
Safety Assessment of Saccharide Humectants as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: February 16, 2021
Panel Meeting Date: March 11-12, 2021

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.; J 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.



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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: February 16, 2021
Subject: Safety Assessment of Saccharide Humectants as Used in Cosmetics

Enclosed is the Draft Tentative Report on the Safety Assessment of Saccharide Humectants as Used in Cosmetics (*saccha032021rep*). Comments relating to the suitability of the current report title (*saccha032021cir ssc*), provided by the CIR Science and Support Committee (CIR SSC), are also enclosed for the Panel's consideration. After its review of the available data on these ingredients at the September 2020, the Panel issued an Insufficient Data Announcement (IDA) for these 7 ingredients, with the following data requests:

- 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%

In response to the IDA, the following data (enclosed) were received from the Council, and have been added to the draft report (and are highlighted in report text):

- Chemical properties of Arabinose (*saccha032021data1*)
- Methods of production of Arabinose (*saccha032021data2*) and Saccharide Isomerate (*saccha032021data2*; *saccha032021data3*)
- Composition/Impurities data on Saccharide Isomerate (*saccha032021data2*; *saccha032021data3*)
- Dermal penetration statement on Saccharide Isomerate (*saccha032021data2*)
- Acute oral toxicity data on Saccharide Isomerate (*saccha032021data2*)
- In vitro genotoxicity data on Saccharide Isomerate (*saccha032021data2*; *saccha032021data3*)
- Animal (*saccha032021data2*) and human (*saccha032021data2*; *saccha032021data3*) skin irritation data on Saccharide Isomerate
- Animal (*saccha032021data2*) and human (*saccha032021data3*) skin sensitization data on Saccharide Isomerate
- Animal (*saccha032021data2*) and in vitro (*saccha032021data3*) phototoxicity/photosensitization data on Saccharide Isomerate
- Ocular irritation data on Saccharide Isomerate (*saccha032021data2*)

Additionally, the report has been revised to include 2021 FDA VCRP data that were received in January of this year. Saccharide Isomerate, most frequently used saccharide humectant, was used in 494 formulations in 2020 and is being used in 352 formulations in 2021. These data are also enclosed for the Panel's review (*saccha032021FDA*).

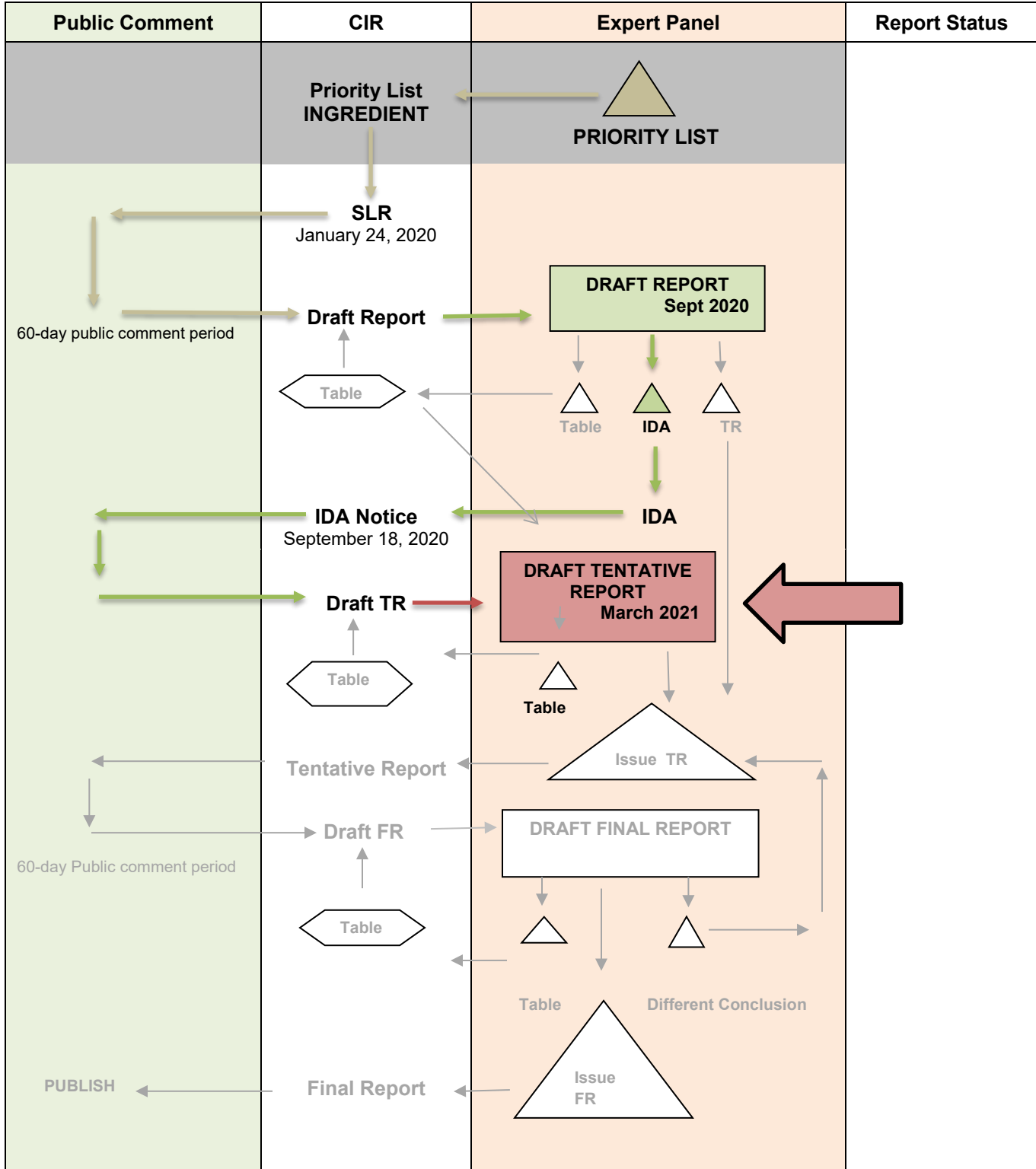
Also included in this package for your review are the report history (*saccha032021hist*), flow chart (*saccha032021flow*), literature search strategy (*saccha032021strat*), ingredient data profile (*saccha032021prof*), and minutes from the September 2020 Panel meeting (*saccha032021min*).

Based on the proceedings and comments from the September 2020 meeting, a draft Discussion has been included. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Report with a safe as used, safe with qualifications, insufficient data, unsafe, or split conclusion.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Saccharide Humectants

MEETING March 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

Saccharide Humectants Data Profile* - March 11-12, 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; 1/7/2021

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>
SciFinder (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/fcnavigation.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/HPVISlogin>

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 contradictory.

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.

Safety Assessment of Saccharide Humectants as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
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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.; J 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.

ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 7 saccharide humectants 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 [TBD]

INTRODUCTION

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

Anhydrogalactose	Arabinose	Saccharide Isomerate
Anhydroglucitol	Psicose	
Anhydroxylitol	Saccharide Hydrolysate	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all 7 saccharide humectants are reported to function as skin-conditioning agents – humectant in cosmetics (See Table 1).¹ Anhydrogalactose is also reported to function as an antioxidant, and Anhydroglucitol also functions as an oral care agent.

Because Saccharide Hydrolysate 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 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}

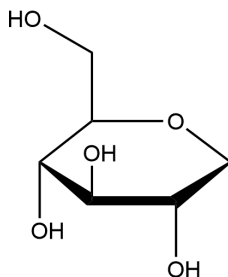


Figure 1. Anhydroglucitol

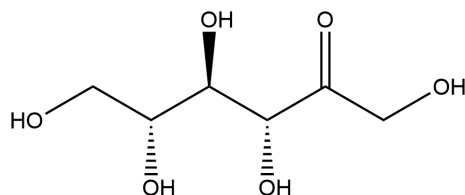


Figure 2. Psicose

The definitions, structures, and CAS Nos. of all the saccharide humectants included in this safety assessment are presented in Table 1.¹

Chemical Properties

Chemical properties of saccharide humectants are presented in Table 2.^{3,7-14} Anhydrogalactose, Anhydroxylytol, Psicose, and Saccharide Hydrolysate are water-soluble. Of the ingredients that are being reviewed, Saccharide Isomerate has the highest molecular weight (MW; > 1.4 MDa).¹³ According to an industry source, the absence of acidic or basic properties, as well as strong electrophilic groups, in 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 such as proteins and polypeptides with activation of sensitization processes.¹⁴

Method of Manufacture

Methods of manufacture specific to cosmetics were neither found in the published literature, nor were such methods submitted as unpublished data. However, these ingredients are chemical entities known and utilized in other industries, and, general methods, not specific to the cosmetics industry, are thus known. Such are described below.

Anhydrogalactose

Anhydrogalactose may be prepared by enzymatic saccharification of agar, using a combination of agarolytic enzymes.¹⁵ 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.¹⁶

Anhydroglucitol

A single-enzyme process for the production of Anhydroglucitol has been designed.¹⁷ The process involves the acid pre-hydrolysis of agarose into agarobiose and the enzymatic hydrolysis of agarobiose into Anhydroglucitol and galactose.

Arabinose

Arabinose is produced by catalytic decarboxylation of D-gluconic acid, sodium salt.¹⁸ 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.¹⁹ Details relating to this process were not provided. According to another source, Psicose has been produced from fructose using the enzyme tagatose 3-epimerase.²⁰

Saccharide Isomerate

According to a supplier of this ingredient, Saccharide Isomerate (plant-derived) 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.²¹ 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

Composition and impurities data specific to cosmetics were neither found in the publicly available literature, nor were such methods submitted as unpublished data. However, these ingredients are chemical entities known and utilized in other industries, and, general composition/impurities profiles, not specific to the cosmetics industry, are thus known. Such are described below.

Saccharide Hydrolysate

According to the *Food Chemicals Codex* description, invert sugar 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 invert sugar are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of invert sugar. Other acceptance criteria for invert sugar 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

According to a supplier of this ingredient, Saccharide Isomerate also contains water, citric acid, and sodium citrate.²¹ 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).²² Of the saccharide humectants 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).²³ These are the highest use concentrations in rinse-off and leave-on products reported for the saccharide humectants 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 saccharide humectants 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 saccharide humectants 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.²⁴ 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 saccharide humectants 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 invert sugar 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).

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).

Saccharide Isomerate

A statement from a supplier of this ingredient indicates that dermal absorption studies were not performed because, other than Saccharide Isomerate (a mixture), it contains water, citric acid, and sodium citrate.²¹ According to another source, Saccharide Isomerate 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) $\mu\text{mol/l}$, 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 $\mu\text{mol/l}$) 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 $\mu\text{mol/l}$. Data from this study relating to toxicity are included in the Short-Term Oral Toxicity section of this report.

Psicose

U-[¹⁴C]Psicose (2 μCi) was administered by stomach tube to rats (number and strain not stated).³⁵ Of the exhaled [¹⁴C]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-[¹⁴C]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-[¹⁴C]Psicose is suggestive of easy passage through 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 [¹⁴C]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-[¹⁴C]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 [¹⁴C]Psicose was studied using 30 male Wistar rats.³⁶ All of the rats were fasted for 24 h. Approximately 0.6 ml of [¹⁴C]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. [¹⁴C]Psicose entered the blood after oral dosing, and the maximum blood concentration ($48.5 \pm 15.6 \mu\text{g/g}$) was observed at 1 h. Urinary excretion was 20% within 1 h and 33% within 2 h. The values for radioactivity (from administered [¹⁴C]Psicose) in the liver were 41.4 ± 28.7 , 126.3 ± 45.0 , 200 ± 86.3 , and $127.5 \pm 32.6 \mu\text{g/g}$ 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 [¹⁴C]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 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$. Amounts of Anhydroglucitol detected in the following organs were as follows: diabetic kidney (1.5 and 2.6 $\mu\text{g/ml}$), liver (0.8 and 1.6 $\mu\text{g/ml}$), spleen (1.4 and 1.6 $\mu\text{g/ml}$), skin (0.5 and 1.1 $\mu\text{g/ml}$), and brain (< 0.5 $\mu\text{g/ml}$). 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 $\mu\text{g/ml}$ and 9.0 $\mu\text{g/ml}$ 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 $\mu\text{g/g}$ and 4.4 $\mu\text{g/g}$ 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 [¹⁴C]Psicose was studied using 30 male Wistar rats.³⁶ All of the rats were fasted for 24 h. Approximately 0.6 ml of [¹⁴C]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 [¹⁴C]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 [¹⁴C]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 [¹⁴C]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 [¹⁴C]Psicose was absorbed and eliminated rapidly.

U-[¹⁴C]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 [¹⁴C]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-[¹⁴C]Psicose. Liver glycogen contained 1% of the radioactivity, and only 0.6% of the radioactivity was exhaled as [¹⁴C]carbon dioxide. The authors noted that these results indicate that i.v.-administered U-[¹⁴C]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 $\mu\text{g/ml}$.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 per day. The mean Anhydroglucitol excretion in the urine was ~ 4.76 mg per day. 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 raffinose, 0.05% of ingested lactose, and 17.5% of ingested 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, $63.3 \pm 4.1\%$ (mean + standard deviation) of administered L-arabinose was excreted in the urine. Within 12 h, $73.1 \pm 4.5\%$ 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 LD₅₀ 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 LD₅₀ was > 2 g/kg. In an acute oral toxicity study on Arabinose, the LD₅₀ 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 LD₅₀ 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 was evaluated (animal species not stated) in accordance with OECD TG 401.²¹ An LD₅₀ 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 up to 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 (2.0 ± 0.2 g) or mean liver weight (12.7 ± 0.7 g) 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 disposition. 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. 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.⁴⁶ 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 saccharide humectants 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 was evaluated for genotoxicity in the Ames test (according to OECD TG 471).²¹ The test substance was classified as non-genotoxic. The genotoxicity of a Saccharide Isomerate and aqua 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 μ l/plate). Results were classified as negative. A Saccharide Isomerate and aqua 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 to 5000 μ g/plate) was neither mutagenic nor pro-mutagenic with or without metabolic activation. In the same assay, a Saccharide Isomerate and aqua 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 aqua 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 was also classified as non-genotoxic in the micronucleus test (according to OECD TG 487).²¹

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 $\mu\text{g/ml}$ during the 2-h incubation period.⁷ The MTT assay was also used to evaluate the cytotoxicity of Anhydrogalactose and D-anhydrogalactose using B16F10 mouse melanoma cells and RAW264.7 cells (mouse macrophages).¹⁶ The cells were treated for 24 h with concentrations up to 100 $\mu\text{g/ml}$ (B16F10 cells) and up to 200 $\mu\text{g/ml}$ (RAW264.7 cells). There was no statistically significant inhibition of growth of either cell type at the concentrations of Anhydrogalactose and 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 $\mu\text{g/ml}$) 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.¹⁶ 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 $\mu\text{g/ml}$. Arbutin (up to 100 $\mu\text{g/ml}$) served as the positive control. The extracellular melanin concentration of melanoma cells treated with 100 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ 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 B16F10 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).¹⁶ 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, 10², 10³, 10⁴, and 10⁵-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 10⁴ or 10⁵ dilution. In contrast, *S. mutans* colonies were formed on a minimal agar plate inoculated with bacterial dilutions of either 10⁴ or 10⁵, 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 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/cm²/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 cm² 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 was evaluated (animal species not stated) according to OECD TG 404.²¹ 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) was also evaluated for skin irritation potential in a repeated application test involving guinea pigs (strain not stated).²¹ 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) in human subjects (number not stated).²¹ 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 aqua 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 aqua 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 aqua 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 aqua trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic 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 was performed in accordance with OECD TG 406.²¹ 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.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 aqua 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 aqua 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 aqua 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 aqua trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic 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

Animal

Saccharide Isomerate

The photosensitization/phototoxicity potential of Saccharide Isomerate (20% v/v) was evaluated using guinea pigs (number and strain not stated).²¹ Details relating to the test protocol are not included in this study summary. Neither photosensitization nor phototoxicity was observed in this study.

Human

Saccharide Isomerate

The phototoxicity of a Saccharide Isomerate and aqua trade name material (MW > 1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA) was evaluated in an in vitro assay (OECD TG n°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.

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% Anhydroxylytol (and undeclared percentages of xylytol 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) was evaluated for ocular irritation potential in accordance with OECD TG 405.²¹ 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 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.^{19,53} 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, invert sugar (also known as 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 saccharide humectants as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, all 7 saccharide humectants are reported to function as skin-conditioning agents – humectant in cosmetics. Anhydrogalactose is also reported to function as an antioxidant, and Anhydroglucitol functions as an oral care agent.

In the *Food Chemicals Codex* description, invert sugar (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 invert sugar are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of invert sugar. Other acceptance criteria for invert sugar 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 saccharide humectants 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 saccharide humectants that are 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 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 [¹⁴C]Psicose was studied using male rats and male mice. [¹⁴C]Psicose was absorbed well after oral dosing, and eliminated rapidly after both oral and i.v. administration. In another oral dosing study, U-[¹⁴C]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 LD₅₀ 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 LD₅₀ 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. LD₅₀ 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 LD₅₀ 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 LD₅₀ of > 2 g/kg was reported for undiluted Saccharide Isomerate 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 (2.0 ± 0.2 g) 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 disposition. 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 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 aqua 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 aqua 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 aqua trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) at doses up 5000 µg/plate; and Saccharide Isomerate and aqua 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 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. An HRIPT involving 213 subjects was used to evaluate the skin irritation and sensitization potential of an eye cream containing 2.75% Saccharide Isomerate. The product did not have dermal irritation or sensitization potential in this study.

Saccharide Isomerate 20% (v/v) was evaluated for skin irritation potential (animal species not stated), and was classified as non-irritating and non-corrosive. Saccharide Isomerate (20% v/v) 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) was non-irritating and non-corrosive to the skin. A Saccharide Isomerate and aqua 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 aqua 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 aqua 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 aqua 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. The skin sensitization potential of a Saccharide Isomerate and aqua 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 aqua 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 aqua 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 evaluating the skin sensitization potential of a Saccharide Isomerate and aqua 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) in guinea pigs (number not stated). The phototoxicity of a Saccharide Isomerate and aqua 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 was evaluated using 53 female subjects. The eye cream did not have the potential for causing ocular irritation. Saccharide Isomerate (20% v/v) was practically non-irritating to 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.

DRAFT DISCUSSION

Anti-melanogenic activity of Anhydrogalactose in B16F10 melanoma cells and human epidermal melanocytes was observed in in vitro experiments. However, the Panel noted that in vitro data may identify a hazard, but the risk cannot be determined in the absence of in vivo data. Concern about anti-melanogenic activity was mitigated by the high exposure concentration and uncertainty as to whether the model used is actually predictive of in vivo effects. 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 saccharide humectants. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

CONCLUSION

To be determined.

TABLES**Table 1.** Definitions, structures, and reported functions^{1, CIR Staff}

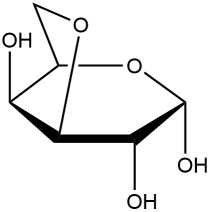
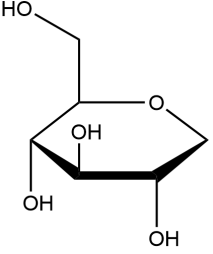
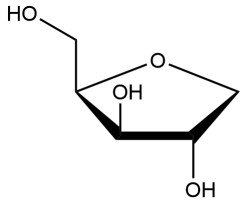
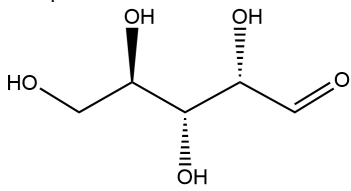
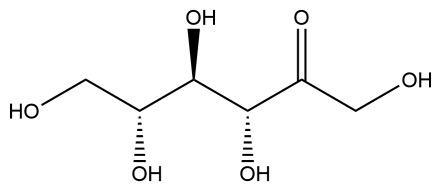
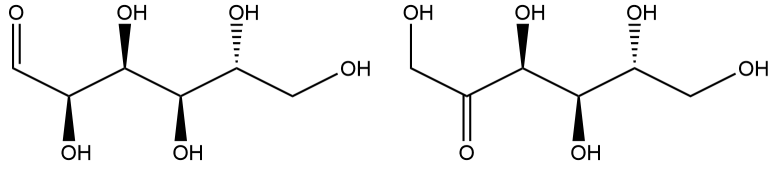
Ingredient CAS No.	Definition	Function(s)
Anhydrogalactose 28251-55-0	Anhydrogalactose is the organic compound that conforms to the structure: 	Antioxidants; Humectants; Skin-Conditioning Agents - Humectant
Anhydroglucitol 154-58-5	Anhydroglucitol is the organic compound that conforms to the structure: 	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 20°C)	1.435	3
Melting point (°C)	< 50	3
Boiling point (°C at 760 mmHg)	315	3
Vapor pressure (mmHg at 25°C)	2.7 x 10 ⁻⁶	3
Water solubility (g/l at 20°C)	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 (°C)	96	8
Solubility (% w/w at 25°C; 50 °C)	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

Table 3. Frequency (2021) and concentration (2018) of use according to duration and type of exposure.^{22,23}

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Anhydroglucitol		Anhydroxytilol		Saccharide Hydrolysate	
Totals*/Conc. Range	NR	0.17-1	153	0.0028-0.88	33	0.002-4.6
Duration of Use						
<i>Leave-On</i>	NR	0.33-1	123	0.28-0.88	32	0.002
<i>Rinse off</i>	NR	0.28	30	0.0028	1	4.6
<i>Diluted for (bath) Use</i>	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 ^a ;46 ^b	0.88 ^a	10 ^a ; 6 ^b	NR
Incidental Inhalation- Powders	NR	0.9 ^c	46 ^b	0.88 ^c	6 ^b ;10 ^c	0.002 ^c
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						
<i>Leave-On</i>	302	0.001-2.8				
<i>Rinse off</i>	50	0.01-0.7				
<i>Diluted for (bath) Use</i>	NR	NR				
Exposure Type						
Eye Area	13	1				
Incidental Ingestion	NR	NR				
Incidental Inhalation- Sprays	55 ^a ;46 ^b	0.01 ^a				
Incidental Inhalation- Powders	46 ^b	0.02-2.8 ^c				
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 sprays, but it is not specified whether the reported uses are sprays^b Not specified these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories^c It is possible that these products may be powders, but it is not specified whether the reported uses are powders

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-doral 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 disposition. 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. Also, there was no cumulative effect of test substance dosing on glucose metabolism, and there were not statistically significant differences in the following between test and control groups: liver enzymes, renal function markers, and electrolytes. The mild increase in plasma alkaline phosphatase was not considered suggestive of Psicose toxicity. The authors concluded that dosing with Psicose did not cause any harmful effects in dogs.	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	Undiluted (doses not stated)	Not stated	Ames test (OECD TG 471). Bacterial strains not stated.	Details relating to test protocol not included	Non-genotoxic	²¹
Saccharide Isomerate and aqua 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 aqua 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 <i>Salmonella typhimurium</i> strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	¹³
Saccharide Isomerate and aqua 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 <i>Salmonella typhimurium</i> strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	¹³
Saccharide Isomerate and aqua 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 <i>Salmonella typhimurium</i> strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	¹³
Saccharide Isomerate	Undiluted (doses not stated)	Not stated	Micronucleus test (OECD TG 487). Cell type not stated	Details relating to test protocol not included	Non-genotoxic	²¹
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	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.	21
Saccharide Isomerate	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	21
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%)	Guinea pigs (number and strain not stated);	Maximization test (OECD TG 406). Details relating to test protocol not included	Non-sensitizer	3
Saccharide Isomerate	20% (v/v)	Number of animals and species not stated	Maximization test (OECD TG 406). Details relating to test protocol not included.	Non-sensitizer	21
HUMAN					
Irritation					
Saccharide Isomerate	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	21
Saccharide Isomerate and aqua 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 aqua 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 aqua 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 aqua trade name material (MW > 1.4 MDa; Osidic composition: galactose-N-acetylglucuronic acid (GuINAcA)/3-acetylated N-acetylglucuronic 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 aqua trade name material (MW > 1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-N-acetylglucosamine) was evaluated using 100 subjects	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 aqua 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 aqua 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 aqua 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	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	²¹
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
Eyeliners	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



Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: November 20, 2020

SUBJECT: Arabinose

Anonymous. 2020. Method of manufacture: D-Arabinose.

KiaLab. 2015. Toxicological Information D-Arabinose.

November 2020

Method of Manufacture: D-Arabinose

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



Toxicological information D-Arabinose

September 9th, 2015

Product: D-Arabinose

CAS No. 10323-20-3

The potential acute toxicity of D-Arabinose is limited because it is a natural monosaccharide present in animals and humans. The chemical-physical properties of D-Arabinose suggest limited skin and systemic toxicity. 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) (references 1, 2).

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 with development of irritation and the formation of covalent bonds with critical tissue components such as proteins and polypeptides with activation of sensitization processes. This statement is supported by the evidence of the human skin compatibility with monosaccharides similar in structure and/or chemical-physical properties (molecular weight, log P and ability to form hydrogen bonds) such as rhamnose (leave-on formulation containing 10%), mannose (leave-on facial product containing 5%) and glucose (leave-in hair product containing 8%), which did not record irritant and allergenic effects (references 3-7). In this regard, recent studies do not report cases of skin sensitization reactions mediated by D-Arabinose (references 8, 9).

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Toxicological information D-Arabinose

September 9th, 2015





Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: November 30, 2020

SUBJECT: Saccharide Isomerate

DSM Nutritional Products, Ltd. 2020. CIR call for data for " Safety Assessment of Saccharide Humectants as Used in Cosmetics" - 2020 (November 30, 2020 memo).



To
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Date
November 30, 2020

To
Carol Eisenmann, Ph.D.

From
Dalida Chouchi
Global Regulatory Affairs Manager
Personal Care and Aroma Chemicals
phone +41 79 343 9032
email : Dalida.chouchi@dsm.com

Subject

CIR call for data for "Safety Assessment of Saccharide Humectants as Used in Cosmetics" -
2020

Dear Mrs. Carol Eisenmann, Ph.D.

Following our conversation (8th October 2020) and the recent exchange, regarding the call for data requested by the Expert Panel for Cosmetic Ingredient Safety: "Safety Assessment of Saccharide Humectants as Used in Cosmetics", specifically saccharide isomerate, DSM Nutritional Products would like to inform PCPC and the CIR expert panel that despite business trade secret concerns, DSM would like to share the following information, which supports the safety of PENTAVITIN® (Saccharide isomerate).

Background information:

Saccharide isomerate (CAS 100843-69-4) is a carbohydrate complex formed from a base catalyzed rearrangement of mixture of saccharides.

Saccharide isomerate is manufactured by DSM Nutritional Products. It has been used safely in personal care applications for decades under the trade name PENTAVITIN®.

PENTAVITIN®

Composition & manufacturing process, use level:

Saccharide isomerate is manufactured by DSM Nutritional Products under the tradename PENTAVITIN®. It is 100% natural and plant derived. The saccharide isomerate is formed by a base catalyzed isomerisation of plant derived D-glucose of Kernel Corn and is similar to that of the carbohydrate complex found in human skin.

PENTAVITIN® consists beside water, citric acid, and sodium citrate only of saccharide isomerate. Saccharide isomerate is a mixture of mono and disaccharides mainly glucose (CAS: 50-99-7) and fructose (57-48-7).

PENTAVITIN® is ECOCERT and COSMOS approved, as well as NATRUE certified.

PENTAVITIN® has a low order of toxicology concern and is non-sensitizing. The carbohydrate complex of PENTAVITIN® mimics the NMF, the skin's own moisturizer, compatibility is assured.

PENTAVITIN® imparts its moisture attracting properties by binding to the ε-amino acid group of the lysine portion of keratin. These conferred capacities cannot be washed out and PENTAVITIN® loss occurs only by the natural process of exfoliation. Molecular weight ranges from 120- 400 Daltons and the recommended use level is up to 5% for leave-on and rinse-off products.

Impurities:

We hereby confirm that we produce PENTAVITIN® without using solvents, and therefore PENTAVITIN® does not contain residual solvents from our manufacturing process.

Exposure:

According to 2019 VCRP data, saccharide isomerate is reported to be used in 455 cosmetic products (406 leave-on products and 49 rinse-off products) saccharide isomerate is being used at maximum use concentration of up to 2.8% in leave-on products.

Saccharide isomerate is listed in *the list of additive for Quasi-drugs* (notification number MHLW0327004, March 27, 2008) and *The Japanese Standards of Quasi-drug Ingredients (JSQI)*.

Safety data overview:

PENTAVITIN® consists beside water, citric acid, and sodium citrate only of saccharide isomerate. Saccharide isomerate is a mixture of mono and disaccharides mainly glucose (CAS: 50-99-7) and fructose (57-48-7).

The CIR Expert Panel (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 (CIR 2014).

PENTAVITIN® is derived from sugars of Kernel Corn, with a long history safe use as a food ingredient.

The following studies were performed with PENTAVITIN®: please see Safety Data Overview by Dr. Stefan Kaiser (Toxicologist)

- Acute oral toxicity (limit test), OECD 401
- Acute dermal irritation test, OECD 404
- Repeat application dermal irritation study in guinea pigs
- Occlusive patch test (human study)
- Acute eye irritation test, OECD 405
- Skin sensitization Study, OECD 406
- Ames test, OECD 471
- *In vitro* micronucleus test, OECD 487
- Photosensitization/phototoxicity study in guinea pigs

Conclusion:

We demonstrate the safe use level of 5% by the studies mentioned above. They were all conducted with either pure PENTAVITIN® or at least 20% PENTAVITIN®.

Dermal absorption studies were not performed with PENTAVITIN®, because it consists beside water, citric acid, and sodium citrate, only of saccharide isomerate. Saccharide isomerate is a mixture of mono and disaccharides mainly glucose and fructose. Even if fructose and glucose would penetrate by 100% through the skin, there would be no safety concern, because they are both not toxic at the levels which would reach the systemic circulation. Citric acid and sodium citrate were assessed by the CIR and considered safe at the levels used in PENTAVITIN® (Fiume et al. 2014).

We hope that the information being provided is useful for demonstrating the safety of Saccharide isomerate (PENTAVITIN®).

References:

- Cosmetic Ingredient Review CIR (2014) Safety Assessment of Monosaccharides, Disaccharides, and Related Ingredients as Used in Cosmetics. Final report. Release Date 04 April 2014.
- DSM article: Happi June 2018 Urban Skin Hydration Is a Global Challenge (Dr Volker Rosenberg) p74-76.
- DSM Safety Data Overview for PENTAVITIN®. November 2020.
- Fiume MM, Heldreth BA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG, Shank RC, Slaga TJ, Snyder PW, Andersen FA (2014) Safety Assessment of Citric Acid, Inorganic Citric Salts, and Alkyl Citrate Esters as Used in Cosmetics. Int J Toxicol 33; Suppl 2:16S-46S.

Please contact the undersigned if there are any further questions.

Yours faithfully,
Dr. Dalida Chouchi
Global Regulatory Affairs Manager

PENTAVITIN®

Safety Data Overview

The following safety studies have been performed with PENTAVITIN®.:

Acute toxicity: Acute oral toxicity (limit test), OECD 401
Test Item: 100% PENTAVITIN®.
Result: LD50 > 2000 mg/kg bw

Skin irritation: a) Acute dermal irritation test, OECD 404
Test Item: 20% (v/v) PENTAVITIN®.
Result: non-irritant and non-corrosive to the skin

b) Repeat application dermal irritation study in guinea pigs
Test Item: 20% (v/v) PENTAVITIN®.
Result: non-irritant and non-corrosive to the skin

c) Occlusive patch test (human study)
Test Item: 20% (v/v) PENTAVITIN®.
Result: non-irritant and non-corrosive to the skin

Eye irritation: Acute eye irritation test, OECD 405
Test Item: 20% (v/v) PENTAVITIN®.
Result: practically non-irritant to eyes

Skin sensitization: Magnusson & Kligman Maximization Study, OECD 406
Test Item: 20% (v/v) PENTAVITIN®.
Result: non-sensitizing

Mutagenicity: Ames test, OECD 471
Test Item: 100% PENTAVITIN®.
Result: not mutagenic

Genotoxicity: *In vitro* micronucleus test, OECD 487
Test Item: 100% PENTAVITIN®.
Result: Not genotoxic

Phototoxicity: Photosensitization/phototoxicity study in guinea pigs
Test Item: 20% (v/v) PENTAVITIN®.
Result: not photosensitizing and not phototoxic

Kind regards



Dr. Stefan Kaiser
Sr. Toxicologist

Page 6 of 6

CIR call for data for "Safety Assessment of Saccharide Humectants as Used in Cosmetics" - 2020



Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: November 30, 2020

SUBJECT: Saccharide Isomerate

Anonymous. 2020. Summary information Saccharide Isomerate.

November 2020

Summary Information – Saccharide Isomerate

All four trade name materials under the INCI name Saccharide Isomerate have large molecular weights which would prevent dermal penetration.

None of the ingredients contain free glucose or fructose, and all the ingredients may have a low level (<10 ppm) of isopropanol

Ingredient	Method of Manufacture	Composition/ Molecular Weight	Dermal Irritation and Sensitization	Dermal Irritation	Genotoxicity	Phototoxicity
Trade name 1	Catalyzed rearrangement of a mixture of saccharides / purification	High molecular weight polysaccharide > 1,4M Da (eq Dextran) Osidic composition : Glucuronic acid- Mannose-Galactose- Galacturonic acid-N- acetylglucosamine	SACCHARIDE ISOMERATE (and) AQUA Evaluation of the sensitizing potential with HRIPT method This study was realized on 100 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non irritating, non sensitizing. MARZULLI-MAIBACH METHOD. Induction Phase: 3 times a week during 48 hours. Concentration test : 0.5-1.5% SACCHARIDE ISOMERATE	SACCHARIDE ISOMERATE (and) AQUA Evaluation of the cutaneous compatibility with occlusive patch test method 24 hours. This study was realized on 10 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non irritating. Concentration test : 0.5-1.5% SACCHARIDE ISOMERATE	SACCHARIDE ISOMERATE (and) AQUA Evaluation of the mutagenicity /genotoxicity with bacterial reverse mutation method The results obtained in the reserved experimental conditions allowed to conclude that the product is non mutagenic, non pro-mutagenic. The test was performed in accordance with OECD Guideline 471 (Ames test). Based on the results obtained in this study, it can be concluded that the test item does not induce point mutations or frame-shifts in the genome of the bacterial strains with or without metabolic activation regardless of the procedure.	

					Concentration tested: 0.06 -5.00 µL/plate, 0.5- 1.5% SACCHARIDE ISOMERATE	
Trade name 2	Catalyzed rearrangement of a mixture of saccharides / purification	High molecular weight polysaccharide > 1,4M Da (eq Dextran) Osidic composition : Rhamnose-Glucose-Galactose-Galacturonic acid-N-acetylglucosamine				
Trade name 2 mixed with water	Catalyzed rearrangement of a mixture of saccharides / purification, HTAC : Hydrothermolysis accelerated with CO2 supercritical (for mix with water)	High molecular weight polysaccharide 20000 Da (eq Dextran) Osidic composition: Rhamnose-Glucose-Galactose-Galacturonic acid-N-acetylglucosamine	SACCHARIDE ISOMERATE (and) AQUA Evaluation of the sensitizing potential with Marzulli-Maibach method . This study was realized on 102 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non irritating, non sensitizing. - During the induction period (3 weeks), the repeated applications of the product under occlusive patch, on a	SACCHARIDE ISOMERATE (and) AQUA Evaluation of the cutaneous compatibility with occlusive 48 hours patch test method - pure This study was realized on 11 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is not irritant. Concentration test : 0.5-1.5% SACCHARIDE ISOMERATE	SACCHARIDE ISOMERATE (and) AQUA Evaluation of the mutagenicity/genotoxicity with bacterial reverse mutation method. The results obtained in the reserved experimental conditions allowed to conclude that the product is non mutagenic, non pro-mutagenic. Ames test according to the OECD #471. The test was performed on five Salmonella typhimurium strains with and without metabolic activation. The test substance with the mixture contains 0.5-1.5% SACCHARIDE ISOMERATE was evaluated at	

			<p>panel of 102 test subjects with all types of skin on body, induced no reaction of irritation. Concentration test : 0.5-1.5% SACCHARIDE ISOMERATE</p>		<p>concentrations of 5000, 1600, 500, 160 and 50 µg/plate.</p>	
Trade name 3	<p>Catalyzed rearrangement of a mixture of saccharides / purification, HTAC : Hydrothermolysis accelerated with CO2 supercritical (for mix with water)</p>	<p>High molecular weight polysaccharide 15000 Da (eq Dextran) Osidic composition : Galacturonic acid-N-acetylglucosamine</p>	<p>SACCHARIDE ISOMERATE (and) AQUA Evaluation of the sensitizing potential with Marzulli-Maibach method This study was realized on 109 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non irritant and no allergic reaction was observed. - During the induction period (The applications had to be repeated 9 times to the same site over a period of 3 consecutive weeks,</p>	<p>SACCHARIDE ISOMERATE (and) AQUA EVALUATION OF THE ACUTE CUTANEOUS TOLERANCE OF A COSMETIC PRODUCT ON ADULT VOLUNTEERS: 24-HOUR OCCLUSIVE SINGLE PATCH TEST METHOD UNDER DERMATOLOGICAL CONTROL the product is classified NON IRRITATING. This study was realized on 10 volunteers. Concentration test : 0.5-1.5%</p>	<p>SACCHARIDE ISOMERATE (and) AQUA - Evaluation of the mutagenicity - OCDE 471 The results obtained in the reserved experimental conditions allowed to conclude that the product is non mutagenic, non pro-mutagenic. Ames test. The test was performed on five Salmonella typhimurium strains with and without metabolic activation. Concentration tested: 0.06 -5.00 µL/plate, 0.5-1.5% SACCHARIDE ISOMERATE.</p>	

			<p>period necessary to induce a possible allergy), the repeated applications of the product under occlusive patch, on a panel of 109 test subjects with all types of skin on body, induced no reaction of irritation.</p> <p>Concentration test : 0.9% SACCHARIDE ISOMERATE</p>	SACCHARIDE ISOMERATE		
Trade name 4	Catalyzed rearrangement of a mixture of saccharides / purification	<p>High molecular weight polysaccharide > 1,4M Da (eq Dextran)</p> <p>Osidic composition : Galactose - N-acetyl glucosamine - N-acetylguluronic acid (GulNAcA) / 3-Acetylated N-acetylguluronic acid (3OAc-GulNAcA)</p>	<p>SACCHARIDE ISOMERATE (and) AQUA Evaluation of the sensitizing potential with Marzulli-Maibach method. This study was realized on 52 volunteers (with 26 volunteers with sensitive skin). The results obtained in the reserved experimental conditions allowed to conclude that no significant reaction of contact allergy was observed. Induction period (The</p>	<p>SACCHARIDE ISOMERATE (and) AQUA - Evaluation of the cutaneous compatibility with occlusiv 48 hours patch test method This study was realized on 11 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non irritating. Concentration test : 0.5-1.5%</p>	<p>SACCHARIDE ISOMERATE (and) AQUA- Evaluation of the mutagenicity/genotoxicity with bacterial reverse mutation method. The results obtained in the reserved experimental conditions allowed to conclude that the product does not show any mutagenic nor pro-mutagenic activity. The test was performed in accordance with OECD Guideline 471 (Ames test). The test was performed on five Salmonella typhimurium strains with and without</p>	<p>ACCHARIDE ISOMERATE (and) AQUA - Evaluation of phototoxic potential with and without UVA according the OECD guideline n°432. The results obtained in the reserved experimental conditions allowed to conclude</p>

			<p>applications had to be repeated 9 times to the same site over a period of 3 consecutive weeks). Concentration test : 0.5-1.5% SACCHARIDE ISOMERATE</p>	<p>SACCHARIDE ISOMERATE</p>	<p>metabolic activation. The test substance with the mixture contains 0.5-1.5% SACCHARIDE ISOMERATE was evaluated at concentrations of 5000, 1600, 500, 160 and 50 µg/plate.</p>	<p>that the product is non phototoxic. The phototoxic potential of a test substance consisting of 0.5-1.5% saccharide isomerate. Cytotoxicity was evaluated with test substance at 8 concentrations (maximal concentration : 1000 µg/mL).</p>
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TO: Bart Heldreth Ph.D.
Executive Director – Cosmetic Ingredient Review

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: October 29, 2020

SUBJECT: CIR Report Title: Saccharide Humectants

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to comment on the CIR report, Safety Assessment of Saccharide Humectants as Used in Cosmetics.

As far as we are aware, this is the first time a function is being used in the title of a CIR report. We disagree with naming a report based on a function of the ingredients. In this case, some of the ingredients included in this report have functions in addition to humectant, e.g., antioxidant. Humectant is also not a function unique to just these saccharide ingredients as there are other saccharides, such as Sucrose and Fructose (previously reviewed by CIR), that also have humectant listed as a function that are not included in this report. Therefore, we do not consider that “Saccharide Humectants” adequately describes the ingredients in this report. To be consistent with other CIR reports, the title of this report should represent the structures of the ingredients included in the report.

We defer to Dr. Liebler and Dr. Peterson to modify the title of this report to better reflect the structures of the ingredients included in the report.