLER: Yeah, only that, it's probably a sentence or two, and it would go under the method of manufacture part of our report.

MR. JOHNSON: Okay.

DR. PETERSON: I also think you can add the composition, because, you know, the method of manufacturing is really talking about (audio skip). I don't know, you worry about that, but I mean, some of the impurities in this method of manufacturing that was given to us they give us the percentage of the different components and Anhydroxylitol is a percentage of the whole mixture, but they actually give the composition.

So I guess my question is should that composition go in too. One company reported that this was the composition of the cosmetic ingredient that they're using, it has Anhydroxylitol. And that is what is being used in the toxicity testing. So, I think it needs to be in the report somewhere that it's not just the pure compound but rather this mixture that contains also these other things.

DR. BERGFELD: Dan?

DR. LIEBLER: Yeah, I think that that information is on the first page of that SSC-PCPC memo that we got in Wave 2. And, so, the information that Lisa indicated, which is provide in a little table there, that could be listed under composition and impurities in our report, under Anhydroxylitol.

You know, the manufacturer reported that a product containing Anhydroxylitol also contained, dot, dot, dot.

MR. JOHNSON: Okay. Okay.

DR. BERGFELD: Any other discussion? So, I'm going to go back --

MR. JOHNSON: Dr. Bergfeld?

DR. BERGFELD: Go ahead.

MR. JOHNSON: Yes, after you address that particular issue that you're about to address, I'd like to refer the panel to the draft discussion. But I can wait on that.

DR. BERGFELD: Well, we haven't had a vote on the motion yet, but I'd like Dr. Belsito to perhaps restate it.

DR. BELSITO: They're all safe as used in the present practices and concentrations.

DR. BERGFELD: And that's been seconded, has it not? David, did you second that?

DR. COHEN: Yes, I seconded it.

DR. BERGFELD: Okay. And then there was a question in which I believe has now been answered, but we'll discuss that in a moment. So, all those opposed to this motion? Abstaining? The motion pass, so we have safe as used.

Now the discussion, Wilbur, what would you like to see or hear about in the discussion?

MR. JOHNSON: Yes, I call the panel's attention to PDF Page 33. As you see there's information contained in the draft discussion. Is there any additional information that should be added?

DR. BERGFELD: You want to refer to why you've put in this Anhydroxylitol? Would you want to do anything with that in the discussion?

DR. BELSITO: No, I mean, I don't think we need to put that in the discussion.

DR. LIEBLER: No need.

DR. BERGFELD: No need.

DR. BELSITO: What we felt needed to be added is the following: Saccharide Isomerate is a low molecular weight composed of sucrose and fructose, so we don't have a concern for lack of DART data. It's mitigated -- I'm sorry. Saccharide Isomerate is essentially sucrose and fructose, so the concern for lack of DART data is mitigated.

And the high molecular weight -- this is the one that had the two molecular weights, correct?

DR. LIEBLER: Right, this is the one where two different forms were reported.

DR. BELSITO: All right. So, the smaller version of it, the lack of DART data was mitigated by the fact that it's composed of sucrose and fructose, so we already noted that and safe as used. And the higher molecular weight wouldn't be absorbed. So that was an important part of the discussion as to why we felt we didn't need DART data. Otherwise, I think our team felt the discussion was complete.

DR. BERGFELD: Dr. Cohen?

DR. COHEN: Don, we agreed with that last statement you just made. And, there was one other sort of edit issue, our team suggested the removal of the term "Humectants" in the title. It's a function term and doesn't reflect totality of the uses of these saccharides in products. So, it didn't seem appropriate.

DR. BELSITO: Yeah, we agree with that. That's what I said, the present report term Saccharide Humectants, the problem is we've already issued a report about saccharides in 2019. So it's not up for review until I'll be almost 83. So, our team suggested that the only option was to list the ingredients, all seven of the ingredients that we're looking at, as the title.

DR. COHEN: Yeah, we would go with that. I think that makes sense and gets rid of the functional description in the title.

DR. BERGFELD: Bart, can you respond?

DR. HELDRETH: Yeah, that's fine. I mean, that is of course -- those of you who've been with the panel for a number of years realized that that's the way we named all of our reports in the past. We've been trying to make it a little more concise and have a simple name, but from what I've heard from the team meeting, and from today, it doesn't sound like there is an easy simple name. So a listing is perfectly fine.

DR. BERGFELD: Now, because this is going -- it's going to go out as a tentative final, is that correct? So there'll be time for response from industry if they care to respond. Okay.

DR. HELDRETH: That's right, it'd be a tentative report and it'll come back at least one more time.

DR. LIEBLER: Oh, one more comment. Wilbur?

MR. JOHNSON: Yes.

DR. LIEBLER: Will you email me to send me an email and I'll response to it with a little text on the method of manufacture, and composition and impurities for the xylitol. Okay?

MR. JOHNSON: Anhydroxylitol?

DR. LIEBLER: Yeah.

MR. JOHNSON: Sure.

DR. LIEBLER: If you'd like me to help you draft a little method of manufacture and impurities from that SSC-PCPC memo.

MR. JOHNSON: Most certainly, I'll do that.

DR. LIEBLER: Okay. If you need a hand, let me know.

MR. JOHNSON: Okay, thank you.

DR. BERGFELD: Any other comments? Any other comments regarding the saccharide ingredient group? Well, we move a motion of safety on this, and we had discussion. We'll move on to the next ingredient, which is Sage, and this is Dr. Cohen's.

Safety Assessment of Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate 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.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.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. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088
cirinfo@cir-safety.org

ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 7 saccharides/saccharide derivatives in cosmetic products; all of these ingredients are reported to function as skin-conditioning agents – humectant in cosmetics. The Panel reviewed data relevant to the safety of these ingredients in cosmetic formulations, and concluded that Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The safety of the following 7 ingredients, as used in cosmetics, is reviewed in this safety assessment:

Anhydrogalactose	Psicose
Anhydroglucitol	Saccharide Hydrolysate
Anhydroxylitol	Saccharide Isomerate
Arabinose	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all 7 ingredients are reported to function as skin-conditioning agents – humectant in cosmetics (See Table 1).[1] Other reported functions include antioxidant, humectant, skin protectant, and oral care agent.

Because Saccharide Hydrolysate, also known as invert sugar, contains glucose and fructose, and saccharides/saccharide mixtures are being reviewed in this report, it is important to note that the Expert Panel for Cosmetic Ingredient Safety (Panel) has evaluated the safety of glucose and fructose (monosaccharides), as well as other monosaccharides and disaccharides. In 2019, the Panel published a report with a conclusion stating that the monosaccharides, disaccharides, and related ingredients are safe in the present practices of use and concentration in cosmetics described in the safety assessment.[2] This report is available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically 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 are provided by the cosmetics industry, as well as by other interested parties.

Of the 5 discrete saccharides that are reviewed in this safety assessment, Anhydrogalactose is supplied as the L-stereoisomer; while the other 4 (Anhydroglucitol, Anhydroxylitol, Arabinose, and Psicose) are each defined as the D-stereoisomers. For any one of the monosaccharides reviewed in this report, available relevant data on a different stereoisomer may be included, as these data may have some value in the safety assessment of isomer(s) under review. In such instances, the *Dictionary* name (including capitalization) will not be used (e.g., L-arabinose). Since Saccharide Hydrolysate and Saccharide Isomerate are defined as products by various processes, various stereochemistries (and connectivities) are possible.

An Australian Industrial Chemicals Scheme (formerly National Industrial Chemicals Notification and Assessment Scheme (NICNAS)) public report on Anhydroxylitol is available.[3] Data summaries from that report are included in this safety assessment.

CHEMISTRY

Definition and Structure

All of the ingredients in this report are hygroscopic, saccharides or saccharide derivatives. Such ingredients are commonly used for their moisturizing (humectant) properties. For example, Anhydroglucitol (CAS No. 154-58-5), a pyranoid polyol, is similar in structure to that of glucose, except for an unsubstituted methylene group at the C1 position (i.e. no hydroxyl group; Figure 1).[1,4,5] Psicose (CAS No. 23140-52-5) has been defined as a C-3 epimer of D-fructose (Figure 2).[1,6]

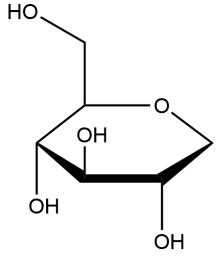


Figure 1. Anhydroglucitol

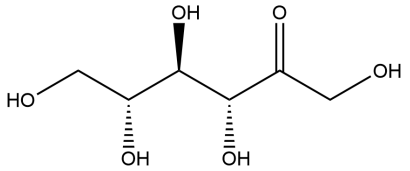


Figure 2. Psicose

The definitions, structures, and CAS Nos. of all the saccharide ingredients included in this safety assessment are presented in Table 1.[1]

Chemical Properties

Properties of the ingredients reviewed in this report are presented in Table 2.[3,7-14] Anhydrogalactose, Anhydroxylitol, Psicose, and Saccharide Hydrolysate are water-soluble. Anhydroxylitol has a molecular weight of 134.13 Da.[10] The available data indicate that Saccharide Isomerate with different molecular weights (MW) is being marketed. The weight range for the lower MW Saccharide Isomerate is 120 - 400 Da.[15] The reported values for higher MW Saccharide Isomerate are 15,000 Da, 20,000 Da, and > 1.4 MDa.[13] Throughout the report text, the molecular weight of the Saccharide Isomerate being tested will be identified in parentheses.

Method of Manufacture

Anhydrogalactose

Anhydrogalactose may be prepared by enzymatic saccharification of agar, using a combination of agarolytic enzymes.[16] According to another source, the following 3 steps are required for production of high purity Anhydrogalactose from agarose: acid pre-hydrolysis of agarose; enzymatic saccharification; and purification of Anhydrogalactose.[17]

Anhydroglucitol

A single-enzyme process for the production of Anhydroglucitol has been designed.[18] The process involves the acid pre-hydrolysis of agarose into agarobiose and the enzymatic hydrolysis of agarobiose into Anhydroglucitol and galactose.

Anhydroxylitol

Anhydroxylitol results from the dehydration of xylitol under acidic conditions.[19] Glucose has been identified as a by-product in the reaction medium.

Arabinose

Arabinose is produced by catalytic decarboxylation of D-gluconic acid, sodium salt.[20] Additional processes used to prepare the final product include, ultrafiltration, chromatography, crystallization, grinding, and drying.

Psicose

It has been reported that Psicose is easily generated by heating sugar preparations.[21] Details relating to this process were not provided. According to another source, Psicose has been produced from fructose using the enzyme tagatose 3-epimerase.[22]

Saccharide Isomerate

According to a supplier of this ingredient, Saccharide Isomerate (plant-derived; MW = 120 - 400 Da) is formed by a base catalyzed isomerization of plant-derived D-glucose of kernel corn, and is similar to that of the carbohydrate complex found in human skin.[15] The product of this process is a mixture of mono and disaccharides, mainly glucose and fructose.

The method of manufacture for 3 other trade name materials (MW > 1.4 MDa) from an anonymous source is described as catalyzed rearrangement of a mixture of saccharides/purification.[13] The method of manufacture for 1 of the 3 trade name materials mixed with water (MW of 20,000 Da) and a fourth trade name material mixed with water (MW of 15,000 Da) from the same source is described as catalyzed rearrangement of a mixture of saccharides/purification and hydrothermolysis accelerated with carbon dioxide supercritical.

Composition and Impurities

Anhydroxylitol

According to a chemical supplier, a trade name mixture that contains Anhydroxylitol has the following composition: xylitylglucoside (35 - 50%), Anhydroxylitol (24 - 34%), xylitol (5 - 15%), water (15 - 17%), and glucose (0 - 5%).[19]

Saccharide Hydrolysate

According to the *Food Chemicals Codex* description, Saccharide Hydrolysate is marketed as invert sugar syrup and contains dextrose (glucose), fructose, and sucrose in various amounts, as represented by the manufacturer.[9] In accordance with the *Food Chemicals Codex,* the acceptance criteria for Saccharide Hydrolysate are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of Saccharide Hydrolysate. Other acceptance criteria for Saccharide Hydrolysate in the *Food Chemicals Codex* relate to lead content (not more 0.1 mg/kg) and sulfated ash content (not more than 0.2%).

Saccharide Isomerate

As stated earlier in the report text, the available data indicate that Saccharide Isomerate with different MW is being marketed. The weight range for the lower MW Saccharide Isomerate is 120 - 400 Da.[15] The reported values for higher MW Saccharide Isomerate are 15,000 Da, 20,000 Da, and > 1.4 MDa. According to a chemical supplier, Saccharide Isomerate (MW = 120 - 400 Da) is a mixture of mono and disaccharides (mainly glucose and fructose), and also contains water, citric acid, and sodium citrate.[15] Regarding the presence of impurities, the supplier confirms that Saccharide Isomerate is produced without using solvents. Therefore, Saccharide Isomerate does not contain residual solvents.

A source provided composition data on Saccharide Isomerate trade name materials.[13] Data on one of the trade name materials (MW > 1.4 MDa) indicate an Osidic composition of glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine. Data on another trade name material (MW > 1.4 MDa), and the same trade name material mixed with water (MW of 20,000 Da), indicate an Osidic composition of rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine. A third trade name material (MW of 15,000 Da) has an Osidic composition of galacturonic acid-*N*-acetylglucosamine. A fourth trade name material (MW > 1.4 MDa) has an Osidic composition of galactose-*N*-acetyl glucosamine-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA).

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2021 VCRP data, Saccharide Isomerate is reported to be used in 352 cosmetic products (302 leave-on products and 50 rinse-off products).[23] Of the saccharide ingredients reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2018 indicate that Saccharide Hydrolysate is used at maximum use concentrations up to 4.6% in rinse off products (skin cleansing products), and that Saccharide Isomerate is used at maximum use concentrations up to 2.8% in leave-on products (face and neck skin care preparations, not spray).[24] These are the highest use concentrations in rinse-off and leave-on products reported for the ingredients that are reviewed in this safety assessment. Further use data are presented in Table 3.

According to VCRP and Council survey data, the following 3 ingredients are not currently in use in cosmetic products: Anhydrogalactose, Arabinose, and Psicose.

Cosmetic products containing the ingredients that are being reviewed may be applied to the skin, or, incidentally, may come in contact with the eyes (e.g., Saccharide Isomerate at concentrations up to 1% in eye shadows). Anhydroglucitol (at concentrations up to 0.17% in bubble baths) is used in products that come in contact with mucous membranes. Anhydroxylitol and Saccharide Isomerate are also used in products that come in contact with mucous membranes; however, use concentrations were not reported for these 2 ingredients in products of this type in the Council's use concentration survey. Products containing the ingredients that are being reviewed 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.

Anhydroxylitol is reported to be used in products (other fragrance preparations) that are sprayed; however, there are no reported concentrations of use of this ingredient in products of this type in the Council's use concentration survey.[23] 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.[25-28] 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.[25,26]

The ingredients that are being reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[29]

Non-Cosmetic

Anhydroglucitol

The use of Anhydroglucitol to monitor new classes of therapies for managing post-meal glucose in patients with diabetes has been reported.[30] The use of Anhydroglucitol is included in the International Diabetes Federation guideline for management of post-meal glucose as an emerging technology to measure postprandial glucose levels.

Arabinose

The stereoisomer, L-arabinose, is used in the bacterial mutagenesis test system that is known as the *Salmonella*/arabinose-resistant (Ara^r) assay system.[31] In the Ara^r assay system, L-arabinose is added to molten soft agar.

Psicose

Psicose (rarely found in nature) is a sugar substitute that has 70% of the sweetness of sucrose, but almost zero calories.[6]

Saccharide Hydrolysate

Saccharide Hydrolysate is a direct food substance affirmed generally recognized as safe (GRAS) by the US FDA [21 CFR 184.1859]. This ingredient is used in food with no limitation other than current good manufacturing practice.

According to one source, the indications for use of Saccharide Hydrolysate in an obstetrics and gynecology center in the US have been limited to diabetic women during the intrapartum period.[32]

TOXICOKINETIC STUDIES

Dermal Penetration

Arabinose

The dermal/percutaneous absorption of D-Arabinose is limited by its hydrophilicity (log P = -2.22) and ability to form hydrogen bonds (4 donor groups and 5 acceptor groups).[14]

Anhydroxylitol

According to the Australian Industrial Chemicals Scheme, based on the low molecular weight of Anhydroxylitol (134 Da), there is potential for dermal absorption and passage across the gastrointestinal tract.[3] However, this may be limited by its high water-solubility (674 g/l), and low partition coefficient (log P_{ow} = -2).

Saccharide Isomerate

A statement from a supplier of Saccharide Isomerate (MW = 120 – 400 Da) indicates that dermal absorption studies were not performed because, other than containing Saccharide Isomerate, it contains water, citric acid, and sodium citrate.[15] According to another source, Saccharide Isomerate (120 – 400 Da) is uniquely bound at the corneocytes to the free amino group of lysine found in the keratin of the stratum corneum.[33] This unique binding mechanism to the skin and scalp ensures that the active ingredient is not washed off, but continues to improve hydration until removed by the natural process of desquamation.

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Anhydroglucitol

The fate of Anhydroglucitol (stereochemistry not stated) in white laboratory rats after dosing was studied.[34] Anhydroglucitol (2 to 7 mg, in saline) was administered orally as a single dose to 5 rats as follows: 2 mg (1 rat), 5 mg (3 rats), and 7 mg (1 rat). The concentration of Anhydroglucitol in the serum of 11 untreated rats was 47 ± 24 (standard deviation) µmol/l, and no Anhydroglucitol was found in the urine. These control data suggest that Anhydroglucitol is efficiently reabsorbed by rat kidney tubuli. In the 5 test rats, the serum Anhydroglucitol concentration increased rapidly after oral dosing. The peak concentration in the serum was observed at 1 h post-dosing, suggesting that Anhydroglucitol was readily absorbed by the gut. Of the 5 mg dose that was administered, 1.4 to 1.6 mg was recovered in the urine in 48 h. There was no urinary excretion of Anhydroglucitol after 48 h.

In another experiment involving 12 white laboratory rats, Anhydroglucitol (7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) daily for 7 wk.[34] Six rats served as controls. Blood and urine samples were collected (schedule for collection of samples not stated). In test animals, a high serum Anhydroglucitol concentration (62 to 126 µmol/l) was maintained in the 12 rats. The concentration of Anhydroglucitol in the serum of the 6 control rats (not dosed with Anhydroglucitol) ranged from 24 to 62 µmol/l. Data from this study relating to toxicity are included in the Short-Term Oral Toxicity section of this report.

Psicose

U-[^{14}C]Psicose (2 µCi) was administered by stomach tube to rats (number and strain not stated).[35] Of the exhaled [^{14}C]carbon dioxide, 26% was exhaled within 7 h and 80% was exhaled within 24 h. Much of the radioactivity was rapidly excreted in the urine, whereby 95% of the excreted radioactivity was recovered within the first 7 h. Of the excreted radioactivity recovered, at least 70% was U-[^{14}C]Psicose. The remaining 30% of the radioactivity in the urine was associated with unidentified products of metabolism. The authors noted that rapid excretion of orally administered U-[^{14}C]Psicose is suggestive of easy passage though the wall of the small intestine. It then enters the blood and is eliminated through the kidneys. The authors also stated that the increased metabolism to [^{14}C]carbon dioxide and the finding that 39% of the radioactivity is retained by the carcass for 72 h after oral feeding suggests that a large portion of the U-[^{14}C]Psicose is metabolized by intestinal microorganisms. It was noted that some of these metabolites are absorbed into the metabolic system of the rat.

The intestinal absorption, organ distribution, and urinary excretion of [^{14}C]Psicose was studied using 30 male Wistar rats.[36] All of the rats were fasted for 24 h. Approximately 0.6 ml of [^{14}C]Psicose solution (30 mg, 120 kilobecquerels (kBq)) was administered at an oral dose of 100 mg/kg. The rats were killed at 10, 30, 60, and 120 min post-administration. [^{14}C]Psicose

entered the blood after oral dosing, and the maximum blood concentration (48.5 ± 15.6 µg/g) was observed at 1 h. Urinary excretion was 20% within 1 h and 33% within 2 h. The values for radioactivity (from administered [^{14}C]Psicose) in the liver were 41.4 ± 28.7, 126.3 ± 45.0, 200 ± 86.3, and 127.5 ± 32.6 µg/g liver tissue at 10, 30, 60, and 120 min, respectively. Other organs (lung, thymus, spleen, heart, brain, skin, and muscle) showed lower radioactivity, whereas the kidney showed higher radioactivity. At 7 d after oral dosing, the remaining amounts of the test substance in the whole body were < 1%. After reviewing the results of this experiment, the authors concluded that [^{14}C]Psicose was absorbed well after oral dosing and eliminated rapidly.

Parenteral

Anhydroglucitol

The distribution of Anhydroglucitol was evaluated using normal and diabetic rats, and perfused rat bodies.[4] The 3 non-diabetic male Sprague-Dawley used were identified as having very low, very high, and medium concentrations of plasma Anhydroglucitol. The variable plasma concentrations were, perhaps, due to less controlled feeding conditions. Another group of 3 rats was rendered diabetic by intravenous (i.v.) streptozocin injection. Animals of both groups were thoroughly depleted of blood, after which various organs and tissues were immediately removed. The perfusion experiment involved 2 male Sprague-Dawley rats (controls). An isotonic solution containing heparin was used as the perfusion solution, which was infused through a cannula inserted into the pulmonary trunk through the right ventricle. At the end of perfusion, several organs were removed. The plasma of control rats contained 3 to 12 µg/ml of Anhydroglucitol. In the 3 normal rats, Anhydroglucitol was distributed throughout the rat bodies. Low, but highly variable, concentrations were present in lipid-rich tissues, such as adipose tissue and the testis. The liver and kidney contained much higher concentrations, though they were less than the corresponding plasma concentrations. The authors noted that these observations are indicative of Anhydroglucitol distribution that was dependent on the concentration equilibrium between the circulation and the intra- and inter-cellular water spaces. The concentration of Anhydroglucitol in the brain appeared to have been less dependent on the concentration in the plasma. Other results are summarized below.

In all 3 diabetic rats, the Anhydroglucitol concentration in plasma was < 0.5 µg/ml. Amounts of Anhydroglucitol detected in the following organs were as follows: diabetic kidney (1.5 and 2.6 µg/ml), liver (0.8 and 1.6 µg/ml), spleen (1.4 and 1.6 µg/ml), skin (0.5 and 1.1 µg/ml), and brain (< 0.5 µg/ml). Anhydroglucitol depletion during perfusion was demonstrated in several organs, except for the spleen. The plasma of the 2 rats perfused for 100 min and 300 min contained 8.8 µg/ml and 9.0 µg/ml of Anhydroglucitol, respectively. Anhydroglucitol was almost completely depleted from the lung, liver, and kidney of the rat perfused for 300 min. In the other rat (100-min perfusion), it was completely depleted only from the lung. Also, in this rat (100-min perfusion), the concentrations of Anhydroglucitol in the liver and kidney were considerably lower than what would have been expected based on its concentration in the plasma. The spleens of both perfused rats contained 5.1 µg/g and 4.4 µg/g of Anhydroglucitol . The authors noted that these 2 values were as high as could have been expected for the spleen of an untreated rat with a plasma Anhydroglucitol concentration similar to that of the 2 perfused rats. The authors noted that the observations made in this study indicated that Anhydroglucitol readily diffused from the circulation into the inter- and intra-cellular water spaces. They also suggested that the plasma membranes of cells in the organs were permeable to Anhydroglucitol.

Psicose

The intestinal absorption, organ distribution, and urinary excretion of [^{14}C]Psicose was studied using 30 male Wistar rats.[36] All of the rats were fasted for 24 h. Approximately 0.6 ml of [^{14}C]Psicose solution (30 mg, 120 kBq) was administered i.v. at a dose of 100 mg/kg. The rats were killed at 10, 30, 60, and 120 min post-administration. After i.v. dosing of [^{14}C]Psicose, radioactivity in the blood decreased (half-life = 57 min). Also, the excretion of radioactivity in the urine was up to ~ 50% within 1 h. High counts of radioactivity were detected in the liver and kidney. An experiment involving mice, summarized below, is also included in this study.

After fasting for 24 h, 10 male C3H mice were injected i.v. with [^{14}C]Psicose (20 KBq in saline, dose of 100 mg/kg).[36] At 30 min post-injection, the animals were perfused and whole-body frozen sections from the sagittal plane were prepared. Autoradiography results indicated high signals of ^{14}C-labeled -Psicose in the liver, kidney, and bladder, but no accumulation in the brain. After reviewing the results of rat and mouse i.v. dosing experiments in this study, the authors concluded that [^{14}C]Psicose was absorbed and eliminated rapidly.

U-[^{14}C]Psicose (15 mg; 1.5 µCi in 0.5 ml of saline) was injected i.v. in a series of fasted rats (number and strain not stated).[35] Urine and exhaled [^{14}C]carbon dioxide were collected for 6 h. During this period, 97% to 98% of the radioactivity was excreted in the urine, where it was associated with U-[^{14}C]Psicose. Liver glycogen contained 1% of the radioactivity, and only 0.6% of the radioactivity was exhaled as [^{14}C]carbon dioxide. The authors noted that these results indicate that i.v.-administered U-[^{14}C]Psicose is rapidly removed by the kidney and is metabolized to only a small degree.

Human

Anhydroglucitol

Anhydroglucitol is present in human blood, and the average plasma concentration is in the vicinity of 20 µg/ml.[5] A remarkable decrease in plasma Anhydroglucitol is observed in diabetes mellitus.

The origin and disposal of Anhydroglucitol , a major polyol in the human body, was studied using 36 normal subjects (20 men and 16 women).[37] The amount of urinary Anhydroglucitol was measured 3 times in each subject. The mean Anhydroglucitol

supplement through foods was estimated to be ~ 4.38 mg/d. The mean Anhydroglucitol excretion in the urine was ~ 4.76 mg/d. An Anhydroglucitol balance study was performed using a subgroup (6 men and 2 women) of the 36 normal subjects. Total dietary calorie intake was fixed to 35 kcal/real body weight (kg) of individual subjects. Fasting plasma Anhydroglucitol and 24-h urinary Anhydroglucitol were monitored over 3 consecutive days, and their mean values were calculated. In another subgroup (6 men and 3 women), the subjects were observed for urinary Anhydroglucitol excretion after a breakfast meal. The subjects fasted for 14 h before urination. The study results implied that urinary excretion of Anhydroglucitol occurred soon after food ingestion, and that the amount excreted in the urine was closely correlated with daily supplement through foods. The fundamental kinetics of Anhydroglucitol were recognized as follows: Anhydroglucitol in the body originates mainly from foods, is well absorbed in the intestine, and is little degraded and metabolized in the body.

Psicose

In a study involving 26 human subjects (16 males and 10 females) on a normal diet (composition not stated), 24-h urine samples were collected.[38] All subjects were healthy and undergoing normal physical activity. Individual sugars (Psicose; stereochemistry not stated) included in the urine were determined using gas chromatography, accounting for over 90% of the total neutral sugars. Psicose was the most common neutral sugar that was found in human urine. The excretion of total neutral sugars in the urine ranged from 0.1 to 4.1 mmol/24 h, based on 28 urine samples from 26 subjects. The excretion of Psicose in the urine ranged from 0.1 to 2.7 mmol/24 h. The authors stated that there is uncertainty regarding the source of Psicose in the urine. They noted that Psicose was absent from the urine of 6 patients who were maintained on total parenteral nutrition (method of feeding that bypasses the gastrointestinal tract), suggesting an exogenous origin of the sugar.

Psicose is present in human urine in amounts of 15 to 30 mg/l, presumably from a dietary source because it disappears from the urine of subjects who have fasted for 48 h.[35]

Oral

Arabinose

After an overnight fast, 40 normal volunteers drank an isosmotic solution containing raffinose (8 g), lactose (20 g), and L-arabinose (2 g) in 250 ml of water.[39] The median 5-h urinary sugar excretion was 0.26% of ingested oral dose of raffinose, 0.05% of ingested loral dose of lactose, and 17.5% of ingested oral dose of L-arabinose.

Parenteral

Arabinose

The metabolic stability of L-arabinose was investigated using 5 normal subjects.[39] A sterile, pyrogen-free solution containing 500 mg of L-arabinose in 5 ml of water was injected intravenously into each subject. Within 5 h, 63.3 ± 4.1% (mean + standard deviation) of administered L-arabinose was excreted in the urine. Within 12 h, 73.1 ± 4.5% was excreted in the urine.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute dermal and oral toxicity studies summarized below are presented in Table 4.

The dried extract of a trade name mixture containing 25% to 35% Anhydroxylitol was evaluated for acute dermal toxicity in rats (number not stated), according to Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 402.[3] No mortalities or gross pathological changes were observed, and the LD_{50} was > 2 g/kg.

The acute oral toxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was evaluated in rats (number not stated), according to OECD TG 401.[3] No mortalities, or gross pathological changes were observed, and the LD_{50} was > 2 g/kg. In an acute oral toxicity study on Arabinose, the LD_{50} was calculated to be 12.1 g/kg in male rats and 11.6 g/kg in female rats (number not stated).[40] The acute oral toxicity of 50% aqueous Psicose was evaluated using 5 groups of 8 male Wistar rats.[41] The groups received single oral doses ranging from 8 g/kg to 20 g/kg. Animal deaths were reported as follows: 3 rats (14 g/kg dose group), 3 rats (17 g/kg dose group), and 8 rats (20 g/kg dose group). The calculated LD_{50} values were 16.3 g/kg (using the Behrens-Karber method) and 15.8 g/kg (using the Litchfield-Wilcoxon method). In another study, each of 6 beagle dogs received a single oral dose in water (by plastic syringe) of Psicose (1 g/kg and 4 g/kg).[42] Each animal received the control on day 1, the 1 g/kg dose on day 2, and the 4 g/kg dose on day 3. Histological examination of tissues was not performed. A mild, dose-dependent increase ($p < 0.05$) in plasma alkaline phosphatase activities was observed between 12 h and 48 h after dosing. It was concluded that Psicose did not induce severe toxicity in dogs. The acute oral toxicity of undiluted Saccharide Isomerate (MW = 120 - 400 Da) was evaluated (animal species not stated) in accordance with OECD TG 401.[15] An LD_{50} of > 2 g/kg was reported.

Short-Term and Chronic Toxicity Studies

The short-term and chronic toxicity studies summarized below are presented in Table 5.

In an experiment involving 12 white laboratory rats, Anhydroglucitol (stereochemistry not stated; 7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) daily for 7 wk.[34] No apparent toxic signs were observed. (Results relating to the distribution and excretion of Anhydroglucitol after oral dosing are included in the section on Toxicokinetic Studies.) A 28-d oral toxicity study on a tradename mixture comprising ~ 25% Anhydroxylitol (and unstated quantities of xylitol and

xylitylglucoside) was performed using groups of at least 10 rats (5 males and 5 females per group), according to OECD TG 407.[3] The test substance was administered at doses of 15, 150, and 1000 mg/kg/d. There were no treatment-related necropsy changes or changes in mortality. Given the uncertainty relating to the cause of myocarditis in animals of the highest dose group and the limited histopathology data, the authors noted that it was not possible to clearly establish a no-observed-adverse-effect-level (NOAEL) for the test substance. Diarrhea was a finding reported in a short-term toxicity test in which rats were given feed containing 5% Arabinose.[40] Additional findings were not reported. Six Sprague-Dawley rats were fed a normal diet and consumed 2% Psicose-supplemented water for 14 d.[43] At the end of the experiment, the animals were killed and body, testes, and liver weights were determined. There was no difference in mean testes weight or mean liver weight between treated and control rats. Groups of 7 male Wistar rats were fed diets containing 10%, 20%, 30%, and 40% Psicose for 34 d.[41] One rat fed 30% and 5 rats fed 40% Psicose died during the experimental period. Liver and kidney weights were heavier ($p < 0.05$) in rats fed the 10% diet than in rats fed the 0 and 30% diets. Many of the effects observed in this study were assumed to be secondary to a decrease in food consumption or the consumption of large amounts of a non-nutritive, poorly absorbed substance. It is not clear whether or not the cause of Psicose-induced liver enlargement was due to liver glycogen deposition. The authors concluded that the feeding of diets extremely high in Psicose appears to be harmful to the intestinal tract. In another study, Psicose (0.2 g/kg) was fed to 5 beagle dogs daily for 12 wk.[44] During the course of the experiment, plasma triglyceride concentrations increased in the control group, whereas they remained low in the group fed Psicose. With the exception of a change in lipid levels (lipid lowering effect), dosing with Psicose did not cause clinical signs or changes in biochemical parameters. There were no statistically significant differences in liver enzymes or renal function markers between test and control groups. The authors concluded that dosing with Psicose did not cause any harmful effects in dogs.

The chronic oral toxicity of Psicose was evaluated using groups of 18 male Wistar rats.[45] The test group had free access to a commercial rodent diet containing 3% Psicose, and the control group to diet containing 3% sucrose, for 12 or 18 mo. The rats actually ingested 1.28 g/kg/d Psicose and 1.22 g/kg/d sucrose. Liver and kidney weights were found to be statistically significantly heavier in the 3% Psicose group at 12 mo and 18 mo, when compared to the control group. Histopathological examination of the liver at 18 mo revealed slight fatty degeneration and hepatocellular fibrosis in the group fed 3% Psicose in the diet. The mean value for pathological lesions (liver) in the test group was statistically significantly higher ($p < 0.0498$; i.e., slight difference) when compared to the control group. These results were not observed at 12 mo. The authors concluded that this study found the effects of long-term dietary administration of 3% Psicose to rats to be increased liver and kidney weights, with no gross pathological findings correlated with this hypertrophy

A 25% aqueous solution of L-arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck for periods up to 2 yr.[46] The study involved 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females). No untoward effects were observed in rats. However, some of the mice (number not stated) developed symptoms of shock and died. The mice also had white necrotic masses in subcutaneous tissue of the neck. These chronic toxicity data are from a carcinogenicity study on L-arabinose. Protocol details and results relating to tumor formation are presented in the section on Carcinogenicity Studies.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies of the ingredients that are being reviewed were neither found in the published literature, nor were these data submitted.

GENOTOXICITY

The in vitro and in vivo genotoxicity studies summarized below are presented in Table 6.

In the Ames test (according to OECD TG 471), the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was classified as non-mutagenic.[3] The same test substance was also classified as non-mutagenic in a chromosome aberration assay (according to OECD TG 473) using human peripheral blood lymphocytes. (Further details were not provided for these studies.) Undiluted Saccharide Isomerate (MW = 120 - 400 Da) was evaluated for genotoxicity in the Ames test (according to OECD TG 471).[15] The test substance was classified as non-genotoxic. The genotoxicity of a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated using the Ames test (OECD TG 471), with and without metabolic activation.[13] Test substance concentrations ranged from 0.5% to 1.5% (at doses ranging from 0.06 to 5 µl/plate). Results were classified as negative. A Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated in the Ames test (according to OECD TG 471) using 5 *Salmonella typhimurium* strains.[13] The test substance (doses up 5000 µg/plate) was neither mutagenic nor pro-mutagenic with or without metabolic activation. In the same assay, a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) was also classified as neither mutagenic nor pro-mutagenic. Similarly, a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA) had the same classification in this assay. (Further details were not provided for these studies.) Undiluted Saccharide Isomerate (MW = 120 - 400 Da) was also classified as non-genotoxic in the micronucleus test (according to OECD TG 487).[15]

The micronucleus test (according to OECD TG 474) was used to evaluate the genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol.[3] Mice received a dose of ≤ 2000 mg/kg/d for 2 d. The test substance was classified as non-genotoxic. However, according to the Australian Industrial Chemicals Scheme, it is not clear that the test substance was systemically absorbed and reached the bone marrow. (Further details were not provided for this study.)

CARCINOGENICITY STUDIES

Subcutaneous

Arabinose

The carcinogenicity of L-arabinose was evaluated using 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females).[46] (Results relating to chronic subcutaneous toxicity are included in that section of this report.) A 25% aqueous solution of L-arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck twice per week for periods up to 2 yr. Control animals (60 rats and 60 mice) were injected with water. In rats, a total of 11 tumors was observed after dosing with the test substance. The tumor types observed (mostly at 22 to 24 mo) in rats included urinary bladder papilloma, lymphangiosarcoma of the subcutis, adenofibroma of the breast, and carcinoma of the uterus. In mice, no tumors were observed. Injection site tumors were not observed in rats. The great majority of the benign and malignant tumors found in test and control rats were at sites remote from the nape of the neck. Furthermore, the numbers and sites of these neoplasms were found to be similar when results for test and control rats were compared. Therefore, the authors noted that it is unlikely that the development of most of the tumors was related to test substance administration.

ANTI-CARCINOGENICITY STUDIES

Psicose

The effect of Psicose on cell proliferation was evaluated in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, using the following cancer cell lines: human cervical cancer (HeLa), human hepatocarcinoma (HepG2), human hepatocarcinoma (HuH-7), and immortalized human skin keratinocytes (HaCaT).[47] The assay was initiated when the cells were in the logarithmic growth phase. The following concentrations of Psicose were added to the medium: 1 mM, 5 mM, 10 mM, 20 mM, and 50 mM. After exposure to the test substance for 24 h, 48 h, and 72 h, MTT was added and the plates were incubated for 4 h. Psicose did not have an antiproliferative effect on the cell lines at any of the concentrations tested.

OTHER RELEVANT STUDIES

Cytotoxicity

Anhydrogalactose

In the MTT assay, Anhydrogalactose was not cytotoxic to melanin-producing murine B16 melanoma cells or human epidermal melanocytes at concentrations of 12.5, 25, and 50 µg/ml during the 2-h incubation period.[7] The MTT assay was also used to evaluate the cytotoxicity of Anhydrogalactose or D-anhydrogalactose using B16F10 mouse melanoma cells and RAW264.7 cells (mouse macrophages).[17] The cells were treated for 24 h with concentrations up to 100 µg/ml (B16F10 cells) and up to 200 µg/ml (RAW264.7 cells). There was no statistically significant inhibition of growth of either cell type at the concentrations of Anhydrogalactose or D-anhydrogalactose tested.

Anti-Melanogenic Activity

Anhydrogalactose

A study was performed to determine whether Anhydrogalactose exerts anti-melanogenic activity in murine B16F10 melanoma cells and human epidermal melanocytes.[7] The effect on melanogenesis at non-cytotoxic concentrations was determined by measuring α-melanocyte stimulating hormone (α-MSH)-induced intracellular and extracellular melanin levels in the 2 cell types. The cells were pretreated with Anhydrogalactose (50 µg/ml) for 1 h prior to exposure to α-MSH (100 nM). Melanin content was assayed 3 d later. Anhydrogalactose markedly inhibited melanin secretion.

The skin-whitening activity of L-Anhydrogalactose (95.6% pure) was evaluated using B16F10 mouse melanoma cells.[17] The melanoma cells were induced for melanin production by treatment with α-MSH, and were cultured for 1 h with L-Anhydrogalactose and D-anhydrogalactose at concentrations up to 100 µg/ml. Arbutin (up to 100 µg/ml) served as the positive control. The extracellular melanin concentration of melanoma cells treated with 100 µg/ml L-Anhydrogalactose was statistically significantly lower than that of cells treated with the same concentration of arbutin or D-anhydrogalactose. Particularly, the extracellular melanin concentration of melanoma cells treated with 100 µg/ml Anhydrogalactose was only 23.9% of melanoma cells treated with 100 nM α-MSH. The authors noted that these study results suggested that treatment with Anhydrogalactose strongly suppressed melanin production in B1610 melanoma cells.

Anti-Inflammatory Activity

Anhydrogalactose

Nitrite levels in the culture media of RAW264.7 mouse macrophages (stimulated by lipopolysaccharide (LPS) to produce nitrite) were measured in an experiment investigating the possible anti-inflammatory activity of Anhydrogalactose (95.6% pure).[17] Cellular nitrite levels increase considerably under inflammatory conditions. The macrophages were incubated for 24 h with

Anhydrogalactose and D-anhydrogalactose at concentrations up to 200 µg/ml. Statistically significant ($p < 0.05$) suppression of nitrite production was observed at concentrations of 100 µg/ml and 200 µg/ml Anhydrogalactose. Nitrite levels in the culture media of cells treated with 100 µg/ml and 200 µg/ml Anhydrogalactose were 64.5% and 38.8% of those in LPS-treated controls. Anhydrogalactose also had a nitrite-suppressing effect, only at a concentration of 200 µg/ml. However, the effect of the D-anhydrogalactose was statistically significantly lower when compared to the Anhydrogalactose. The authors noted that Anhydrogalactose had statistically significant anti-inflammatory activity.

Antimicrobial Activity

Anhydrogalactose

The inhibitory activity of Anhydrogalactose against *Streptococcus mutans* ATCC 25175 growth was evaluated in the spot assay by monitoring the bacterial cell mass concentration and counting the colonies formed on the growth medium.[48] Bacterial cells were diluted to 10, 10^2, 10^3, 10^4, and 10^5-fold, and each diluted cell suspension was spotted on the growth medium. The bacteria were cultured for 30 h on growth medium supplemented with 10 g/l (w/v) Anhydrogalactose. Growth inhibitory activity of Anhydrogalactose was compared to that of xylitol (10 g/l). Spot assay results indicated that the numbers of *S. mutans* colonies were lower in the presence of Anhydrogalactose than in the presence of xylitol or in growth medium without sugar. When Anhydrogalactose (10 g/l) was present in the growth medium, *S. mutans* colonies were not formed; that is, when plates were seeded with bacterial inocula of either 10^4 or 10^5 dilution. In contrast, *S. mutans* colonies were formed on a minimal agar plate inoculated with bacterial dilutions of either 10^4 or 10^5, when 10 g/l xylitol was supplied as the sole carbon source.

Effect of Epidermal Barrier Recovery

Psicose

The effect of topical application of aqueous Psicose on epidermal permeability barrier recovery rate after barrier disruption (by tape stripping) was evaluated using male hairless mice of the HR-1 strain (number not stated).[49] Use of a control in this study was not indicated. Permeability barrier function was evaluated by measurement of transepidermal water loss. Skin on both flanks was treated by repeated tape stripping until the transepidermal water loss reached 7 to 10 mg/cm^2/h. Immediately after tape stripping, 100 µm of a 0.1 M aqueous solution of Psicose was applied to the skin. Transepidermal water loss was then measured at the same sites at 1 h, 2 h, 6 h, and 24 h later. Barrier recovery results were expressed as % recovery because of the day-to-day variations in the extent of barrier disruption. Psicose accelerated barrier recovery of tape-stripped skin. This effect on barrier recovery rate appeared within 1 h. The authors stated that Psicose may influence phase transition of the lipid bilayers of lamellar bodies and cell membrane, which is a crucial step in epidermal permeability barrier homeostasis.

DERMAL IRRITATION AND SENSITIZATION

The dermal irritation and sensitization studies summarized below are presented in Table 7.

The skin irritation potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in 3 New Zealand White albino rabbits, according to OECD TG 404.[3] The test substance (dose per cm^2 not stated) was applied to the skin for 4 h, and there was no evidence of skin irritation. The skin irritation potential of 20% (v/v) Saccharide Isomerate (MW = 120 - 400 Da) was evaluated (animal species not stated) according to OECD TG 404.[15] Details relating to the test protocol are not included. The test substance was classified as non-irritating and non-corrosive to the skin. Saccharide Isomerate (20% v/v; MW = 120 - 400 Da) was also evaluated for skin irritation potential in a repeated application test involving guinea pigs (strain not stated).[15] There was no evidence of skin irritation or corrosion.

An occlusive patch test was used to evaluate the skin irritation potential of Saccharide Isomerate (20% v/v; MW = 120 - 400 Da) in human subjects (number not stated).[15] Details relating to the test protocol are not included. The test substance was non-irritating and non-corrosive to the skin. The skin irritation potential of a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated using 10 subjects.[13] In the 24-h occlusive patch test, the material was applied at concentrations of 0.5% to 1.5%. Skin irritation was not observed. A Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated for skin irritation potential in a study involving 11 subjects.[13] In the 48-h occlusive patch test, the material was applied at concentrations of 0.5% to 1.5%. There was no evidence of skin irritation. Another study involved evaluation of the skin irritation potential of a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) using 10 subjects.[13] The material (0.5% to 1.5%) was applied to the skin for 24 h in an occlusive patch test. Skin irritation was not observed. A Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA) was evaluated for skin irritation potential in a study involving 11 subjects.[13] In the 48-h occlusive patch test, the material was applied at concentrations of 0.5% to 1.5%. There was no evidence of skin irritation.

The skin sensitization potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in the maximization test, according to OECD TG 406.[3] A minimum of 10 test and 5 control guinea pigs is specified in this protocol. The undiluted test substance was applied during induction, and the challenge concentration was 50% (actual concentration = 17.5%). Skin sensitization was not observed. A skin sensitization study (maximization test) on 20% (v/v) Saccharide Isomerate (MW = 120 - 400 Da) was performed in accordance with OECD TG 406.[15] Skin sensitization was not observed. (Further details were not provided for this study.)

A human repeated insult patch test (HRIPT) involving 213 subjects was used to evaluate the skin irritation and sensitization potential of an eye cream containing 2.75% Saccharide Isomerate (MW not stated).[50] Occlusive patches were used; the dose per area was not stated. Neither skin irritation nor sensitization was observed. The skin sensitization potential of a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated in an HRIPT involving 100 subjects.[13] Test concentrations ranged from 0.5% to 1.5%. The test substance was non-irritating and non-sensitizing. An HRIPT was performed to evaluate the skin sensitization potential of a Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) in 102 subjects.[13] The same test concentrations were applied. The material was a non-irritant and a non-sensitizer. The skin sensitization potential of a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) was evaluated in another HRIPT involving 109 subjects.[13] The induction concentration is 0.9%, but the challenge concentration is not stated. There was no evidence of skin irritation or allergenicity. An HRIPT was performed to evaluate the skin sensitization potential of a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA) in 52 subjects (26 with sensitive skin).[13] Induction concentrations ranged from 0.5% to 1.5%. The challenge concentration is not stated. No significant reaction of contact allergy was observed.

Photosensitization/Phototoxicity

In Vitro

Saccharide Isomerate

The phototoxicity of a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA) was evaluated in an in vitro assay (OECD TG 432), with and without long-wavelength ultraviolet light (UVA)[13]. The test substance (contained 0.5% to 1.5% Saccharide Isomerate) was evaluated for cytotoxicity at test substance concentrations up to 1000 µg/ml (8 concentrations total in range [not stated]). Details relating to the test protocol are not included in the study summary. The test substance was classified as non-phototoxic over the range of concentrations tested.

Animal

Saccharide Isomerate

The photosensitization/phototoxicity potential of Saccharide Isomerate (20% v/v; MW = 120 - 400 Da) was evaluated using guinea pigs (number and strain not stated).[15] Details relating to the test protocol are not included in this study summary. Neither photosensitization nor phototoxicity was observed in this study.

OCULAR IRRITATION STUDIES

The ocular irritation studies summarized below are presented in Table 8.

The ocular irritation potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in 3 New Zealand White albino rabbits, according to OECD TG 405.[3] Transient conjunctival irritation was observed, and the test substance was classified as slightly irritating to the eyes.

Saccharide Isomerate (20% v/v; MW = 120 - 400 Da) was evaluated for ocular irritation potential in accordance with OECD TG 405.[15] The animal species tested and details relating to the study protocol are not included in the study summary. The test substance was classified practically non-irritating to the eyes. (Further details were not provided for this study.)

The ocular irritation potential of an eye cream containing 2.75% Saccharide Isomerate (MW not stated) was evaluated using 53 female subjects.[51] Trace increases in palpebral conjunctival irritation observed in 3 subjects were said to have been unrelated to use of the eye cream. It was concluded that the eye cream did not have the potential for causing ocular irritation.

CLINICAL STUDIES

Case Reports

Arabinose (L-arabinose)

A pediatric patient presented with large amounts of L-arabinose and L-arabitol (Arabinose metabolite) in the urine.[52] The sugar L-arabinose mainly originated from the fruit formula in the child's diet. Highly elevated levels of L-arabitol were also found in the plasma and cerebrospinal fluid. The authors stated that the accumulation of L-arabinose and L-arabitol suggested a disturbance in L-arabinose metabolism at the level of L-arabitol degradation. Therefore, they presumed that the enzyme L-arabitol dehydrogenase was deficient in the pediatric patient.

Psicose and Saccharide Hydrolysate

A male patient had urticarial attacks over a period of 6 mo after eating foods such as hamburgers, spaghetti, and cakes, and after consuming certain drinks.[21,53] When the patient was given a refreshing drink (type not stated), urticarial lesions developed within 2 h. The ingredients of the drink were then given separately, with a week between each test. Two ingredients of the drink, Saccharide Hydrolysate and high-fructose corn syrup (containing mostly glucose and 0.07% Psicose), induced urticarial lesions.

High-fructose corn syrup caused the stronger reaction, and a skin test on this ingredient (3 mg) yielded a positive reaction. Psicose was partly purified using thin layer chromatography, and yielded a positive skin reaction when applied at a dose of 21.8 µg. The authors concluded that Psicose was responsible for the urticarial attacks in the male patient.

Other Clinical Reports

Psicose

The safety of long-term ingestion of Psicose was studied using 17 normal subjects (males and females).[54] A randomized, double-blind, placebo-controlled crossover experiment was performed. The subjects consumed Psicose (5 g) with meals 3 times per day for 12 continuous weeks. Physical examinations, blood examinations, and urine analyses were performed. There was no evidence of abnormal effects or clinical problems.

RISK ASSESSMENT

Dermal

Anhydroxylitol

A risk assessment was performed by the Australian Industrial Chemicals Scheme.[3] Data on typical use patterns of cosmetic product categories in which Anhydroxylitol may be used were obtained from a 2010 Scientific Committee on Cosmetic Safety (SCCS) Notes of Guidance, 7th revision.[55] The use patterns involved the following 8 product types: body lotion, face cream, eyeliner, lipstick, makeup remover, shower gel, shampoo, and hair conditioner. Systemic exposure was based on a trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol) in each product. In the absence of dermal absorption data, the default dermal absorption of 100% was assumed for calculation purposes.[52,56] An adult body weight of 60 kg was also assumed for calculation purposes. The worst-case scenario estimation using these assumptions is for a person who is a simultaneous user of all 8 products, each containing 1.5% Anhydroxylitol (from trade mixture at concentration of 5%). This would result in a systemic dose of 8.550 mg/kg/d of the trade mixture.

The repeated dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol) using the worst-case exposure scenario (from the use of multiple products) of 8.550 mg/kg/d and the NOAEL of 1000 mg/kg/d for xylitol (from 2-yr dietary studies). An MoE value of ≥ 100 was considered acceptable to account for intra- and inter-species differences. Using the NOAEL of 1000 mg/kg/d, an MoE of 117 was estimated for cosmetic products containing up to 5% of the trade mixture (equivalent to 1.5% Anhydroxylitol). Thus, based on the available information, it was concluded that use of Anhydroxylitol up to a concentration of 1.5% in cosmetic products is not considered to pose an unreasonable risk to public health.

SUMMARY

The safety of 7 saccharides/saccharide derivatives, as used in cosmetics, is reviewed in this safety assessment. The available data indicate that Anhydroxylitol has a molecular weight of 134.13 Da. Saccharide Isomerate with different molecular weights (MW) is being marketed. The weight range for the lower MW Saccharide Isomerate is 120 - 400 Da. The reported values for higher MW Saccharide Isomerate are 15,000 Da, 20,000 Da, and > 1.4 MDa).

According to the *Dictionary*, all 7 ingredients reviewed in this safety assessment are reported to function as skin-conditioning agents – humectant in cosmetics. Other reported functions include antioxidant, humectant, skin protectant, and oral care agent.

In the *Food Chemicals Codex* description, Saccharide Hydrolysate is marketed as invert sugar syrup and contains dextrose (glucose), fructose, and sucrose in various amounts, as represented by the manufacturer. In accordance with the *Food Chemicals Codex*, the acceptance criteria for Saccharide Hydrolysate are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of Saccharide Hydrolysate. Other acceptance criteria for Saccharide Hydrolysate in the Food Chemicals Codex relate to lead content (not more 0.1 mg/kg) and sulfated ash content (not more than 0.2%).

According to 2021 VCRP data, Saccharide Isomerate is reported to be used in 352 cosmetic products (302 leave-on products and 50 rinse-off products). Of the ingredients reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2018 indicate that Saccharide Hydrolysate is being used at maximum use concentrations up to 4.6% in rinse off products (skin cleansing products), and that Saccharide Isomerate is being used at maximum use concentrations up to 2.8% in leave-on products (face and neck skin care preparations, not spray). These are the highest use concentrations in rinse-off and leave-on products reported for the ingredients that are being reviewed in this safety assessment.

Psicose is a sugar substitute that has 70% of the sweetness of sucrose, but almost zero calories. The cosmetic ingredient Saccharide Hydrolysate contains fructose and glucose, and Saccharide Hydrolysate is also a direct food substance affirmed as GRAS by the US FDA.

According to one source, Saccharide Isomerate (MW not stated) is uniquely bound at the corneocytes to the free amino group of lysine found in the keratin of the stratum corneum. This unique binding mechanism to the skin and scalp ensures that the active ingredient is not washed off, but remains until removed by the natural process of desquamation.

Anhydroglucitol (2 to 7 mg, in saline) was administered orally to 5 rats as follows: 2 mg (1 rat), 5 mg (3 rats), and 7 mg (1 rat). Anhydroglucitol was readily absorbed by the gut, and there was no urinary excretion of anhydroglucitol after 48 h. In another study, Anhydroglucitol (7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) to rats daily for 7 wk. A high serum Anhydroglucitol concentration (62 to 126 µmol/l) was maintained in the animals tested.

The intestinal absorption, organ distribution, and urinary excretion of [^{14}C]Psicose was studied using male rats and male mice. [^{14}C]Psicose was absorbed well after oral dosing, and eliminated rapidly after both oral and i.v. administration. In another oral dosing study, U-[^{14}C]Psicose (2 µCi) was administered by stomach tube to rats. Much of the radioactivity was rapidly excreted in the urine, whereby 95% of the excreted radioactivity was recovered within the first 7 h.

Anhydroglucitol is present in human blood, and the normal average plasma concentration is in the vicinity of 20 µg/ml. The origin and disposal of Anhydroglucitol, was studied using normal subjects. It was concluded that Anhydroglucitol in the body originates mainly from foods, is well absorbed in the intestine, and is little degraded and metabolized in the body. According to the Australian Industrial Chemicals Scheme, based on the low molecular weight of Anhydroxylitol (134 Da), there is potential for dermal absorption and passage across the gastrointestinal tract. However, this may be limited by its high water-solubility (674 g/l), and low partition coefficient (log P_{ow} = -2).

After an overnight fast, normal volunteers drank an isosmotic solution containing raffinose (8 g), lactose (20 g), and L-arabinose (2 g) in 250 ml of water. The median 5-h urinary excretion was 17.5% of ingested L-arabinose. In a study involving human subjects on a normal diet, 24-h urine samples were collected. The excretion of Psicose (most common neutral sugar found in human urine) ranged from 0.1 to 2.7 mmol/24 h. Results from another study involving human subjects indicate that Psicose is present in human urine in amounts of 15 to 30 mg/l. The diet is presumed to be the source of Psicose because it disappears from the urine of subjects who have fasted for 48 h.

In an acute dermal toxicity study involving rats (number not stated), an LD_{50} of > 2 g/kg was reported for a trade name mixture containing 25% to 35% Anhydroxylitol. No mortalities or gross pathological changes were observed.

An oral LD_{50} of > 2 g/kg was also reported for the same trade name mixture containing 25% to 35% Anhydroxylitol in a study involving rats (number not stated). No mortalities or gross pathological changes were observed. LD_{50} values of 12.1 g/kg and 11.6 g/kg were reported for male and female rats (number not stated), respectively, in an acute oral toxicity study on Arabinose. In an acute oral toxicity study on 50% aqueous Psicose involving groups of 8 male Wistar rats, calculated LD_{50} values (2 different methods used) of 15.8 g/kg and 16.3 g/kg were reported. Bleeding in the mucous layers of the stomach or small intestine (17 g/kg or 20 g/kg dose groups) was observed at necropsy. Single oral doses of 1 g/kg and 4 g/kg administered to 6 Beagle dogs did not induce severe toxicity in dogs. A dose-dependent increase ($p < 0.05$) in plasma alkaline phosphatase activity was reported. However, histological examination of the liver or other tissues was not performed. An acute oral LD_{50} of > 2 g/kg was reported for undiluted Saccharide Isomerate (MW = 120 - 400 Da) in a study in which the species tested is not stated.

A 28-d oral toxicity study on a tradename mixture comprising ~25% Anhydroxylitol (and unstated quantities of xylitol and xylitylglucoside) was performed using groups of least 10 rats. Doses up to 1000 mg/kg/d were tested. Minimal focal myocarditis was observed in 3 animals of the highest dose group; due to uncertainty relating to the cause of myocarditis and limited histopathology data, the Australian Industrial Chemicals Scheme noted that it was not possible to clearly establish a NOAEL for the test substance in this study. No apparent toxicity signs were observed after Anhydroglucitol (stereochemistry not stated) was administered orally (in drinking water) to 12 white rats daily for 7 wk. Rats (number not stated) given feed containing 5% Arabinose in a short-term oral toxicity test developed diarrhea.

Six Sprague-Dawley rats were fed a normal diet and consumed 2% Psicose-supplemented water for 14 d. There was no difference in mean testes weight between treated and control rats. The short-term oral toxicity of Psicose was evaluated using groups of 7 male Wistar rats. The groups were fed diets containing 10%, 20%, 30%, and 40% Psicose for 34 d. Liver and kidney weights were heavier ($p < 0.05$) in rats fed the 10% diet than in rats fed the 0 and 30% diets. It was also noted that it is not clear whether or not the cause of Psicose-induced liver enlargement was due to liver glycogen deposition. Many of the effects observed were assumed to be secondary to a decrease in food consumption or the consumption of large amounts of a non-nutritive, poorly absorbed, osmotically active substance. However, it was noted that Psicose appears to be harmful to the intestinal tract. In another short-term study, Psicose (0.2 g/kg) was fed to 5 beagle dogs daily for 12 wk. Dosing with Psicose did not cause any harmful effects in dogs. The mild increase in plasma alkaline phosphatase was not considered suggestive of Psicose toxicity.

A group of 18 male Wistar rats had free access to a commercial rodent diet containing 3% Psicose for 12 or 18 mo. The hematological and chemical values were not suggestive of overt Psicose toxicity and, overall, no adverse effects were seen after feeding with 3% Psicose in the diet. The effects of long-term 3% Psicose administration in the diet to rats were found to be increased liver and kidney weights, with no gross pathological findings correlated with this hypertrophy. In a carcinogenicity study on L-arabinose involving 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females), there was no histologic evidence of an injurious effect of the injected test substance on any internal organ, especially the liver and kidneys, in mice or rats.

The genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was evaluated in a bacterial reverse mutation assay. Results were classified as negative in this assay. The same test material was non-genotoxic in a chromosome aberration assay using human peripheral blood lymphocytes. Undiluted Saccharide Isomerate (MW = 120 - 400 Da)

was classified as non-genotoxic in both the Ames test and the micronucleus test in vitro. Ames test results for the following Saccharide Isomerate trade name materials were also negative, with and without metabolic activation: Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) at 0.5% to 1.5% (at doses ranging from 0.06 to 5 µl/plate); Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) at doses up 5000 µg/plate; Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) at doses up 5000 µg/plate; and Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA) at doses up 5000 µg/plate.

The micronucleus test was used to evaluate the genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol. Mice received a dose of ≤ 2000 mg/kg/d (route of administration not specified) for 2 d, and results were negative. However, it is not clear that the test substance was systemically absorbed and reached the bone marrow in this in vivo assay.

The carcinogenicity of L-arabinose was evaluated using 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females). A 25% aqueous solution of L-arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck twice per week for periods up to 2 yr. In rats, a total of 11 tumors was observed. Tumors were not observed in mice. The great majority of the benign and malignant tumors found in test and control rats and mice were at sites remote from the nape of the neck. It was concluded that it is unlikely that development of most of the tumors was related to test substance administration.

In the in vitro MTT cell proliferation assay involving various cancer cell lines, Psicose did not have an antiproliferative effect over the range of concentrations tested (1 mM to 50 mM). The following results relate to use of the MTT assay to evaluate the cytotoxicity of Anhydrogalactose and D-anhydrogalactose in various cell types. Anhydrogalactose was not cytotoxic to melanin-producing murine B16 melanoma cells or human epidermal melanocytes at concentrations of 12.5, 25, and 50 µg/ml. Anhydrogalactose and D-anhydrogalactose at concentrations up to 100 µg/ml (B16F10 cells) and up to 200 µg/ml (RAW264.7 cells) did not cause statistically significant growth inhibition.

Anhydrogalactose markedly inhibited melanin secretion at a concentration of 50 µg/ml in murine B16F10 melanoma cells and human epidermal melanocytes. The cells were pretreated with the test substance for 1 h prior to exposure to α-MSH. In a similar assay, Anhydrogalactose strongly suppressed melanin production in B1610 mouse melanoma cells. The extracellular melanin concentration of melanoma cells treated with 100 µg/ml Anhydrogalactose was statistically significantly lower than that of cells treated with the same concentration of arbutin (positive control) or D-anhydrogalactose.

The anti-inflammatory activity of Anhydrogalactose and D-anhydrogalactose was evaluated at concentrations of 100 µg/ml and 200 µg/ml using RAW264.7 mouse macrophages. Cellular nitrite levels, which increase considerably under inflammatory conditions, were monitored. Anhydrogalactose had statistically significant anti-inflammatory activity at both concentrations. The stereoisomer D-anhydrogalactose had a nitrite-suppressing effect, only at a concentration of 200 µg/ml; however, the effect of D-anhydrogalactose was statistically significantly lower when compared to Anhydrogalactose.

In an antimicrobial assay, *S. mutans* colonies were not formed when Anhydrogalactose (10 g/l) was present in the growth medium.

The effect of topical application of aqueous Psicose (0.1 M aqueous solution) on epidermal permeability barrier recovery rate after barrier disruption (by tape stripping) was evaluated using male hairless mice of the HR-1 strain (number not stated). The test substance accelerated barrier recovery.

The dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was classified as non-irritating to the skin of 3 New Zealand White albino rabbits, when applied for 4 h using a semi-occlusive patch. The same test substance was evaluated in the maximization test using a minimum of 10 guinea pigs in the test group. At a challenge concentration of 50% (actual concentration = 17.5%), the test substance did not induce skin sensitization.

Saccharide Isomerate 20% (v/v; MW = 120 - 400 Da) was evaluated for skin irritation potential (animal species not stated), and was classified as non-irritating and non-corrosive. Saccharide Isomerate (20% v/v; MW = 120 - 400 Da) was also evaluated for skin irritation potential in a repeated application test involving guinea pigs. Results were negative for skin irritation or corrosion.

In an occlusive patch test involving human subjects (number not stated), Saccharide Isomerate (20% v/v; MW = 120 - 400 Da) was non-irritating and non-corrosive to the skin. A Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was applied for 24 h to the skin of 10 subjects in an occlusive patch test. Test concentrations ranging from 0.5% to 1.5% did not induce skin irritation. In a 48-h occlusive patch test involving 11 subjects, a Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine), results were negative for skin irritation potential at concentrations of 0.5% to 1.5%. The same concentrations of a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) did not cause skin irritation in a 24-h occlusive patch test involving 10 subjects. A Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition:

galactose-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA) was evaluated for skin irritation potential in a 48-h occlusive patch test involving 11 subjects. There was no evidence of skin irritation at concentrations ranging from 0.5% to 1.5%.

Skin sensitization was not observed in a maximization test (animals) on 20% (v/v) Saccharide Isomerate (MW = 120 - 400 Da). An HRIPT involving 213 subjects was used to evaluate the skin irritation and sensitization potential of an eye cream containing 2.75% Saccharide Isomerate (MW not stated). The product did not have dermal irritation or sensitization potential in this study. The skin sensitization potential of a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated in an HRIPT involving 100 subjects. The material was non-irritating and non-sensitizing at test concentrations of 0.5% to 1.5%. In an HRIPT involving 102 subjects, a Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) was also non-irritating and non-sensitizing at the same test concentrations. The skin sensitization potential of a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) was evaluated in another HRIPT involving 109 subjects. The induction concentration is 0.9%, but the challenge concentration is unknown. Neither skin irritation nor allergenicity was noted. An HRIPT (100 subjects) evaluating the skin sensitization potential of a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA) involved induction concentrations of 0.5% to 1.5% (challenge concentration unknown). There was no significant reaction of contact allergy.

Results were negative in a study evaluating the photosensitization/phototoxicity potential of Saccharide Isomerate (20% v/v; MW = 120 - 400 Da) in guinea pigs (number not stated). The phototoxicity of a Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylguluronic acid (GuINAcA)/3-acetylated *N*-acetylguluronic acid (3OAc-GuINAcA) was evaluated in an in vitro assay. The test substance (contained 0.5% to 1.5% Saccharide Isomerate) was evaluated for cytotoxicity at concentrations up to 1000 µg/ml in the presence of UVA. Results were negative.

In an ocular irritation test (3 New Zealand White albino rabbits) on the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside), slight ocular irritation was observed. The ocular irritation potential of an eye cream containing 2.75% Saccharide Isomerate (MW not stated) was evaluated using 53 female subjects. The eye cream did not have the potential for causing ocular irritation. Saccharide Isomerate (20% v/v; MW = 120-400 Da) was practically non-irritating to the eyes (number of animals and species not stated) in an ocular irritation study.

In a case report, a pediatric patient presented with large amounts of L-arabinose and L-arabitol (an Arabinose metabolite) in the urine. The stereoisomer L-arabinose mainly originated from the fruit formula in the child's diet. It was presumed that the enzyme L-arabitol dehydrogenase was deficient in the child patient. A male patient had urticarial attacks over a period of 6 mo after consuming certain drinks. Two ingredients of the drink, Saccharide Hydrolysate and high-fructose corn syrup (containing mostly glucose and 0.07% Psicose), induced urticarial lesions. Psicose yielded a positive skin reaction when applied at a dose of 21.8 µg.

In a risk assessment for dermal exposure to 8 product types that was performed by the Australian Industrial Chemicals Scheme, the repeated dose toxicity potential was estimated by calculation of the MoE of the trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol). An MoE of 117 was estimated.

DISCUSSION

This assessment reviews the safety of 7 saccharides/saccharide derivatives as used in cosmetic formulations. The Panel concluded that the data included in this review are sufficient for determining the safety of these ingredients as reportedly used in cosmetics. All of the ingredients reviewed in this safety assessment are hygroscopic saccharides or saccharide derivatives. The Panel determined that the data included in this report are sufficient for determining the safety of these ingredients. Specifically, the Panel noted data on Saccharide Isomerate with varying molecular weights (lower MW range: 120 to 400 Da; higher MW of 15,000 Da, 20,000 Da, or > 1.4 MDa). The lower molecular weight Saccharide Isomerate consists primarily of glucose and fructose; in the absence of 28-d dermal toxicity data and developmental and reproductive toxicity data, the Panel noted that any concerns relating to these toxicity endpoints are mitigated based on the predominance of these 2 constituents. Furthermore, the Panel agreed that any concerns relating to this endpoint are also mitigated for the higher molecular weight Saccharide Isomerate, as it would not be expected to be percutaneously absorbed. Thus, the absence of safety concerns relating to Saccharide Isomerate can be expanded to be inclusive of all of the saccharide/saccharide derivatives that are evaluated in this safety assessment.

Anti-melanogenic activity of Anhydrogalactose in B16F10 melanoma cells and human epidermal melanocytes was observed in in vitro experiments. However, the Panel noted that the high exposure concentrations (much higher than would be observed from cosmetic use) in these in vitro studies was not predictive of in vivo effects following exposure via cosmetic use. Furthermore, the Panel agreed that skin lightening is not a cosmetic effect, and that manufacturers should be diligent about ensuring that this effect would not be caused by cosmetic products.

The issue of incidental inhalation exposure from the use of Anhydroxylitol in cosmetic products (fragrance preparations) was discussed by the Panel. 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 ingredient is 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.

Finally, the Panel expressed concern about heavy metals that may be present in any of the ingredients that are being reviewed in this safety assessment. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 7 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Anhydrogalactose*
Anhydroglucitol
Anhydroxylitol
Arabinose*
Psicose*
Saccharide Hydrolysate
Saccharide Isomerate

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

TABLES

Table 1. Definitions, structures, and reported functions[1,CIR Staff]

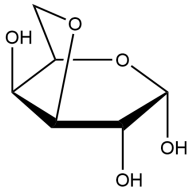
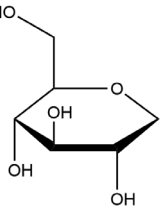
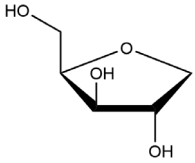
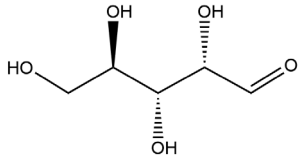
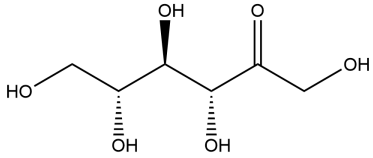
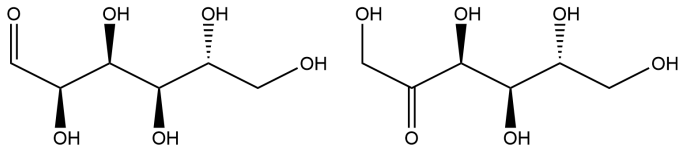
Ingredient CAS No.	Definition	Function(s)
Anhydrogalactose 28251-55-0	Anhydrogalactose is the organic compound that conforms to the structure: 	Antioxidants; Humectants; Skin-Conditioning Agents - Humectant
Anhydroglucitol 154-58-5	Anhydroglucitol is the organic compound that conforms to the structure: 	Humectants; Oral Care Agents; Skin-Conditioning Agents - Humectant
Anhydroxylitol 53448-53-6	Anhydroxylitol is the organic compound that conforms to the structure: 	Skin-Conditioning Agents - Humectant
Arabinose 10323-20-3	Arabinose is the organic compound that conforms to the structure: 	Skin-Conditioning Agents - Humectant
Psicose 23140-52-5	Psicose is the monosaccharide that conforms to the structure: 	Skin-Conditioning Agents - Humectant
Saccharide Hydrolysate 8013-17-0	Saccharide Hydrolysate is an invert sugar derived by the hydrolysis of sucrose by acid, enzyme, or other method of hydrolysis. It is characterized by a content of fructose and glucose. 	Skin Protectants; Skin-Conditioning Agents - Humectant
Saccharide Isomerate 100843-69-4	Saccharide Isomerate is a carbohydrate complex formed from a base catalyzed rearrangement of a mixture of saccharides.	Skin-Conditioning Agents - Humectant

Table 2. Chemical properties

Property	Value/Results	Reference
Anhydrogalactose		
Molecular weight (Da)	162.14	10
log K_{ow}	-2.01 (estimated)	12
Anhydroglucitol		
Molecular weight (Da)	164.16	10
log K_{ow}	-2.17 (estimated)	12
Anhydroxylitol		
Molecular weight (Da)	134.13	10
log K_{ow}	-1.72 (estimated)	12
Anhydroxylitol ~35% in dried extract of tradename mixture (also comprising in part, xylitol and xylitylglucoside)		
Form (of tradename mixture)	Clear, light yellow liquid	3
Density (g/ml at 20ºC)	1.435	3
Melting point (ºC)	< 50	3
Boiling point (ºC at 760 mmHg)	315	3
Vapor pressure (mmHg at 25ºC)	2.7×10^{-6}	3
Water solubility (g/l at 20ºC)	674	3
Partition coefficient (log P_{ow})	-2	3
Arabinose		
Molecular weight (Da)	150.13	10
log K_{ow}	-1.98 (estimated)	12
Log P	-2.22	14
Psicose		
Form	White crystalline solid	8
Molecular weight (Da)	180.156	8
Melting point (ºC)	96	8
Solubility (% w/w at 25ºC; 50 ºC)	74; 83	8
log K_{ow}	-1.46 (estimated)	12
Saccharide Hydrolysate		
Form	Hygroscopic liquid	9
Molecular weight (average; Da)	180.16	11
Solubility	Very soluble in water, glycerin, and in glycols; very sparingly soluble in acetone and in ethanol	9
log K_{ow}	-1.46; -2.43 (estimated)	12
Saccharide Isomerate		
Molecular weight (MDa)	>1.4 (eq dextran)	13
Molecular weight (Da)	20,000	13
Molecular weight (Da)	15,000	13
Molecular weight (Da)	120-400	15

Table 3. Frequency (2021) and concentration (2018) of use according to duration and type of exposure.[23,24]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Anhydroglucitol		Anhydroxylitol		Saccharide Hydrolysate	
Totals*/Conc. Range	**NR**	**0.17-1**	**153**	**0.0028-0.88**	**33**	**0.002-4.6**
Duration of Use						
Leave-On	*NR*	*0.33-1*	*123*	*0.28-0.88*	*32*	*0.002*
Rinse off	*NR*	*0.28*	*30*	*0.0028*	*1*	*4.6*
Diluted for (bath) Use	*NR*	*0.17*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	0.28-0.83	5	NR	2	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	1;10[b];46[c]	0.88[b]	10[b]; 6[c]	NR
Incidental Inhalation- Powders	NR	0.9[a]	46[c]	0.88[a]	6[c];10[a]	0.002[a]
Dermal Contact	NR	0.17-1	146	0.0028-0.88	33	0.002-4.6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	6	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.17	11	NR	NR	NR
Baby Products	NR	NR	1	NR	5	NR

	Saccharide Isomerate	
	# of Uses	Conc. (%)
Totals/Conc. Range	**352**	**0.001-2.8**
Duration of Use		
Leave-On	*302*	*0.001-2.8*
Rinse off	*50*	*0.01-0.7*
Diluted for (bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	13	1
Incidental Ingestion	NR	NR
Incidental Inhalation- Sprays	55[b];46[c]	0.01[b]
Incidental Inhalation- Powders	46[c]	0.02-2.8[a]
Dermal Contact	328	0.001-2.8
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	14	0.27
Hair-Coloring	NR	NR
Nail	9	0.03
Mucous Membrane	7	NR
Baby Products	2	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 powders, but it is not specified whether the reported uses are powders

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

[c] 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

Table 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
				DERMAL		
Anhydroxylitol (25% to 35%)	Rats	Not stated	Dried extract of trade name mixture	Doses up to 2 g/kg. OECD TG 402.3.	No mortalities, abnormal clinical signs, body weight changes, or gross pathological changes observed. The LD_{50} > 2 g/kg.	[3]
				ORAL		
Anhydroxylitol (25% to 35%)	Rats	Not stated	Dried extract of trade name mixture	Doses up to 2 g/kg. OECD TG 401.	No mortalities, abnormal clinical signs, body weight changes, or gross pathological changes were observed. The LD_{50} > 2 g/kg	[3]
Arabinose	Rats (male and female; strain not stated)	Not stated	Not stated	Doses administered and study details not stated. Data summary is from English language translation of Japanese publication abstract	LD_{50} (calculated) = 12.1 g/kg (males) and 11.6 g/kg (females)	[40]
Psicose (50%)	Male Wistar rats (5 groups of 8) male Wistar rats.	5 groups (8 rats per group)	Water	Groups received single oral doses ranging from 8 g/kg to 20 g/kg. Stainless feeding tube attached to 20 ml syringe used for dosing. 14-d observation period initiated after test substance administration. Necropsy performed on animals that died. LD_{50} values calculated using Behrens-Karber method and Litchfield-Wilcoxon method.	Animal deaths: 3 rats (14 g/kg dose group), 3 rats (17 g/kg dose group), and 8 rats (20 g/kg dose group). Animals died within 2 d after dosing. All rats experienced diarrhea at 1 h to 24 h after dosing. Condition of high-dose animals (17 g/kg and 20 g/kg doses) described as quite weak. No evidence of abnormalities in surviving rats after 3 d. At necropsy, bleeding observed in mucous layers of stomach or small intestine in rats of 17 g/kg or 20 g/kg dose group. LD_{50} = 16.3 g/kg (Behrens-Karber method) and 15.8 g/kg (Litchfield-Wilcoxon method)	[41]
Psicose	Beagle dogs	6	Water (100 ml)	Single oral dose (in water, by plastic syringe) of Psicose (1 g/kg and 4 g/kg) or a placebo (water, 100 ml). The control, 1 g/kg of Psicose, and 4 g/kg of Psicose administered on 3 different study days. Each animal received the control on day 1, the 1 g/kg dose on day 2, and the 4 g/kg dose on day 3. Mean values in data presented were representative of 6 dogs (for control and 1 g/kg dose) and 5 dogs (for 4 g/kg dose). All dogs active and had good appetite throughout the study.	4 g/kg dose caused vomiting in 1 dog and transient diarrhea in remaining 5 dogs. Two dogs had transient nausea within 1 h after receiving 1 g/kg dose. Blood glucose slightly decreased, without an increase in the plasma insulin concentration, at 2 h after dosing with the test substance. Mild, dose-dependent increase ($P < 0.05$) in plasma alkaline phosphatase activities observed between 12 h and 48 h after dosing. Histological examination of liver or other tissues not performed. Plasma inorganic phosphorus concentration at 4 g/kg dose slightly higher ($P < 0.05$) at 8-h post-dosing, when compared to control dogs. Though no possible causes of inorganic phosphorus alteration observed, authors stated that dosing with Psicose may mildly exaggerate diurnal pattern of plasma inorganic phosphorus concentration in dogs. Authors concluded that Psicose did not induce severe toxicity in dogs.	[42]

Table 5. Repeated dose toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	Results	Reference
SHORT-TERM TOXICITY – ORAL						
Anhydroglucitol	White laboratory rats	12	Water	Anhydroglucitol (stereochemistry not stated; 7 mg, 0.14 mmol/kg body weight) administered orally (daily for 7 wk. 6 rats served as controls.	Body weight gain (5.2 g/rat/wk) in test animals similar to that of control rats (4.6 g/rat/wk). No apparent toxic signs observed in test animals.	[34]
Anhydroxylitol (~ 25%)	Rats (strain not stated)	At least 10 (5 males, 5 females)	Trade name mixture (with unstated quantities of xylitol and xylitylglucoside)	28-d oral toxicity study (OECD TG 407). Test substance administered at doses of 0 (vehicle was negative control (water)), 15, 150, and 1000 mg/kg/d.	Study results indicated no treatment-related changes in the following: mortality, clinical observations, behavioral assessment, functional performance, sensory reactivity, body weight, food consumption, hematology, blood chemistry, organ weights. Additionally, no treatment-related changes observed at necropsy of animals in highest dose group. However, minimal focal myocarditis observed in 2 males and 1 female of highest dose group. Histopathological examination not performed on animals of other 2 dose groups. The Australian Industrial Chemicals Scheme noted that lesions (type and incidence) observed are typical of findings that are expected in animals of this type, strain (not specified), and age. However, no historical data supporting this statement provided. Given the uncertainty relating to cause of myocarditis in animals of highest dose group and limited histopathology data, the Australian Industrial Chemicals Scheme noted that was not possible to clearly establish a no-observed-adverse-effect-level (NOAEL) for test substance.	[3]
Arabinose (5%)	Rats (strain not stated)	Not stated	Feed	Short-term toxicity test (duration not stated). Data summary is from English translation of Japanese publication abstract. Details relating to test protocol and results not included	Rats given feed containing 5% Arabinose developed diarrhea.	[40]
Psicose (2%)	Sprague-Dawley rats	6	Water	Rats fed normal diet and consumed 2% Psicose-supplemented water for 14 d. Control group (6 rats) fed normal diet and consumed water without Psicose. After 14 d, animals killed and body, testes, and liver weights determined	Mean body weight of treated rats (232 ± 12 g) higher when compared to control group (214 ± 14 g). No difference in mean testes weight (2.0 ± 0.2 g) between treated and control rats. Mean liver weight values were 12 .7 ± 0.7 g (treated rats) and 12.7 ± 0.7 g (controls).	[43]
Psicose (10%, 20%, 30%, and 40%)	Male Wistar rats	7	Diet	Groups of 7 rats fed diets for 34 d. Butylated hydroxytoluene (0.01 g/kg diet) added to all diets as antioxidant. Control group fed t diet without Psicose. After day 34, rats fasted for 3 h and then killed.	One rat fed 30% and 5 rats fed 40% Psicose died during experimental period. Body weight gain, food intake, and food efficiency more extensively suppressed after feeding with higher % Psicose diets (i.e., 30% and 40% diets). Statistically significant difference in body weight gain observed between 0, 10%, 20%, and 30% dietary groups ($P < 0.05$). Rats fed 20%, 30%, and 40% diets experienced diarrhea during first 8 d. Weights of heart and spleen smaller ($P < 0.05$) in rats fed higher Psicose concentration diets. Liver and kidney weights heavier ($P < 0.05$) in rats fed 10% diet than in rats fed the 0 and 30% diets. Cecal enlargement observed in rats fed 10% to 40% diets. Epididymal, perirenal, and mesenteric adipose tissue weights statistically significantly smaller ($P < 0.05$) in rats fed higher Psicose concentration diets. Other results indicated that serum glucose and triacylglycerol concentrations significantly lower ($P < 0.05$) in 30% dietary group than in other groups. Liver triacylglycerol content higher in 10% dietary group than in 0% group. Many effects observed assumed to be secondary to decrease in food consumption or consumption of large amounts of a non-nutritive, poorly absorbed, osmotically active substance. Not clear as to whether or not cause of Psicose-induced liver enlargement due to liver glycogen deposition. Authors concluded that feeding of diets extremely high in Psicose appears to be harmful to intestinal tract.	[41]

Table 5. Repeated dose toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	Results	Reference
Psicose	Beagle dogs	5	Not stated	Psicose (0.2 g/kg) was fed to animals daily for 12 wk. Control group (5 dogs) fed placebo (not stated) according to same procedure.	During course of experiment, plasma triglyceride concentrations increased in control group, but remained low in group fed Psicose. At week 2 and thereafter, plasma total cholesterol concentrations in test group statistically significantly lower ($P < 0.05$) when compared to control group. Platelet count levels in test group statistically significantly lower at week 0 and week 12 ($P < 0.05$). Psicose dosing had no influence on body weight. Except for change in lipid levels (lipid lowering effect), Psicose dosing did not cause clinical signs or changes in biochemical parameters (plasma alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, urea nitrogen, creatinine, total protein, albumin, total cholesterol, triglyceride, total calcium, inorganic phosphorus, sodium, potassium, and chlorine concentrations). Also, no cumulative effect of Psicose dosing on glucose metabolism, and no statistically significant differences in the following between test and control groups: liver enzymes, renal function markers, and electrolytes. Mild increase in plasma alkaline phosphatase not considered suggestive of Psicose toxicity. Authors concluded that dosing with Psicose did not cause harmful effects in dogs.	[44]
CHRONIC TOXICITY – ORAL						
Psicose (3%)	Male Wistar rats	18	Commercial rodent diet	Test animals had free access to diet for 12 or 18 mo. Rats actually ingested 1.28 g/kg/d Psicose and 1.22 g/kg/d sucrose. After 12 mo of feeding, 8 rats from each group fasted prior to collection of blood for hematological analysis. Remaining rats (10 per group) killed at the end of 18 mo, and various organs weighed. Parts of liver and kidney preserved for histopathological examination.	Liver and kidney weights statistically significantly heavier in 3% Psicose group at 12 mo and 18 mo when compared to control group. At 18 mo, liver and kidney weights also statistically significantly heavier in test group when compared to control group. Higher weights also reported for brains, lungs, and pancreas in test animals. At 12 mo, mean corpuscular hemoglobin statistically significantly lower in test group when compared to control group. Hemoglobin and mean corpuscular volume at 18 mo statistically significantly greater in test group than in control group. Histopathological examination of liver at 18 mo revealed fatty degeneration and hepatocellular fibrosis in group fed 3% Psicose in diet, but not in control group. These findings appeared to be slight and local. Mean value for pathological lesions (liver) in test group statistically significantly higher ($p < 0.0498$; i.e., slight difference) when compared to control group. At 12 mo, no difference in histopathological observations (in liver and kidneys) between test and control groups. In kidneys at 18 mo, no difference in total value for pathological lesions between test and control groups. Authors concluded that study found effects of long-term dietary administration of 3% Psicose to rats to be increased liver and kidney weights, with no gross pathological findings correlated with this hypertrophy. They also concluded that hematological and chemical values not suggestive of overt Psicose toxicity, and that, overall, no adverse effects seen after feeding with 3% Psicose in the diet.	[45]
CHRONIC TOXICITY – PARENTERAL						
l-Arabinose (25%)	Bethesda black rats and C57BL mice	60 (30 males, 30 females) per strain tested	Water	Chronic subcutaneous toxicity data from carcinogenicity study on l-arabinose. Aqueous solution of l-arabinose (2 ml [in rats] and 0.5 ml [in mice]) injected subcutaneously into nape of neck for periods up to 2 yr.	Rats tolerated test substance injections without any untoward effects. However, mice developed symptoms of shock, and some died (number not stated). Also, in mice, white necrotic masses identified in the subcutaneous tissue of nape of neck.	[46]

Table 6. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Anhydroxylitol	25% to 35% (doses not stated)	Trade mixture	Ames test (OECD TG 471). Bacterial reverse mutation assay (strains not stated)	Details relating to test protocol not included	Non-genotoxic	[3]
Anhydroxylitol	25% to 35% (doses not stated)	Trade mixture	Chromosome aberration assay (OECD TG 473), using human peripheral blood lymphocytes.	Details relating to test protocol not included	Non-genotoxic	[3]
Saccharide Isomerate (MW = 120-400 Da)	Undiluted (doses not stated)	Not stated	Ames test (OECD TG 471). Bacterial strains not stated.	Details relating to test protocol not included	Non-genotoxic	[15]
Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5% (at doses ranging from 0.06 to 5 µl/plate)	Not stated	Ames test (OECD TG 471), with and without metabolic activation. Bacterial strains not stated.	Dosing with and without metabolic activation. Additional protocol details not stated	No point mutations or frame-shifts in the genome of the bacterial strains tested, with or without metabolic activation. Non-genotoxic	[13]
Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-N-acetylglucosamine)	Doses up to 5000 µg/plate	Not stated	Ames test (OECD TG 471). Five *Salmonella typhimurium* strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	[13]
Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-N-acetylglucosamine)	0.5% to 1.5% (at doses ranging from 0.06 to 5 µl/plate)	Not stated	Ames test (OECD TG 471). Five *Salmonella typhimurium* strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	[13]
Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-N-acetylguluronic acid (GuINAcA)/3-acetylated N-acetylguluronic acid (3OAc-GuINAcA)	Doses up to 5000 µg/plate		Ames test (OECD TG 471). Five *Salmonella typhimurium* strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	[13]
Saccharide Isomerate (MW = 120-400 Da)	Undiluted (doses not stated)	Not stated	Micronucleus test (OECD TG 487). Cell type not stated	Details relating to test protocol not included	Non-genotoxic	[15]
IN VIVO						
dried extract of a trade mixture containing Anhydroxylitol (25% to 35%)	Mice received ≤ 2000 mg/kg/d for 2 d.		Micronucleus test (OECD TG 474), using mouse bone marrow erythrocytes	Protocol details not included	Classified as non-genotoxic. However, the Australian Industrial Chemicals Scheme stated that it is not clear that the test substance was systemically absorbed and reached the bone marrow in this in vivo assay.	[3]

Table 7. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
Irritation					
Trade mixture containing Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside)	~35% Anhydroxylitol	3 New Zealand White albino rabbits	Skin irritation test (OECD TG 404).[3] Test substance applied (dose per cm^2 was not stated) to skin for 4 h using a semi-occlusive patch. Application followed by 72-h observation period.	No evidence of erythema or edema during observation period. Test substance classified as non-irritating to skin.	[3]
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v)	Species and number of animals not stated	Skin irritation test (OECD TG 404). Details relating to test protocol not included.	Test substance classified as non-irritating and non-corrosive to skin.	[15]
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v)	Guinea pigs (number and species not stated)	Repeated application test. Details relating to test protocol not included.	No evidence of skin irritation or corrosion	[15]
Sensitization					
Dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside)	Induction: undiluted; Challenge: 50% (actual concentration = 17.5%). Intradermal injection concentrations not stated	Guinea pigs (number and strain not stated);	Maximization test (OECD TG 406). Details relating to test protocol not included	Non-sensitizer	[3]
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v). Intradermal injection concentrations not stated	Number of animals and species not stated	Maximization test (OECD TG 406). Details relating to test protocol not included.	Non-sensitizer	[15]
			HUMAN		
Irritation					
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v)	Number of subjects not stated	Occlusive patch test. Details relating to test protocol not included.	Test substance classified as non-irritating and non-corrosive to the skin	.[15]
Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%	10	24-h occlusive patch test. Details relating to test protocol not included.	Test substance classified as non-irritant	[13]
Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%	11	48-h occlusive patch test. Details relating to test protocol not included.	Test substance classified as non-irritant	[13]
Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%.	10	24-h occlusive patch test. Details relating to test protocol not included.	Test substance classified as non-irritant	[13]
Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-N-acetylguluronic acid (GuINAcA)/3-acetylated N-acetylguluronic acid (3OAc-GuINAcA)	0.5% to 1.5%	11	48-h occlusive patch test. Details relating to test protocol not included.	Test substance classified as non-irritant	[13]

Table 7. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Sensitization					
Eye cream containing Saccharide Isomerate	2.75% (dose per area not stated)	213 subjects	HRIPT. Product, under an occlusive patch, applied to upper back (between the scapulae and waist, lateral to midline). The. Applications made 3 times per week (Mondays, Wednesdays, and Fridays) for total of 9 applications. Reactions scored 48 h after patch application on Mondays and Wednesdays, and at 72 h post-application on Fridays. After 2-wk non-treatment period, challenge patches applied to original and new sites on back. Challenge reactions scored at 48 h, 72 h, and 96 h.	Non-irritant and non-sensitizer	[50]
Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%	100 subjects	Marzulli-Maibach HRIPT. Induction phase involved three, 48-h applications per week. Additional details relating to test protocol not included.	Non-irritant and non-sensitizer	[13]
Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%	102 subjects	Marzulli-Maibach HRIPT. 3-wk induction phase involved repeated occlusive patch applications. Additional details relating to test protocol not included.	Non-irritant and non-sensitizer	[13]
Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-N-acetylglucosamine)	0.9% (at induction)	109 subjects	Marzulli-Maibach HRIPT. During induction, applications repeated at same test site over period of 3 consecutive weeks. Additional details relating to test protocol not included.	No irritation or allergenicity	[13]
Saccharide Isomerate and water trade name material (MW > 1.4 MDa; Osidic composition: galactose-N-acetylguluronic acid (GuINAcA)/3-acetylated N-acetylguluronic acid (3OAc-GuINAcA)	0.5% to 1.5%	52 subjects (26 with sensitive skin)	Marzulli-Maibach HRIPT. During induction, applications of the test substance were repeated at same test site over period of 3 consecutive weeks. Additional details relating to test protocol not included.	No significant reaction of contact allergy observed	[13]

Table 8. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL					
Dried extract of trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside)	Not stated	3 New Zealand White albino rabbits	Ocular irritation test (OECD TG 405). Instillation followed by 72-h observation period	Slight conjunctival irritation (redness and chemosis) observed, but had fully resolved by end of observation period. Conjunctival irritation first observed at 1 h post-instillation. Test substance classified as slightly irritating to eyes	[3]
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v)	Number of animals and species not stated	Ocular irritation test (OECD TG 405). Details relating to study protocol not included	Practically non-irritating to eyes	[15]
HUMAN					
Eye cream containing 2.75% Saccharide Isomerate	Not stated	56 female subjects: (19 contact lens wearers, 19 non-contact lens wearers, and 18 sensitive eye, non-contact lens wearers); 53 completed study	Protocol for product use in study not stated	Trace increases in palpebral conjunctival irritation observed in 3 subjects (unrelated to use of eye cream). No reports of subjective irritation. Increases in lacrimation, eyelid inflammation, or bulbar conjunctival inflammation not observed. Absence of changes in visual acuity and corneal tissue integrity noted. Eye cream did not have potential for causing ocular irritation.	[51]

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2021 VCRP Data

Anhydrogalactose - No FDA Data

Anhydroglucitol - No FDA Data

Anhydroxylitol

Other Baby Products	01C	1
Eyeliner	03B	1
Eye Lotion	03D	1
Other Eye Makeup Preparations	03G	3
Other Fragrance Preparation	04E	1
Hair Conditioner	05A	1
Hair Straighteners	05C	2
Shampoos (non-coloring)	05F	1
Tonics, Dressings, and Other Hair Grooming Aids	05G	2
Foundations	07C	1
Other Makeup Preparations	07I	1
Bath Soaps and Detergents	10A	4
Other Personal Cleanliness Products	10E	7
Cleansing	12A	15
Face and Neck (exc shave)	12C	37
Body and Hand (exc shave)	12D	9
Moisturizing	12F	45
Night	12G	6
Paste Masks (mud packs)	12H	2
Skin Fresheners	12I	1
Other Skin Care Preps	12J	11
Other Suntan Preparations	13C	1
Total		**153**

Arabinose - No FDA Data

Psicose - No FDA Data

Saccharide Hydrolysate

Baby Lotions, Oils, Powders, and Creams	01B	2
Other Baby Products	01C	3
Eye Lotion	03D	2
Makeup Bases	07F	1
Cleansing	12A	1
Face and Neck (exc shave)	12C	8
Body and Hand (exc shave)	12D	6
Moisturizing	12F	6
Night	12G	1
Other Skin Care Preps	12J	3
Total		**33**

Saccharide Isomerate

Baby Lotions, Oils, Powders, and Creams	01B	2
Eye Lotion	03D	7
Other Eye Makeup Preparations	03G	6
Hair Conditioner	05A	5
Shampoos (non-coloring)	05F	4
Tonics, Dressings, and Other Hair Grooming Aids	05G	3
Other Hair Preparations	05I	2
Foundations	07C	2
Makeup Bases	07F	2
Makeup Fixatives	07H	1
Other Makeup Preparations	07I	1
Basecoats and Undercoats	08A	1
Nail Polish and Enamel	08E	3
Other Manicuring Preparations	08G	5
Bath Soaps and Detergents	10A	4
Douches	10C	1
Other Personal Cleanliness Products	10E	2
Aftershave Lotion	11A	2
Other Shaving Preparation Products	11G	1
Cleansing	12A	16
Face and Neck (exc shave)	12C	100
Body and Hand (exc shave)	12D	31
Moisturizing	12F	82
Night	12G	17
Paste Masks (mud packs)	12H	17
Skin Fresheners	12I	5
Other Skin Care Preps	12J	29
Indoor Tanning Preparations	13B	1
Total		**352**

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: April 2, 2021

SUBJECT: Tentative Report: Safety Assessment of Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate as Used in Cosmetics (release date: March 23, 2021)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate as Used in Cosmetics.

Introduction – In addition to "various stereochemistries" it should be made clear that various structures are possible for Saccharide Isomerate.

Method of Manufacture, Anhydroxylitol – In addition to Glucose, reference 19 also identified Xylitylglucoside and Xylitol as components of the reaction that produces Anhydroxylitol.

Dermal Penetration, Saccharide Isomerate – Reference 33 describes the Saccharide Isomerate using DSM as the company name and Pentavitin as the trade name. Although the MW may not have been specifically stated in the article, they are describing the low molecular (120-400 Da) material.

ADME, Parenteral, Pscose – Did they really confirm that it was Psicose in the liver, kidneys and bladder, or were they just measuring radioactivity from [^{14}C]Psicose?

ADME, Human – If reference 37 showed "that urinary excretion of Anhydroglucitol occurred soon after the food ingestion, it should not say "implied".

Cytotoxicity – It is not clear what the cells were treated with, a mixture of Anhydrogalactose and D-anhydrogalactose, or the compounds individually.

Effect of Epidermal Barrier Recovery – This section should be moved directly after the dermal penetration section.

Photosensitization/Phototoxicity, Human, Saccharide Isomerate – It is not clear why the *in vitro* assay is presented under a Human subheading.

Summary – Please state the compound for which the actual concentration was 17.5%.

Table 5 – The results presented in the Concentration/Dose/Protocol column (reference 44) need to be deleted as they are also presented in the Results column.