Safety Assessment of Mannitol, Sorbitol, and Xylitol as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	August 22, 2019
Panel Meeting Date:	September 16 – 17, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth. Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Priya Cherian
Scientific Writer/Analyst

Date: August 22, 2019

Subject: Draft Tentative Report on Mannitol, Sorbitol, and Xylitol

Enclosed is the Draft Tentative Report on the Safety Assessment of Mannitol, Sorbitol, and Xylitol as Used in Cosmetics (identified as *xylito092019rep* in the pdf document). At the April 2019 meeting, the Panel issued an insufficient data announcement for this ingredient group. The Panel requested phototoxicity data at leave-on use concentrations and irritation and sensitization data at maximum use concentrations. Since the April Panel meeting, the following unpublished data have been received:

1) A summary of a Magnusson Kligman assay using a trade name mixture containing 15% Mannitol and 15% disodium adenosine triphosphate; 0.5% (intracutaneous induction) and 10% (epicutaneous induction and challenge) aqueous dilutions of the trade name mixture were used (*xylito092019data1*)
2) A summary of a phototoxicity assay using a 10% aqueous dilution of a mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate (*xylito092019data1*)
3) A summary of a photosensitization test using a 2% aqueous dilution of a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate (*xylito092019data1*)
4) An HRIPT using a body lotion containing 3% Xylitol (*xylito092019data2)*

Comments on the draft report were submitted by the Council prior to the April meeting, and addressed (*xylito092019 pcpc1*). Also submitted by the Council are comments regarding the phototoxicity potential of Xylitol (*xylito092019pcpc2*). Xylitol

Other documents in this packet include FDA VCRP data (*xylito092019fda*), report history (*xylito092019hist*), flow chart (*xylito092019flow*), search strategy (*xylito092019strat*), minutes from the April 2019 meeting (*xylito092019min*), and an updated data profile (*xylito092019prof*).

After reviewing these documents, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or insufficient data conclusion. Additionally, Discussion items should be identified.

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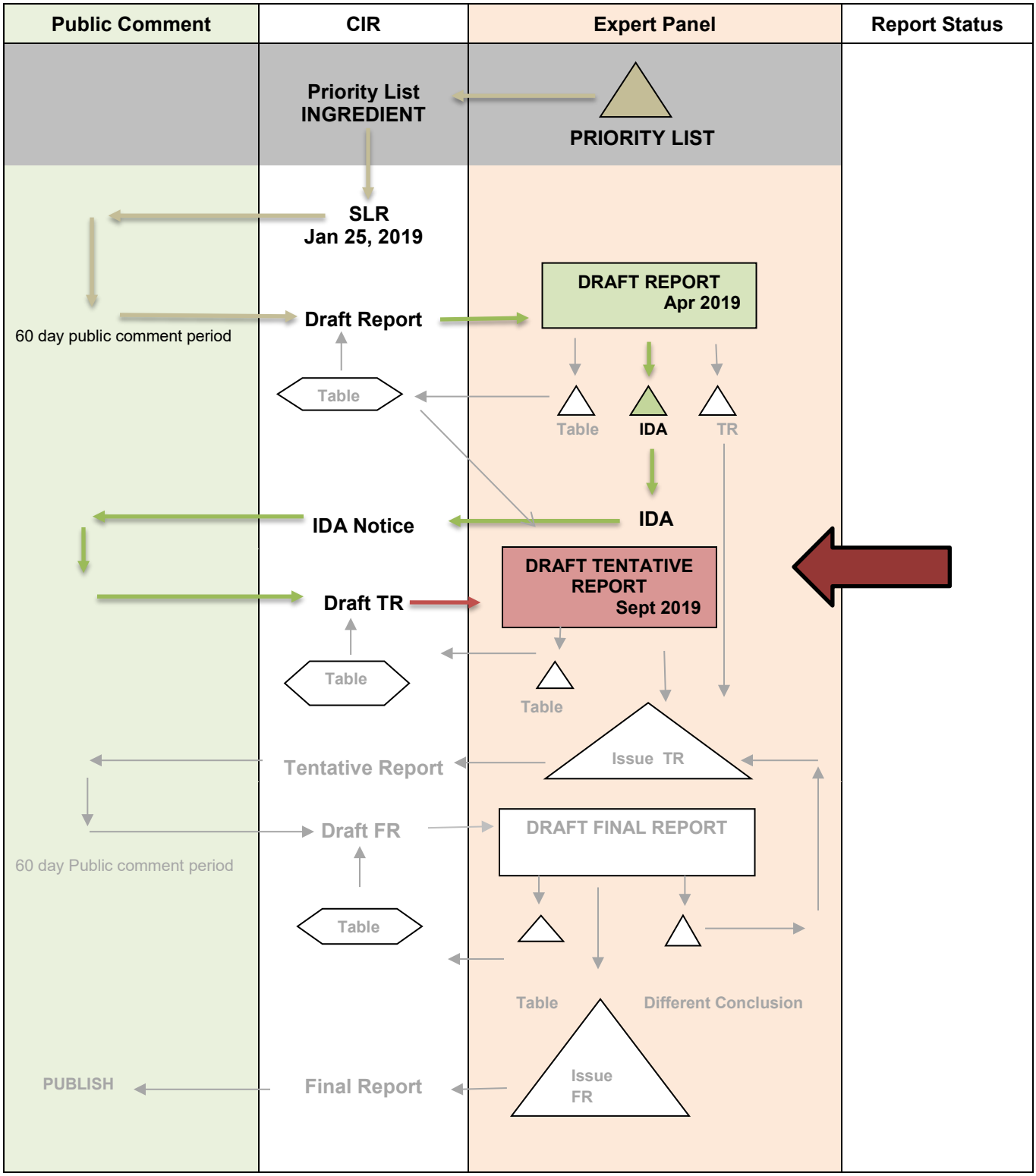
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Mannitol, Sorbitol, and Xylitol

MEETING September 2019



History of Mannitol, Sorbitol, and Xylitol

January 2019

SLR Posted

February 2019

Comments received from Council on SLR

March 2019

Comments received from Council on Draft report

April 2019

Draft report reviewed by the Panel

Issuing of an IDA – insufficiencies including irritation, sensitization, and phototoxicity data

May 2019

Data received from Council (HRIPT on Xylitol)

June 2019

Data received from Council (summary sensitization, phototoxicity, and photosensitization data)

September 2019

Panel reviews Draft Tentative Report

Mannitol, Sorbitol, and Xylitol Data Profile* – September 2019 – Writer, Priya Cherian

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	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
Mannitol	**X**	**X**	X	X	X	X		X	X		X	X		X	X			X					X	X	X			X	X
Sorbitol	**X**	**X**	X	X		X		X		X	X			X				X										X	
Xylitol	**X**	**X**	X	X		X		X	X		X	X		X	X			X		X				X	X			X	

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

[Hexa/Penta-Hydric Alcohols – September 2019 – Priya Cherian]

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Mannitol	69-65-8	x	x	x	x	x	x	x							x	x	x			x
Sorbitol	50-70-4	x	x	x	x	x	x	x							x	x	x			x
Xylitol	87-99-0	x	x	x	x	x	x	x							x	x	x			x

Search Strategy

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

Mannitol cosmetics (0/56) – PubMed
Mannitol toxicity (20/1052) – PubMed
Mannitol dermal (1/40) – PubMed
Mannitol cosmetic (1/76) – Pubmed
Mannitol metabolism
Mannitol cancer
69-65-8 (1/2) – pubmed
Mannitol toxicity (4/20) – Scifinder
Mannitol dermal (0/1) – Scifinder
Mannitol cosmetic (0/108) – Scifinder
69-65-8 (0/3)-SciFinder
Sorbitol Cosmetic (2/59)-pubmed
Sorbitol toxicity (5/1147)-pubmed
50-70-4 (0/1)-pubmed
Sorbitol dermal (0/38)-pubmed
Sorbitol metabolism (10/489)-pubmed
Sorbitol Cancer (0/1555)-pubmed
50-70-4 (0)-scifinder
Sorbitol Cosmetics (0/17)-scifinder
Sorbitol toxicity (1/9)-scifinder
Xylitol cosmetics (2/97) – pubmed
Xylitol toxicity (15/103)-pubmed
Xylitol metabolism-pubmed
Xylitol dermal (1/1) – pubmed
Xylitol toxicity (5/33)- scifinder
87-99-0

All terms also searched in google

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Xylitol, Mannitol, and Sorbitol Minutes

April 2019

Day 1 – Dr. Belsito's Team

DR. BELSITO: So the first question, Dan, do you like the name of this report?

DR. LIEBLER: No, I mean, it --

DR. BELSITO: I didn't think you would.

DR. LIEBLER: You know, I would've preferred it simply -- there are three ingredients -- to simply say, "A safety Assessment of Mannitol, Sorbitol and Xylitol." I did look. This is an established term for this class of molecules. It wasn't kind of made up or anything. But I think it's clearer to just name the ingredients, since there are only three.

DR. KLAASSEN: I agree with that.

DR. BELSITO: Okay. So I've just been looking at the document. I said, you know, you could really say insufficient for sensitization, irritation, and concentration of use, but I said, do I really need it? And there are no case reports that I'm aware of. And I didn't really think I needed it, but I just wanted to point out the fact that these are used, and we don't have sensitization or irritation data at levels they're used at.

DR. LIEBLER: Well, that was my only data need, sensitization at concentration of use; but I always have an asterisk on that, waiting to hear what you and Jim and Wilma think. If you feel we can justify not having explicit sensitization data at concentration of use, then I would be supportive. I thought our data needs, otherwise, were met, since it's a pretty good package.

DR. BELSITO: Yeah. I have actually tested for Xylitol because it's in a lot of toothpaste, and you wonder about it as causing cheilitis, off the top of my head. I don't know what the test concentration is, but I've never seen a positive response. There are absolutely no case reports of these causing any issues. I don't personally think we need it. Let's hear what the Marks team thinks.

DR. SNYDER: Yeah. Safe as used.

DR. BELSITO: Yeah.

DR. SNYDER: So on the organization --

DR. KLAASSEN: It was so nice it was three chemicals.

DR. SNYDER: On the organization --

DR. BELSITO: What?

DR. KLAASSEN: I said this report was nice that it was three chemicals.

DR. BELSITO: Yes.

DR. KLAASSEN: And we actually knew what the structures of the chemicals were.

DR. SNYDER: On the organization on the report on page 15, under developmental and reproductive toxicity, you list the specific alcohol, Mannitol, Sorbitol and then you follow with the studies?

MS. CHERIAN: Okay.

DR. SNYDER: If you could do that for the rest of the tox, under the chronic, have the oral heading and then have whether it's Mannitol, Sorbitol.

MS. CHERIAN: Sure.

DR. SNYDER: Use the same -- that's pretty easy then to follow to the see where things go. Just a little bit of reorganization. Does that make sense, Priya?

MS. CHERIAN: Yes.

DR. SNYDER: Right. Okay.

DR. BELSITO: Okay, anything else on these?

DR. LIEBLER: No. Looks good.

DR. BELSITO: Okay. So then we're moving down to titanium complexes.

Day 1 – Dr. Marks' Team

DR. MARKS: Okay. Well, let's move on to the next ingredients. It's going to be interesting, whether we use the same. I like Priya to compose that table. It's really a nice -- after our initial blush.

Priya, you're up again. You sent us a memorandum in March 15th of this year. Draft Report on a Hexa/Penta-Hydric Alcohols. It's a draft report on Mannitol, Sorbitol, and Xylitol. So, it means it's the first time we've seen these ingredients. As I usually do, Tom and Ron, do you like these 3 ingredients in this family?

DR. SLAGA: Yes.

DR. MARKS: Okay. And then I will read Ron Shank's comments for these. No additional systemic toxic data -- "tox" he used, not toxic -- tox data are needed for these ingredients, which are also food additives. 10 percent Xylitol was positive for phototoxicity. We need more information on this study. All three sugars are used in indoor tanning preparation, suntan preparations. Need HRIP for Mannitol at 60 percent. This

can be used for read across for Sorbitol and Xylitol.

We have no sensitization data. As Ron mentioned, Xylitol is phototoxic at 10 percent, so I felt we needed -- I want to see sensitization data and phototox data at leave-on concentrations for Mannitol, Sorbitol, and I guess we don't have a concentration on Xylitol. Mannitol was 60 percent -- no, I'm sorry. 20 percent for Sorbitol, 2 percent for Xylitol. I'd like to see phototox that does concentrations and HRIPT. Tom, Ron, your comments? Are you okay with systemic tox?

DR. SLAGA: Yeah.

DR. MARKS: And Ron, are you okay?

DR. SLAGA: The only problem is with sensitivity data and phototox.

DR. MARKS: Yeah. So, we would issue an insufficient data announcement tomorrow. I think we'll be seconding that; I'm sure we will, since we didn't -- I don't think I'm missing a Wave 3, am I? No, I think that we're done Wave 3s now.

DR. HILL: I had a few things, and a couple of them are just for discussion. I wrote, with the information given, I didn't think we could draw any conclusions from the DART study for Mannitol.

DR. MARKS: You didn't think we could? Because there's a -- we have DART and oral for Mannitol. That wasn't adequate?

DR. HILL: Why did I not like that? Hang on, I'm sorry. I didn't write on these notes why I didn't like it. I'm hoping I put something more in the report itself, which is -- where is that? Where is that in the report? It's not that there's any structural hits. Let's see. Yeah, I know why. Because I doubt that these really hydrophilic sugars could get into bone to do anything.

DR. MARKS: So, is that -- if they can't get in, are you saying --

DR. HILL: But that was my lack of thorough -- I think I put this down to be sure to raise a question with the toxicologists that are used to looking at this micronucleus test. So, obviously, marrow is vascularized. So, the question is, do this very hydrophilic sugars have access? And there's a reason I ask that, because -- no, this is DART. I'm sorry. I'm looking at the wrong -- my bad. Let me try again. Where is the DART? Okay, here we go.

DR. MARKS: So I think Ron Shank's --

DR. HILL: Method of administration was not specified.

DR. MARKS: I think Ron Shank felt, the systemic tox, nothing additional was needed because these are food additives. So, I think that's probably the reasoning he didn't feel any further tox studies were needed. We actually got a fair amount, when you look across there. And that's, of course, why he said no additional.

DR. HILL: Yeah. You're right. We've got -- okay. I, somehow, took this out of context. We've got 27 amongst Mannitol, 17 amongst -- something about the DART bothered me at the time when I read it. I think it was just method administration not specified, except it says oral, so I don't think that's a problem. Yeah. Lack of detail that was given, I think that was all.

DR. MARKS: Okay.

DR. HILL: But Xylitol genotoxicity, what I wanted to inquire about is whether we know if the Ames tests have metabolic activation or not, and there's a reason I ask that. That was where the micronucleus question came up, because I don't know; do these sugars have access enough to the bone marrow to make sure that that test endpoint is valid for these compounds?

DR. MARKS: Tom, your comment about that?

DR. SLAGA: I didn't have any concern with that.

DR. MARKS: Okay.

DR. HILL: And I also wrote, under the needs section, there was only one study ever in Sprague-Dawley rats at one elevated dose for Sorbitol. Is that -- but yet, they have a very liberal allowance in the Code of Federal Regulations, as overviewed on page 11. Are we missing, somehow, some very significant bodies of study for Sorbitol?

It seems like there must have been a lot of information reviewed where the allowances ended up in the CFR to be that liberal. I mean, Sorbitol's been out there on the market for -- I think I remember when it came along in the early, mid-60s-ish.

DR. MARKS: So, I think, Ron Hill, maybe tomorrow, if you want to synthesize that in a couple points when Wilma asks for discussion points, I can't imagine we're going to get past an IDA, insufficient data announcement, tomorrow because the sensitization datas, for sure, we need. And the phototox data, too, we need. And that can come up as a discussion and see how we feel. We're going to get another look at it, obviously.

DR. SLAGA: Right.

DR. HILL: The reason I ask about Ames in particular is, if you look at the structure of these molecules, there's no reason to think that there should be genotoxicity, unless you have aldehyde oxidation to aldehyde at both ends, so that you could get crosslinking. So, if you didn't do the testing with metabolic activation, I'm not sure you had that answer. But I think it's okay.

DR. SLAGA: I have no concern for genotox.

DR. HILL: Yeah. There's no hits.

DR. SLAGA: I mean, it, obviously, could be metabolized. But to have those metabolized at both ends, I'm not sure.

DR. HILL: Okay. And this is a chemistry question that's relayed back, partly for the dictionary. I think the definition of hydric as pertains to chemistry is of or relating to hydrogen, so that -- does Hexa -- I wanted to rename this group, but it looks like it was drawn from the dictionary names and I don't think those are right. But that's not really a safety assessment; that's semantics.

DR. MARKS: Yeah. Monice, do you want to address that, or Bart should? Bart's the chemist.

MS. FIUME: That would be a Bart question.

DR. HILL: Well, it's that way in the dictionary. They're listed that way. And I think that's probably where it came from. But the dictionary needs to be fixed if that's the case, which it appears to be.

DR. MARKS: Hm. Well, let's bring that up tomorrow also. Okay. Any other comments? Unless, Carol or Alex, do you want to mention about the dictionary? Monice? No? So, let's ask Bart tomorrow and then get his input from a semantic point of view, because you certainly don't want to have a title of a report which is chemically incorrect. Okay. There are no other comments? We'll move on to the next set of ingredients, the titanium complexes.

Day 2 – Group

DR. BELSITO: This is the first time that we're looking at this. And the first comment is that we thought the title was not necessary. It's just three ingredients and we should just list them.

And we thought that it was insufficient for sensitization and irritation at use concentration, possibly. There are really no reports out there. We don't have the data. Quite honestly, I think that we haven't seen issues with these and could go ahead with a safe as used, but just wanted to raise that, that there is not data to support sensitization and irritation.

DR. BERGFELD: So, repeat what you're doing. You're going to go safe, or are you going to go insufficient?

DR. BELSITO: Right at this point, we're just looking at it insufficient for sensitization and irritation.

DR. BERGFELD: Okay.

DR. MARKS: We second that. And the only other need was xylitol is phototoxic at 10 percent. So we wanted to see phototoxicity data on leave-on concentrations.

DR. BERGFELD: Is that agreeable?

DR. BELSITO: That's fine.

Dr. BERGFELD: Any other comments? So moved and seconded.

DR. HILL: I just had a question for the toxicologists, have opportunity, Dr. Shank wasn't here yesterday. When you do the bone marrow assay, is that the sister chromatic exchange? Does -- no, it's the micronucleus test, I'm sorry, had a moment. Is it a valid assay for that compound? Do you get enough penetration through blood flow to bone marrow to be sure that you're getting good answers with these very hydrophilic compounds?

And the reason I ask is the only conceivable way I can see these causing any issue is if both ends were simultaneously oxidized to aldehyde, so you could crosslink something, which doesn't seem at all probable.

But I just wondered if small, very hydrophilic compounds can penetrate enough into bone marrow to cause the micronucleus results to enlighten. Or if not, somebody could look and somebody could send me an email with the answer to that, because I don't know.

DR. KLAASSEN: I've never heard of that being a concern.

DR. HILL: Me neither. Me neither. I mean, obviously there has to be blood flow to bone

marrow. I just wondered.

DR. KLAASSEN: Yeah.

DR. SADRIEH: Blood comes from bone marrow.

DR. HILL: Well, no, I'm not talking about cell synthesis. I'm talking about -- and you're right, but that's not an end, so --

DR. BERGFELD: Tom, you have a comment on that?

DR. SLAGA: No, I just assume it does, because it gets used a lot. Yeah, I don't have any concern. The tests are used a lot, and there are both positive and negative results from many different types of compounds. So I never had a concern if it was being absorbed.

DR. KLAASSEN: Yeah, it's a very popular -- as most of you know, most of the mutagenicity type studies are in vitro. And this is an in vivo test. So therefore, it's used quite a bit because we don't have very many in vitro mutagenicity studies.

DR. HILL: Part of the reason I asked for that is -- not that I have a concern, again -- is that I can't tell was there metabolic activation on the xylitol study with the Ames testing, because it doesn't say.

And the other thing that I just asked was a data request. I only see one systemic study ever, for sorbitol in Sprague Dawley rats. And I feel like there must be a lot of other data out there somewhere that we're not somehow capturing, given that there are limits set by the Code of Federal Regulations, that had to have been set based on something.

DR. BERGFELD: Do you want to make that an official request?

DR. HILL: Yeah, but it's really a writer's request or a data mining request; just to see, there's got to be other information out there and somehow we didn't capture it.

DR. BERGFELD: Thank you. Have we fielded all the questions, then?

DR. BELSITO: Yes.

DR. BERGFELD: Seeing what we have, I'll call the question. All those in favor than in moving forward with an insufficient data announcement? Thank you. Unanimous.

And coming on to our last ingredient, Dr. Marks, which is Palm.

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The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth. Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of Xylitol, Mannitol, and Sorbitol. These ingredients are reported to function as humectants, skin-conditioning agents, or flavoring agents. The Panel considered the available data and concluded that … [to be determined].

INTRODUCTION

This is a safety assessment of Mannitol, Sorbitol, and Xylitol as used in cosmetic formulations. These 3 ingredients are all simple sugar alcohols and are in that way, structurally similar to one another; therefore, they are being reviewed together in this assessment. Each has several functions listed in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), but all three are reported to function as humectants, skin-conditioning agents, or flavoring agents (Table 1).[1]

The United States (US) Food and Drug Administration (FDA) has affirmed that Sorbitol is a direct food substance that is generally recognized as safe (GRAS) for human consumption [21CFR184.1835], and Xylitol is approved for use as a direct food additive [21CFR172.395]. Additionally, Mannitol is GRAS as a nutrient and/or dietary supplement for animals when used in accordance with good manufacturing or feeding practice [21CFR582.5470]. Because these ingredients are affirmed GRAS substances and/or direct food additives, systemic toxicity via the oral route will not be the focus of this safety assessment. Although oral exposure data are included in this report, the primary focus of this safety assessment is topical exposure and local effects.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided 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.

Much of the data included in this safety assessment was found on the US FDA, European Chemicals Agency (ECHA) and World Health Organization (WHO) websites.[2-6] Data summaries are available on the respective websites, and when deemed appropriate, information from the summaries has been included in this report.

CHEMISTRY

Definition and Structure

Mannitol, Sorbitol, and Xylitol are organic compounds that are typically derived from a sugar by reduction.[7] These ingredients occur naturally, however, they are most commonly obtained industrially by the hydrogenation of sugars. The ingredients in this group are all simple sugar alcohols and are in that way, structurally similar. The definitions of the ingredients included in this review, as given in the *Dictionary*, are provided in Table 1. Mannitol and Sorbitol are differentiated solely by the relative orientation of their hydroxyl groups, while Xylitol differs in chain length (Figure 1).

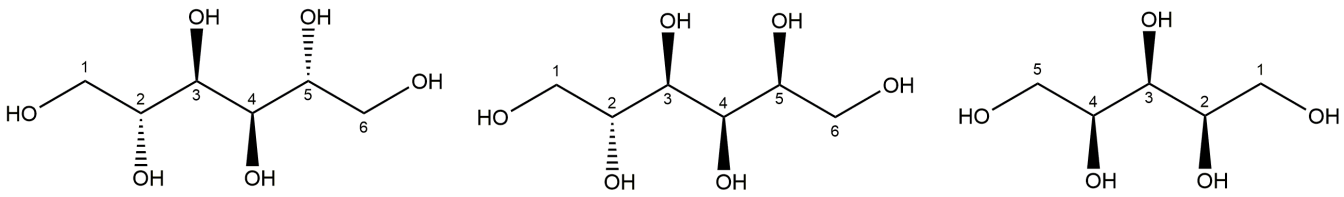


Figure 1. Mannitol, Sorbitol, and Xylitol

Physical and Chemical Properties

Mannitol, Sorbitol, and Xylitol are white, water-soluble powders or granules (Table 2).[8-10] Although Mannitol and Sorbitol are stereoisomers, the two sugar alcohols differ in melting points and water solubility.

Method of Manufacture

The methods below are general to the production and purification of Mannitol, Sorbitol, and Xylitol; no methods specific to cosmetic ingredient manufacture were found in the literature or submitted as unpublished data.

Traditional synthesis of Mannitol and Sorbitol involves the high-pressure hydrogenation of fructose/galactose mixtures in an aqueous solution.[7] When using this method, Raney nickel is used as a catalyst. Alpha-fructose is converted to Mannitol, and beta-fructose and glucose are converted to Sorbitol. The hydrogenation of a 50:50 fructose/galactose mixture generally results in a 25:75 mixture of Mannitol and Sorbitol. Sorbitol itself can also be produced via similar glucose hydrogenation methods.[11] Glucose from wet milling plants is used as the feedstock for the Sorbitol production. The glucose solution is hydrogenated inside of a batch reactor using a nickel or ruthenium catalyst. After the reaction, the catalyst is recovered by filtering the product slurry. The Sorbitol solution is then purified via ion exchange chromatography and filtration through activated charcoal.

Xylitol can be produced synthetically by first extracting xylose from hemicellulose by acid-catalyzed hydrolysis.[7] The xylose is hydrogenated at 80 - 140°C and hydrogen pressures up to 50 atm, in the presence of Raney nickel. The Xylitol solution that is formed undergoes purification via chromatography, followed by concentration and crystallization of the product.

Biosynthetic mechanisms have also been described to produce both Mannitol and Xylitol. Mannitol is produced naturally by many organisms such as bacteria, yeast, fungi, algae, and lichens.[7] Lactic acid bacteria (LAB) have the ability to convert fructose molecules into Mannitol molecules. For example, three fructose molecules can be converted into two Mannitol molecules and one molecule each of lactic acid, acetic acid, and carbon dioxide. The same yield can be formed from two fructose and one glucose molecule. Examples of homofermentative LABs include *Streptococcus mutants* and *Lactobacillus leichmanii*. These homofermentative bacteria produce minimal amounts of Mannitol from glucose most often when bacteria are defective in lactate dehydrogenase activity.[12] Heterofermentative LAB, however, produce Mannitol in larger quantities, using fructose as an electron acceptor and reducing it to Mannitol using the enzyme mannitol-2-dehydrogenase. In addition, the yeast *Zygosaccharomyces rouxii* ferments sugars or sugar alcohols such as glucose, sucrose, fructose, or sorbitol, leading to the production of Mannitol. [21CFR180.25]

In addition, certain yeast strains have the ability to yield large amounts of Xylitol.[7] The genus *Candida* are known to be the best Xylitol producers. In a study, *Candida guilliermondii* and *Candida tropicalis* produced 77.2 g Xylitol from 104 g xylose via high cell densities and a defined medium under aerobic conditions.

Natural extraction is also a method in which Mannitol can be obtained, as Mannitol is found in numerous plants.[7] Traditionally, Mannitol is extracted by a process called Soxhlet extraction. This method involves using ethanol, water, and methanol to steam and hydrolyze the crude material. The resulting Mannitol is then recrystallized from the extract. Natural extraction can also occur via the use of supercritical and subcritical fluids. The super-/sub-critical fluid is pumped through the crude material to extract Mannitol. Then the fluid is simply evaporated to reveal a pure product.

Impurities

According to the *Food Chemicals Codex*, specifications are given for these sugar alcohols.[13] According to specifications, the amount of lead and nickel are not allowed to exceed 1 mg/kg when formulated for use in food. According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), these ingredients should not be composed of more than 0.1% sulfated ash, 100 mg/kg sulfates, 2 mg/kg nickel, or 1 mg/kg lead.[2,4,5]

Natural Occurrence

Mannitol

Mannitol can be found in marine algae, in vegetables such as pumpkins, celery and strawberries, and in the exudate of shrubs and trees, such as the manna ash and olive trees.[14]

Sorbitol

Sorbitol occurs naturally in mountain ash berries and other plants that are part of the Rosaceae family.[15]

Xylitol

Xylitol is found in many plants, including oats, berries, beets, sugar cane, cornhusks, and birch.[16]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US 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 2019 VCRP data, Sorbitol has the highest frequency of use, with a total of 1976 formulations.[17] Sorbitol is most commonly used in moisturizing products (269 formulations), face and neck products (217 formulations), and bath soaps and detergents (205 formulations). Xylitol is reported to have 472 uses, 290 of which are leave-on formulations. Mannitol has a frequency of use of 404 formulations, 104 of which are face and neck products. The results of the concentration of use survey conducted by the Council indicate Sorbitol also has the highest concentration of use; it is used at up to 70% in dentifrices.[18] The highest concentration of use reported for products resulting in leave-on dermal exposure is 60.5% Mannitol in other skin care preparations. Further use data are described in Table 3.

Incidental ingestion and mucous membrane exposure can occur via the use of dentifrices containing Mannitol, Sorbitol, or Xylitol at concentrations up to 4.1, 70, and 14%, respectively.[17,18] Additionally, Sorbitol is used in hair sprays and could be incidentally inhaled; concentrations of these formulations have not been reported. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[19,20] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract, and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[21,22] Mannitol and Sorbitol were reportedly used in face powders at concentrations up to 0.2 and 3.6%, respectively, and could be incidentally inhaled.[18] Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the air.[23-25]

Mannitol, Sorbitol, and Xylitol are not restricted from use in any way under the rules governing cosmetic products in the European Union.[26]

Non-Cosmetic

Mannitol

In the US, Mannitol is a food additive permitted in food or in contact with food on an interim basis pending additional study. [21CFR180.25] Levels may not exceed 98% in pressed mints and 5% in all other hard candy and cough drops, 31% in chewing gum, 40% in soft candy, 8% in confections and frostings, 15% in non-standardized jams and jellies, and at levels less than 2.5% in all other foods. Mannitol is also used as an indirect food additive in substances for use as components of coatings. [21CFR175.300] In addition, Mannitol can be used as a nutritive sweetener, anticaking agent, lubricant and release agent, flavoring agent, stabilizer, thickener, surface-finishing agent, and texturizer. When it is reasonable that daily consumption could result in ingestion of 20 grams of Mannitol, the food must bear the statement "Excess consumption may have a laxative effect." Mannitol is GRAS for animals as a nutrient and/or dietary supplement when used in accordance with good manufacturing or feeding practice. [21CFR582.5470] Mannitol is known to reduce the crystallization of sugars, therefore increasing its shelf life.[7]

In medicine, Mannitol can be used as an osmotic diuretic used to prevent and treat acute renal failure and promote the removal of toxic substances from the body.[27] Mannitol is also used during surgery to prevent kidney failure by altering the osmolarity of the glomerular filtrate, flush dye, and reduce cerebral edema. Mannitol can be inhaled to improve the hydration and surface properties of sputum in cystic fibrosis patients. In addition, it is used in the pharmaceutical formulation of chewable tablets and granulated powders.

Sorbitol

Sorbitol is a GRAS direct food additive used an anti-caking agent, free-flow agent, curing and pickling agent, drying agent, emulsifier, emulsifier salt, firming agent, humectant, nutritive sweetener, sequestrant, stabilizer, thickener, surface-finishing agent, and texturizer. [21CFR184.1835] When used in foods, levels of Sorbitol may not exceed 99% in hard candy and cough drops, 75% in chewing gum, 98% in soft candy, 30% in non-standardized jams and jellies, 30% in baked goods and baking mixes, 17% in frozen dairy desserts, and 12% in all other foods. Sorbitol is approved as an indirect food additive in substances for use as components of coatings [21CFR175.300], and it is GRAS as a substance migrating to food from paper and paperboard products used in food packaging. [21CFR182.90]

Sorbitol may be used in mouthwash and toothpaste, bacterial culture media, and transparent gels.[7,27] Sorbitol may also be used as a cryoprotectant additive in the manufacture of surimi and as a laxative when taken orally or as an enema.

In addition, Sorbitol is a direct food substance that is GRAS for animals when used in accordance with good manufacturing or feeding practice. [21CFR582.5835]

Xylitol

Xylitol is commonly used as a sweetener.[7] Xylitol contains 33% fewer calories and is absorbed at a slower pace than table sugar, allowing it to be a sweetener alternative for those with diabetes. In the US, Xylitol is permitted for direct addition to food for human consumption. [21CFR172.395] This ingredient may be safely used in foods for special dietary uses, provided the amount used is not greater than that required to produce its intended effect.

TOXICOKINETICS STUDIES

Dermal Penetration

Mannitol

The skin permeability of [^{14}C]-Mannitol was studied in Wistar-derived Alderley Park (AP) and Sprague-Dawley (SD) rats.[28] Both whole-skin and epidermal membranes were used. The whole-skin membranes were removed from the dorsal region of the animal, and the epidermal membranes were obtained using a chemical separation technique. Membranes were mounted on static glass diffusion cells with an exposure area of 2.54 cm^2. Samples were placed in a 30 ºC water bath. Physiological saline (0.9%) was used as the receptor fluid. The overall mean permeability coefficient (K_p) values (± standard error (SE)) for whole-skin membranes were 3.23 (± 0.17) x 10^{-4} cm/h (n = 178) for the AP rat samples and 2.89 (± 0.17) x 10^{-4} cm/h (n = 150) for the SD rat samples. The mean K_p values obtained for epidermal membranes were 2.30 (± 0.27) x 10^{-4}cm/h (n = 30) and 0.89 (± 0.15) x 10^{-4} cm/h (n = 22) for the AP and SD rat samples, respectively.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Oral

Mannitol

[^{14}C]-D-Mannitol was given orally to non-fasted rats at a dose of 240 mg/kg.[29] (The method of oral administration was not specified.) Approximately 50% of the radioactivity was recovered in the expired $^{14}CO_2$. No other details regarding this study were reported. In a similar study, the same test substance was given to fasted and non-fasted rats in a dose of 500 mg/kg bw. Method of administration was not stated. Fasted rats oxidized 40% of the dose to $^{14}CO_2$, and non-fasted rats oxidized 68%. In non-fasted rats, 9.75% was stored in the carcass, 1.28% in the liver, and 6.32% was excreted in the urine.

Human

Oral

Mannitol

Mannitol is absorbed from the gastrointestinal tract of man [and animals], and it is not expected to accumulate.[30] The substance is partially metabolized and the remains are excreted in the urine. There is evidence that intestinal flora may convert Mannitol into more readily utilized substances. This transformation may influence the actual amount of Mannitol absorbed and metabolized by the liver.

Ten subjects fasted overnight and were given 28 to 100 g of [U-^{14}C]-Mannitol orally as a 5% aqueous solution.[29] Within this dose range, approximately 20% of the given dose was excreted unchanged in the urine. In the first two h following ingestion, the radioactivity in the blood increased. Radioactivity remained at a plateau for 2 to 4 h. Expired $^{14}CO_2$ increased for 8 h after ingestion. Oral doses of 40 g or more caused frequent bowel movements, diarrhea, and excretion in the stool of a higher percentage of the dose. Only minimal amounts of radioactivity occurred in the urine and stools 48 h after ingestion.

Sorbitol

Sorbitol administered orally to humans is absorbed and metabolized rapidly through normal glycolytic pathways.[31] The substance is ultimately metabolized into carbon dioxide and water. When 35 g of Sorbitol were given to diabetic and healthy adults, less than 3% of the Sorbitol was excreted in the urine, and an immeasurably small amount was found in the blood.

Xylitol

Xylitol is slowly absorbed from the digestive tract, and 25 - 50% is absorbed in the small intestine.[32] Upon entering the hepatic metabolic system, it is further metabolized into fructose-6-phosphate, triose-phosphate, and ribose-5-phosphate.

Five healthy subjects were used to study the absorption of Xylitol.[33] Each subject was intubated with a mercury-weighted polyvinyl tube, passed until the distal orifice was 250 to 300 cm from the teeth. Test substances were given as either 5 or 10 g of Xylitol plus an equal amount of glucose in 200 mL water, or 15 or 30 g of Xylitol plus an equal amount of glucose in 600 mL of water. The test substance also contained polyethylene glycol (PEG) as a nonabsorbable reference marker. After ingestion, ileal fluid was aspirated for 3 to 4 h in a series of samples. Blood samples were collected at 60 and 120 min, and urine samples were collected from 0 to 12 h and from 12 to 24 h after ingestion. Xylitol was nearly completely absorbed in most subjects (72 to 92%). Plasma samples at 1 and 2 h after the test meal showed no Xylitol. Urine analysis showed negligible amounts of Xylitol at 0 - 12 or 12 - 24 h after ingestion.

Oral, Inhalation, and Parenteral

Mannitol

The effect of route of administration on bioavailability was compared in a study in which 18 healthy male volunteers were given an oral, inhaled, or intravenous dose of Mannitol.[34] Oral doses consisted of 500 mg Mannitol in 50 mL water and intravenous doses were given as 500 mg of Mannitol in a 10% intravenous solution. The study used a low resistance inhaler provided with 635 mg aerosolized Mannitol. The mean bioavailability of the orally ingested and inhaled Mannitol was 63% and 59%, respectively. Mean urinary excretion over a period of 24 h was approximately 55% for the inhalation and oral doses, and 87% for the intravenous dose.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute toxicity studies in animals summarized below are described in Table 4.

Animal

Several acute oral toxicity studies were performed. When Mannitol was given to rats and mice at doses of up to 5 g/kg bw, all animals survived.[35] Oral LD_{50}s of up to 22 g/kg bw and 17.3 g/kg bw were reported for mice and rats given Mannitol, respectively.[29,34] Sorbitol acute oral toxicity studies resulted in LD_{50}s of 23.2 g/kg bw (male mice), 25.7 g/kg bw (female mice), 17.5 g/kg bw (male rats), and 15.9 g/kg bw (female rats).[36] For Xylitol, the lowest LD_{50}s in mice, rats, and rabbits were reported to be 12.5 g/kg bw, > 4 g/kg bw, and 25 g/kg bw, respectively.[32,37] The vehicles used in these acute oral toxicity studies were not provided.

Inhalation studies were performed on animals. In one study, rats (10/group) were given up to 98 mg/kg of Mannitol via inhalation for 1 h.[34] No other details regarding study methods were reported. Over the 14-day observation period, a reduction of body weight gain was observed in males. Decreases in lung/bronchi weight, as well as effects on the respiratory tract, were observed in both male and females. In a different study, six mice were exposed to aerosolized Xylitol (5%) in water for 150 min. No adverse effects were reported.[38]

Human

Inhalation

In a study involving humans, 10 subjects were exposed to 1 (2 - 10 min exposure time), 5 (15 - 33 min exposure time), or 10 mL (30 - 49 min exposure time) of 5% Xylitol.[38] Xylitol was prepared by adding 5 g of crystal sugar to 100 mL of sterile water. Subjects were exposed to aerosolized saline as a control. The mass median aerodynamic diameter of the aerosol was 1.63 µ with a geometric standard deviation (GSD) of 1.71 µ. Fifty-percent of the subjects reported a stuffy nose after administration of the highest dose level. Cough, chest tightness, and phlegm production was among the other symptoms reported by subjects. No effects regarding electrolytes, lung function, osmolarity, or bronchoalveolar lavage were observed.

Short-Term Studies

Details of the short-term, subchronic, and chronic toxicity studies summarized below are provided in Table 5.

Dermal

A 30-day dermal study was performed on 4 groups of 5 female albino rabbits.[39] Sorbitol (30% in equal parts of water and propylene glycol; 0.5 mL) was applied to an area of 10 cm x 10 cm on the right flank of the animal. No macroscopic changes were noted. Microscopic examination after 10 days of treatment revealed moderate acanthosis with cellular vacuolization and a thinning out of collagen fibers of the superficial portions of the dermis.

Oral

Multiple short-term studies were available for this ingredient group. No adverse effects were reported when B6C3F1 mice (groups of 5/sex) were fed diets containing up to 10% Mannitol for 14 days.[35] Studies using rats were also performed. Groups of 5 F344/N rats/sex were fed diets containing 0.6, 1.25, 2.5, 5, or 10% Mannitol for 14 days. No deaths were reported, and all groups had similar increases in body weight. In a study involving Sorbitol, two adult mongrel dogs (one male and one female) were given Sorbitol (90% w/vol in aqueous solution) at doses of 0.675 and 1.35 g/kg bw.[36] Doses were given three times daily for 3 days. At the highest dose, the stomach appeared hyperemic. No evidence of hepatotoxicity was observed when Sprague-Dawley rats (20 rats/sex/dose) were given Xylitol via gavage for 14 days.[40] Rats were dosed with 0, 2.5, or 5 g/kg/d, or with a dose of 1.25 g/kg/d, followed by 10 g/kg/d.

Inhalation

An inhalation study was performed using Sprague-Dawley rats for 7 days (5/sex/dose).[6] When given 5 or 9 mg of Mannitol/L of air, no effects were reported. In a similar study, CD-1 rats (10/sex/dose) were given 0, 0.9, 2.5, or 6.9 mg/kg Mannitol via a nose-only apparatus for 2 wks. No significant treatment related effects were observed. When Beagle dogs

(3/sex/group) were dosed for 2 wks with up to 197 mg/kg/d Mannitol, spongy and froth-filled lungs, lung congestion/ hemorrhage, and pigment in the submandicular lymph node was observed. At all dose levels (25, 100, and 197 mg/kg/d Mannitol), peribronchiolar infiltration and foamy alveolar macrophages were apparent. In a similar study, Beagle dogs (3/sex/group) were given either saline (control) or aerosolized Xylitol formulated with water (4 mg/L) for 15, 30, or 60 min.[41] Animals were dosed for 14 consecutive days. All animals survived to their scheduled sacrifice and no statistically significant difference among exposed and control groups were observed in body weights or food consumption. No other signs of toxicity were observed.

Subchronic Toxicity Studies

Oral

Groups of 10 B6C3F1/N mice/sex were fed diets containing 0, 0.3, 0.6, 1.2, 2.5, or 5.0% Mannitol for 13 wks.[35] Mean body weight gains were higher than controls in all dose groups except for males given 5.0% Mannitol. No other adverse effects were observed. In a similar study, F344 rats (groups of 10/sex) were given diets containing 0, 0.3, 0.6, 1.25, or 5% Mannitol for 13 wks. Mean body weight gains of the high-dose group males were 9.6% lower compared to controls. Mean body weight gains in all other groups were similar to the control group. No compound-related clinical signs were observed. Rats (16/group) were given 0, 10, or 20 g/kg/d of Xylitol in the diet for 13 wks.[32,37] Slightly reduced weight gains and transient diarrhea was observed at the highest dose level. Rats (number of animals was not provided) were given Xylitol (0.5 or 1.73 g/kg) via gavage for 90 days.[37] Diarrhea and slight weight gain was observed in a different study involving rats (number of animals not provided) given Xylitol at up to 1.73 g/kg via gavage for 90 days.[32] Transient diarrhea and soft stools were also observed in a study using monkeys given 1, 3, or 5 g/kg/d Xylitol for 13 wks (number of animals was not reported).[42] No other adverse effects were reported.

Chronic Toxicity Studies

Oral

Female Sprague-Dawley rats were given Mannitol in doses of 0, 1, 5, or 10% for 27 mos.[29] The number of rats used in the study was not stated. The mortality of the rats receiving 10% Mannitol was 68%. No other Mannitol-induced effects were reported. Fifteen male Wistar rats were given Sorbitol in the diet at concentrations of 10 or 15% for 17 mos.[36] No negative effects on weight gain, reproduction, or histopathological appearances of the main organs were observed. In a different study, Beagle dogs (8/sex/dose) were given 0, 2, 5, 10, or 20% Xylitol in their diet for 2 yrs.[42] Biochemical investigations yielded results within the usual biological range, however, during the first year, a slightly elevated serum alkaline phosphatase and serum protein value was observed in the highest dose group as well as slightly heavier livers.

Inhalation

A study using Beagle dogs (4/sex/group) was performed for 26 wks using 0, 43, or 197 mg/kg/d Mannitol, via inhalation.[6] Coughing occurred throughout and after study in the high-dose group, and during the first week in the mid-dose group. Minimal laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node were observed in the high-dose group. No other treatment related effects were noted. In a different study, Mannitol given to dogs (number of animals was noted stated) via inhalation at up to 834 mg/kg/d for 26 wks caused coughing during and immediately after dosing.[34] Coughing primarily occurred early in the treatment phase, and then reduced down to a minimum. Salivation and emesis were also observed. Enlargements of the mandibular lymph nodes were observed in 2 out of the 4 treated animals. One out of four treated females given 716 mg/kg Mannitol per day displayed erythrophagocytosis or lymphadenitis, however, this effect was not present in male dogs.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Mannitol

Pregnant mice, rats, and hamsters were given oral doses of Mannitol.[29] Method of administration was not specified. Rats and mice were given 1.6 g/kg for 10 days, and hamsters were given 1.2 g/kg for 5 days. No other details regarding these studies were provided. No maternal or fetotoxic symptoms were observed.

Sorbitol

A reproductive study on 30 rats extended over four generations using 10 or 15% Sorbitol in the diet for 17 mos did not reveal any abnormalities.[36] No other details regarding this study were provided.

In a three-generation study, groups of 12 male and 24 female Charles River CD (SD) BR rats were fed a diet containing 0, 2.5, 5, or 10% Sorbitol.[43] After 14 wks of exposure to Sorbitol via diet, rats were mated, and gave rise to litters F_{1a} and F_{1b}. F_{1a} rats were weaned and killed, while 12 male and 24 females of the F_{1b} litter were then mated. Likewise, the resulting F_{2a} rats were killed, and the F_{2b} litter was mated, giving rise to litters F_{3a} and F_{3b}. No clinical signs of toxicity were observed to treatment in the F_0, F_{1b}, or F_{2b} rats. Reduced weight gain was recorded in response to Sorbitol in both sexes at the 10% level. This effect was more prominent in females, and in the F_0 generation than in the F_{1a} or F_{2b} generation. Cecal enlargement was consistently observed during necropsy of all treated rats. Significant increases in serum calcium were observed in F_0 males

and females exposed to 10% Sorbitol, and in F_{1b} males exposed to either 5 or 10% Sorbitol. Variations in T_3, thyroid stimulating hormone (TSH), and gonadal weights were observed, but were considered to have no toxicological significance due to a lack of consistency. No adverse effects were observed after microscopic evaluation of lesions of the gonads and other selected tissues.

Administration of 1600 mg/kg/bw of Sorbitol to pregnant rabbits for 13 days (days of gestation and route of administration not stated) had no effects on maternal or fetal survival.[44] The number of abnormalities seen in either soft or skeletal tissues of the test groups was similar to controls. No other details regarding this study were provided.

Xylitol

A three-generation study was conducted in NMRI mice.[2] Groups of 12 females and 3 males were placed in a group and given 20% Xylitol. No abnormalities of condition or behavior were observed in the successive generation. Gross examination revealed no abnormalities attributable to Xylitol treatment. CD rats (20/sex/group) were given 2, 5, 10, or 20% Xylitol in the diet in a three-generation study. [32] A control group received 20% rice starch, and a comparison group received 20% sucrose. At the low diet levels, food intake was comparable with controls in all generations. At the 10 and 20% level, food intake was slightly lowered. No treatment related effects were noted regarding mating performance or pregnancy rate. Cecal enlargement was noted at terminal necropsy of F_{2b} parents of both sexes in all Xylitol-treated groups. At the 20% level, lower values for viable litter size at birth were noted. There was no indication of a treatment effect on occurrence of terata. No histopathological abnormalities were noted. In a different study, female rabbits (20/group) were given 0, 2, 5, 10, or 20% Xylitol in the diet on days 7 - 19 of gestation. Male rabbits were left untreated. No reproductive, teratogenic, or embryotoxic effects were observed.

GENOTOXICITY

In Vitro

Mannitol

According to studies conducted by the US National Toxicology Program (NTP), Mannitol was non-mutagenic in a bacterial reverse mutation assay (*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537; 10 mg/plate), mouse lymphoma $TK^{+/-}$ assay, or in a sister chromatid exchange assay in Chinese Hamster Ovary (CHO) cells (doses not stated).[45,46] Mannitol was non-mutagenic in a host-mediated assay using *S. typhimurium* G46 and TA1530 and *Saccharomyces cerevisiae* strain D3, in a cytogenic assay in rat bone marrow, or in human W1-38 cells at concentrations of 2, 20, and 200 µg/mL.[47] It is not stated whether or not metabolic activation was used in these studies. In a different study, the mutagenic potential of Mannitol (0.3 - 10,000 µg/plate) was studied in an Ames test using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA 100, and in *Escherichia coli* WP2 (uvrA), with and without metabolic activation.[48] The test substance was considered to be non-mutagenic.

Sorbitol

An Ames test performed on Sorbitol using *S. typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 yielded negative results (with metabolic activation; doses not stated).[49,50] Negative results were also obtained when Sorbitol (5 mg/plate) was used in chromosomal aberration assays using CHO cells and Chinese hamster lung fibroblasts without metabolic activation. Sorbitol was not genotoxic in host mediated assays of mutagenicity in mice using *Salmonella* strains G46 and TA1530, and *Sacc. cerevisiae* strain D3 as indicator strains. The doses and use of metabolic activation were not stated in this study.

Xylitol

An Ames test was performed on Xylitol using *S. typhimurium* strains TA 100 and TA 98 (up to 500 mg/plate; unknown if metabolic activation was used).[51] No detectable mutagenic activity was reported. A different Ames test was performed using *S. typhimurium* strains TA 1535, 1537, and 1538, with and without metabolic activation.[32] Cells were exposed to 0, 15.6, 31.25, 62.5, or 125 mg/plate. A two-fold increase in the revertants above background could be observed with *S. typhimurium* TA 1538 at the highest concentration level. However, this result could not be reproduced, and the positive control, methylcholanthrene, resulted in a 15-fold increase of the revertant colonies above background. All other strains yielded negative results. A sister chromatid exchange was performed on Xylitol using diploid human fibroblastic cells (HE 2144) and pseudodiploid Chinese hamster cell line (Don-6) at concentrations of up to 76.1 mg/mL.[37] No induction of sister chromatid exchange was observed in either test system. It is unknown whether or not metabolic activation was used in these studies.

In Vivo

Mannitol

Mannitol was not clastogenic in a mouse bone marrow micronucleus test in which doses of 3000 mg/kg/d Mannitol was administered for 3 days intraperitoneally.[34] Results of a dominant lethal assay in rats at doses of 20, 200, 2000, and 5000

mg/kg of D-Mannitol by gavage were negative.[35] A chromosomal aberration study in rat bone marrow also yielded negative results (doses not stated). No other details regarding these studies were given.

Sorbitol

A chromosomal aberration assay performed in mouse bone marrow yielded negative results.[50] No other details regarding this study were provided.

Xylitol

A mammalian erythrocyte micronucleus test was performed using SPF mice (3/sex/group) according to Organization for Economic Co-operation and Development test guidelines (OECD TG) 474.[32] Xylitol was dissolved in phosphate-buffered saline and given to animals via gavage. The doses given were 0, 1820, 3280, and 5333 mg/kg/bw. Smears of the bone marrow of both femora were prepared, and 4000 erythrocytes per animal were checked for micronuclei. No significant increase of micronuclei containing erythrocytes were observed in the bone marrow of the treated mice.

CARCINOGENICITY STUDIES

Details of the carcinogenicity studies summarized below are provided in Table 6.

Mannitol

A diet containing D-Mannitol (98 - 100% pure (25 or 50 g/kg)) was given to groups of 50 F344/N rats/sex and 50 B6C3F1 mice of each sex for 103 wks.[14,35] An increased incidence of the dilation of the gastric fundal gland was observed in dosed female rats compare to that of controls. Mild nephrosis characterized by focal vacuolization of the renal tubular epithelium was seen in increased incidence in dosed mice of each sex. The test substance was considered to be non-carcinogenic.

In a different study, 10% Mannitol was given to 50 Wistar rats/group/sex via diet for 104 - 107 wks.[52] In both sexes, pelvic nephrocalcinosis, which in females was directly associated with pelvic hyperplasia, was noted. No significant increase in tumor incidence was noted. A low incidence of benign thymomas was observed when Wistar-derived SPF albino rats were given 1, 5, or 10% Mannitol in the diet for 94 wks.[29] No other details regarding this study were provided.

Female Wistar rats (100/group) were given diets containing 0, 1, 5, or 10% Mannitol for 30 mos.[29] A slightly increased incidence of tissue masses in the cervix and/or uterus was noted in the treated groups compared to control animals. Evaluation of mortality, behavior, organ and body weights, and subcutaneous tissue masses were similar to controls. In a similar study, female Fischer rats (100/sex/group) were given 0, 1, 5, or 10% Mannitol in the diet for 30 mos. A slight increase in the incidences of tissue masses in the anogenital area, cervix, and uterus were noted in the high-dosed group. Focal medullary hyperplasia and medullary pheochromocytoma was higher in the high-dose group compared to the control group, however, no clear dose response was seen.

Sorbitol

Sprague-Dawley rats (75/sex/group) were given 0 or 20% Sorbitol in the diet for 78 wks.[36] Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly in dosed animals of both sexes.

Xylitol

Xylitol was fed to 100 mice/sex (strain not stated) in the diet at concentrations of 0, 2, 10, or 20%.[53] Animals were treated for their entire life span. An increased incidence of crystalline calculi was noted in the urinary bladder in male mice treated with 10 or 20% Xylitol. A small number of tumors were found in the transitional epithelium in high-dosed males. All treated animals showed fewer renal tumors than control animals. In a different study, Xylitol was given in the diet to 75 rats/sex (strain not stated), at the same concentrations as above. Rats were fed this diet for the majority of their lifespan. A statistically significant increase in the number of pheochromocytomas was observed in male rats treated with 20% Xylitol ($P < 0.05$) compared to the controls. The total number of tumor-bearing rats was similar between treated and control groups.

OTHER RELEVANT STUDIES

Corneal Healing Promotion

The protective effect of Mannitol on corneal damage caused by benzalkonium chloride (BAC) (a preservative in timolol maleate eye drops) was studied using rat debrided corneal epithelium.[54] After corneal epithelium abrasion, eye drops were instilled into rat eyes five times a day. The corneal healing rate and cell viability were higher following treatment with a solution consisting of 0.005% BAC and 0.5% Mannitol than after treatment with BAC alone. After 36 h, corneal wounds of rat eyes instilled with 0.02% BAC solution were 75% healed, while those instilled with 0.02% BAC solution plus 0.5% Mannitol were 90.1% healed. The healing rate constant ($k_{H)}$ for rat eyes instilled with commercially available timolol maleate eye drops containing 0.5% mannitol was significantly higher than that for eyes instilled with timolol eyedrops alone.

Anti-Inflammatory/Anti-Irritant Effects

The ability of Xylitol to alleviate irritation and inflammation of sodium lauryl sulfate (SLS)-induced acute dermal irritation was studied in 23 male SKH-1 hairless mice per group.[55] The dorsal region skin was exposed to either 5% SLS alone, or a combination of 5% SLS with 8.26% or 16.52% Xylitol. At both concentrations, Xylitol was able to prevent the irritant-induced red blood cell velocity (RBCV) elevation in the dermal capillaries. A decreased lymphocyte number was observed in the epidermis when animals treated with Xylitol and SLS, compared to SLS alone. The addition of Xylitol also effectively decreased myeloperoxidase (MPO) activity in the skin.

Deposition in Bronchoalveolar Fluid (BALF)

Sprague-Dawley rats (5/sex) were used in a 7-day inhalation study.[6] Rats were exposed to 5 or 9 mg of Mannitol/L of air for 120 to 240 minutes/day. Rats were killed after treatment. The amount of Mannitol delivered to the lungs was determined by measuring the amount of Mannitol in the bronchoalveolar lavage fluid (BALF). In the low dose group, the mean Mannitol concentration in the BALF was 36.7 µg/mL in males and 43.6 µg/mL in females. In the high dose group, mean Mannitol concentrations in the BALF were 42 and 33.4 µg/mL in males and females, respectively.

Inhalation studies were performed in rats (13 wks) and dogs (26 wks).[6] In rats, the mean Mannitol level in BALF was 0, 3.8, and 3.2 µg/mL in the control, 12.4 mg/kg/d dosed group, and 21 mg/kg/d dosed group, respectively. In dogs, the BALF Mannitol concentrations were below the level of quantification for both the low (43 mg/kg/d) and high doses (179 mg/kg/d).

DERMAL IRRITATION AND SENSITIZATION

Irritation

Xylitol

Xylitol was incorporated at 5% and 10% in both gel and cream formulations through a 60% mixture in ultra-pure water, and administered to New Zealand albino rabbits (3/sex/group).[56] The test substance (0.5 g) was placed on a 2 cm^2 gauze pad and applied to each abraded and intact skin dosing site, and held in place for 4 h with occlusive tape. After patch removal, the degree of erythema and edema was evaluated according to the Draize method. All the tested formulations were classified as non-irritating.

Sensitization

Animal

Mannitol

A Magnusson-Kligman guinea pig maximization test was performed on Pirbright white guinea pigs (number of animals not stated).[57] The test substance was a trade name mixture containing 15% Mannitol and 15% disodium adenosine triphosphate. A 0.5% aqueous dilution of the test substance was used for the intracutaneous induction, and a 10% aqueous dilution of the test substance was used for the epicutaneous induction and challenge. No signs of irritation and skin reactions indicative of an immune response were seen at the readings 24 and 48 h after removal of the challenge patch.

Human

Mannitol

A human repeated insult patch test (HRIPT) was performed on 50 volunteers using a trade name material consisting of 15% Mannitol and 15% disodium adenosine triphosphate.[57] A 10% aqueous dilution of the trade name material was applied to the backs of subjects under an occlusive patch for a total of 9 applications within a 3-week period. After a rest period of two wks, a challenge patch was applied to a previously unexposed area. Readings were taken 24, 48, and 96 h after removal of patches. No skin reactions were noted in any subject during the induction or challenge phase.

Xylitol

An HRIPT was performed on 110 subjects using a body lotion containing 3% Xylitol.[58] Subjects were given a questionnaire. Based on the responses, 100% of the subjects had self-perceived sensitive skin. During the induction phase, the lotion (0.15 mL) was applied on an occlusive patch, and placed on the skin for 24 h. Subjects returned to the facility at 48-h intervals to have sites evaluated and identical patches applied to the same sites. Following the ninth application, the volunteers were dismissed for a rest period of approximately 10 - 15 days. For the challenge phase, a patch was applied to a site previously unexposed to the study material, and removed after 24 h. Sites were graded after additional 24-h and 48-h periods. There was no evidence of sensitization to the test material.

Phototoxicity/Photosensitization

Human

Mannitol

A phototoxicity study was conducted with a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate in 10 volunteers.[57] A 10% aqueous solution of the trade name mixture (0.2 mL) was applied under an occlusive patch to two different areas of the forearm, one irradiated and one non-irradiated. After a 24-h exposure, one site was irradiated with long-wave ultraviolet (UVA) light (320 - 400 nm) for 15 minutes. Skin reactions were scored immediately after light exposure as well as 24 and 48 h later. No reactions were noted on either the irradiated or non-irradiated test material contact site in any subject.

A photosensitization test was performed on 34 subjects with a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate.[57] For three wks, six 24-h induction patches were applied containing a 2% aqueous solution of the trade name mixture. Applications were performed in duplicate; one site was subsequently irradiated with UV light (260 - 400 nm) for 15 minutes each session. After 2 wks, a challenge patch was applied at virgin sites with and without irradiation. At the challenge phase, no skin reactions were exhibited at either the irradiated site or the non-irradiated site.

Xylitol

Xylitol (10%) was incorporated into a cream and a gel, and applied to the skin of male Dunkin-Hartley albino guinea pigs.[56] Four animals were used per formulation containing Xylitol, as well as the positive control, and 2 animals were used as negative controls. Each animal had 4 application sites of approximately 1.5 cm^2 to which aliquots (0.5 g/site) of the test substance or positive control (8-methoxypsoralen (8-MOP)) was applied in duplicate. Sunscreen was placed on the right side of the back to protect from irradiation, while the other side was left uncovered. After application, animals were exposed to UVA light (200 J/cm^2 for 15 minutes). Test sites were graded at 1, 24, 48, and 72 h after exposure using a Draize scoring system. In animals exposed to 10% Xylitol via cream or gel, 3 out of 4 animals displayed a positive reaction, while all controls presented expected reactions. It was determined that Xylitol has moderate phototoxic potential at this UVA dose.

OCULAR IRRITATION STUDIES

In Vitro

Mannitol

Isolated bovine corneas were incubated with Mannitol powder (20 %) or imidazole (positive control) at 32º C for 4 h.[6] Opacity was determined by light transmission through the cornea, and permeability was measured by the rate of sodium fluorescein crossing the cornea with a spectrophotometer. A composite score was derived for each cornea based on the opacity and permeability readings. A score below 25 was considered to be non-irritating. The composite scores of mannitol and imidazole were 0.2 and 142.4, respectively. The test substance was not considered to be an eye irritant.

Animal

Mannitol

Three New Zealand white rabbits were administered 78 mg (0.1 mL) of Mannitol in one eye and observed for irritation for 72 h post administration.[6] Parameters evaluated included corneal capacity, iridial lesions, and conjunctival redness/chemosis. No abnormalities among these parameters were found. The test substance was considered to be non-irritating.

CLINICAL STUDIES

Metabolism

Mannitol

Six adults and three adolescents with cystic fibrosis inhaled dry powder Mannitol (400 mg) twice daily for 7 days.[34] On days 1 and 7, administration only occurred in the morning. The reported mean half lives in adults on day 1 and 7 were 6.10 and 5.42 h, respectively. In adolescents, the mean half-lives on day 1 and 7, were 7.29 and 6.52 h, respectively.

Sorbitol

The metabolism of Sorbitol was studied in 6 normal and 8 diabetic adults.[60] Diabetic patients controlled their diabetes symptoms through diet alone. All subjects fasted overnights, emptied their bladders, and had blood collected from the earlobes for glucose and Sorbitol estimations. Dissolved Sorbitol (35 g in 300 mL) was taken orally. Blood draws occurred in half-hour intervals for 2.5 h. For some subjects, urine was collected for 24 h, and feces for 3 days. In normal subjects, Sorbitol did not have a significant effect on blood sugar levels. However, in all diabetic patients, significant increases in blood-sugar concentrations ranging from 9 to 49 mg/100mL occurred after Sorbitol administration. Neither group had attained measurable levels of Sorbitol in the blood for a prolonged period of time. Excretion of Sorbitol in the urine of all

subjects varied between 0.07 - 0.91 g. The majority of excretion occurred during the first 5 h. No Sorbitol was detected in the urine after 24 h. No unchanged Sorbitol could be detected in the feces of three subjects, and only 10% or less of the administered dose was found in the feces of patients whose gastrointestinal tract had been sterilized by the adequate administration of antibiotics. When 35 g of Sorbitol was given to normal subjects and diabetic patients, less than 3% of the administrated oral dose was excreted in the urine.[36] No other details regarding this study were provided.

SUMMARY

The safety of Mannitol, Sorbitol, and Xylitol as used in cosmetics is reviewed in this assessment. According to the *Dictionary*, these ingredients are all reported to function as humectants, skin-conditioning agents, and flavoring agents. These ingredients have a wide non-cosmetic use in food products. Sorbitol is a direct food substance that is generally recognized as safe (GRAS) for human consumption, and Xylitol is approved for use as a direct food additive [21CFR172.395]. Additionally, Mannitol is GRAS as a nutrient and/or dietary supplement for animals

According to 2019 VCRP data, Sorbitol is reported to be used in 1976 formulations, 269 of which are used in moisturizing products and 217 in face and neck products. Mannitol and Xylitol are reported to be used in 404 and 472 formulations, respectively. The results of the concentration of use survey conducted by the Council, indicated Sorbitol also has the highest concentration of use; it is used at up to 70% in dentifrices. The highest concentration of use reported for products resulting in leave-on dermal exposure is 60.5% Mannitol in other skin care preparations.

The skin permeability of [^{14}C]-Mannitol in Wistar-derived AP rats and SD rats, was studied. The mean K_p values obtained for epidermal membranes were 2.30 (± 0.27) x 10^{-4} cm/h (n = 30) and 0.89 (± 0.15) x 10^{-4} cm/h (n = 22) for the AP and SD rat samples, respectively. In an oral ADME study, [^{14}C]-D-Mannitol was given to rats. Approximately 50% of the radioactivity was recovered in the expired [^{14}C]-CO_2. A similar study was performed in rats given 500 mg/kg bw [^{14}C]-D-Mannitol. Non-fasted rats oxidized 68% of the given dose; 9.75% was stored in the carcass, 1.28% in the liver, and 6.32% was excreted in the urine.

Radioactivity plateaued 2 to 4 h after 10 fasted subjects were given 28 to 100 g of [U-^{14}C]-Mannitol orally as a 5% aqueous solution. The mean bioavailability of orally ingested Mannitol was 63% when 18 males were given a dose of 500 mg Mannitol in 50 mL water. The mean bioavailability of Mannitol in 18 males given 635 mg Mannitol via inhalation was 59%. In normal and diabetic subjects, less than 3% of an administrated oral dose of 35 g Sorbitol was excreted in the urine. Plasma samples taken one and two h after the ingestion of Xylitol and glucose in water from 5 subjects revealed no Xylitol. Urinalysis showed negligible amounts of Xylitol at 0 - 12 or 12 - 24 h after dose.

The lowest acute oral LD_{50}s of Mannitol were reported to be greater than 5 g/kg bw in mice and 13.5 g/kg bw in rats. Sorbitol acute oral toxicity studies resulted in LD_{50}s of 23.2 g/kg bw (male mice), 25.7 g/kg bw (female mice), 17.5 g/kg bw(male rats), and 15.9 g/kg bw (female rats). The lowest LD_{50}s in mice, rats, and rabbits were reported to be 12.5 g/kg bw, > 4 g/kg bw, and 25 g/kg bw, respectively. Decreases in lung/bronchi weight and a reduction of body weight gain were observed when rats were exposed to 98 mg/kg of Mannitol via inhalation for 1 h. When 6 mice were exposed to aerosolized Xylitol (5%) in water for 150 minutes, no adverse effects were observed. Fifty percent of humans administered 10 mL of 5% Xylitol in water for 30-49 minutes reported a stuffy nose. Cough, chest tightness, and phlegm production was also reported.

Moderate acanthosis with cellular vacuolization and a thinning out of collagen fibers of the superficial portions of the dermis was observed when albino rabbits were dosed dermally with Sorbitol (30%) for 30 days.

No adverse effects were reported when B6C3F1 mice were given up to 10% Mannitol for 14 days. Female F344/N rats fed diets containing 10% Mannitol for 14 days displayed a lower weight gain than females given lower doses of Mannitol and control females. No other adverse effects were reported in this study. No evidence of hepatotoxicity was observed when Sprague-Dawley rats were given up to 10 g/kg/d Xylitol via gavage for 14 days. The stomachs of two adult mongrel dogs appeared hyperemic after 3 doses/day of 1.35 g/kg bw Sorbitol (90%) was given for 3 days.

In an inhalation study, SD rats were exposed to 5 or 9 mg of Mannitol/L of air. No adverse effects were reported. Similarly, no adverse effects were reported when CD-1 rats were given up to 6 mg/kg Mannitol for 2 wks. Froth-filled lungs, lung congestion/hemorrhage, and pigment in the submandibular lymph node was observed in beagle dogs given 197 mg/kg/d Mannitol for 2 wks via inhalation. In a different study, Beagle dogs were given aerosolized Xylitol (4 mg/L) for up to 60 minutes for 14 days. No exposure-related adverse effects were reported.

Mean body weights were increased compared to controls when B6C3F1/N mice were given diets containing 0.3, 0.6, 1.2, and 5% (females) Mannitol for 13 wks. However, increased mean body weight was not observed in males given 5% Mannitol. In a similar study, F344 rats given 5% Mannitol displayed a 9.6% depression in weight gain compared to control rats. Diarrhea and slight weight gain were noted when rats were given 20 g/kg/d of Xylitol in the diet for 13 wks. Similar

symptoms were reported in monkeys given 1, 3, or 5 g/kg/d Xylitol for 13 wks. Reduced sleep activity was reported in rats given 1.73 g/kg Xylitol via gavage for 90 days.

In Female Sprague-Dawley rats given Mannitol in concentrations of up to 10% for 27 mos, the mortality rate was reported to be 68% (in highest dosed rats). No negative effects, excluding slight diarrhea, was observed in male Wistar rats given Sorbitol (10 or 15%) in the diet for 17 mos. A slightly elevated serum alkaline phosphatase and serum protein value (compared to controls) was noted in Beagle dogs given 20% Xylitol in the diet for 2 years.

Beagle dogs were given 0, 43, or 179 mg/kg d Mannitol via inhalation for 26 wks. Minimal laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node were observed in the high-dose group. In a different study, Mannitol was given to dogs at doses of up to 834 mg/kg/d for 26 wks via inhalation. Enlargements of the mandibular lymph nodes were observed in 2 out of the 4 treated animals. One out of four treated females given 716 mg/kg Mannitol per day displayed erythrophagocytosis or lymphadenitis.

No maternal or fetotoxic symptoms were observed when mice and hamsters were given oral doses of Mannitol (1.6 g/kg for 10 days in mice; 1.2 g/kg for 5 days in hamsters). A reproductive study on 30 rats extended over four generations using 10 or 15% Sorbitol in the diet for 17 mos did not reveal any abnormalities. Reduced weight gain, cecal enlargement, and significant rises in serum calcium were observed in a three-generation reproductive study using rats. No adverse effects were reported when pregnant rabbits were given 1600 mg/kg/bw of Sorbitol for 13 days. Reproduction, lactation, and pup growth were normal in rats given a diet containing 20% Xylitol for 4 mos. Similarly, no adverse effects were reported with rabbits were given Xylitol in concentrations of up to 20% on gestation days 7 - 19. No test substance related abnormalities were noted in a three-generation study involving NMRI mice given 20% Xylitol in the diet.

Mannitol was non-mutagenic in a bacterial reverse mutation assay, mouse lymphoma $TK^{+/-}$ assay, a sex-linked recessive lethal mutation test, sister chromatid exchange assay (concentrations not stated). Mannitol was non-mutagenic in cytogenic assays at concentrations of 2, 20, and 200 µg/mL. Additionally, Mannitol was considered to be non-mutagenic when used in an Ames test at up to 10,000 µg/plate. An Ames test performed on Sorbitol using *S. typhimurium* yielded negative results (concentrations not stated). Negative results were also obtained in chromosomal aberration assays (5 mg/plate) and host mediated assays. Ames tests performed on Xylitol at up to 500 mg/plate yielded negative results. A sister chromatid exchange assay performed on Xylitol at up to 7.1 mg/mL resulted in negative results.

Mannitol was not clastogenic in a mouse bone marrow micronucleus tests (3000 mg/kg/d Mannitol for 3 days). Results of a dominant lethal assay in rats at doses of up to 5000 mg/kg of D-Mannitol by gavage were negative. A chromosomal aberration study in rat bone marrow also yielded negative results. A chromosomal aberration assay performed in mouse bone marrow yielded negative results. Similarly, a mammalian erythrocyte micronucleus test performed on Xylitol (up to 5333 mg/kg/bw) using SPF mice, resulted in negative results.

Rats and mice were given a diet containing D-Mannitol (98 – 100% pure (25 or 50 g/kg)) for 103 wks. The test substance was considered to be non-carcinogenic. Pelvic nephrocalcinosis was observed in Wistar rats given 10% Mannitol in the diet for 104 - 107 wks. A low incidence of benign thymomas was observed when Wistar-derived SPF albino rats were given 1, 5, or 10% Mannitol in the diet for 94 wks. A slight increase in the incidences of tissue masses in the anogenital area, cervix, and uterus were noted when female Fischer rats were given 10% Mannitol in the diet for 30 mos. Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly in Sprague-Dawley rats given 20% Sorbitol in the diet for 78 wks. A small number of tumors were found in the transitional epithelium of male mice treated with 20% Xylitol. Animals treated with 2, 10, or 20% Mannitol showed fewer renal tumors than control mice. A statistically significant increase in the number of pheochromocytomas was observed in male rats treated with 20% Xylitol for their entire life span, however, the total number of tumor-bearing rats was similar between treated and control groups.

The protective effect of Mannitol was assessed using rat debrided corneal epithelium. Eye drops containing a BAC solution alone had a 75% healing rate, while eye drops containing a BAC solution with 0.5% Mannitol displayed a 90.1% healing rate. The ability of Xylitol to alleviate irritation and inflammation was studied in SKH-1 hairless mice. A decreased lymphocyte number was observed in the epidermis when animals treated with Xylitol and SLS, compared to SLS alone. The addition of Xylitol also effectively decreased MPO activity in the skin.

Xylitol (5 or 10%) incorporated into a gel or cream was non-irritating to New Zealand rabbit skin. A trade name material consisting 15% Mannitol and 15% disodium adenosine triphosphate was used in a Magnusson-Kligman maximization test (0.5 % and 10% aqueous dilution) and HRIPT (10% aqueous dilution). No signs of sensitization were observed in either study. No sensitization was reported when an HRIPT was performed on 110 subjects using a lotion containing 3% Xylitol.

A phototoxicity and photosensitization study was performed with a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate. The test substances were applied at 10% and 2% aqueous dilutions in the phototoxicity and photosensitization studies, respectively. No skin reactions were noted in either study.

A test substance consisting of Xylitol (5 or 10%) incorporated into a gel or cream was applied to Dunkin-Hartley albino guinea pigs in a phototoxicity assay. In animals exposed to 10% Xylitol via cream or gel, 3 out of 4 animals displayed a positive reaction, while all controls presented a negative reaction. It was determined that Xylitol has moderate phototoxic potential.

In adult cystic fibrosis patients, the reported mean half-lives of inhaled dry powder Mannitol, twice daily, for 7 days, was 5.42 h on day 7. Both normal and diabetic adults were given 35 g Sorbitol orally. In patients without diabetes, Sorbitol did not have a significant effect on blood sugar levels. However, in all diabetic subjects, significant increases in blood-sugar concentrations ranging from 9 to 49 mg/100mL occurred after Sorbitol administration. Thirty-eight bronchiectasis patients were given spray dried Mannitol (420 mg), twice a day, for 2 wks, via inhalation. Adverse effects were reported in 71.1% of subjects given Mannitol, and in 69.4% control subjects. A similar study was performed in 48 subjects given up to 400 mg Mannitol for 2 wks. Headache, aggravated condition, pyrexia, and pharyngolaryngeal pain was among the adverse effects reported. When 10 subjects were exposed to 1, 5, or 10 mL of 5% Xylitol, adverse effects such as a stuffy nose, cough, chest tightness, and phlegm production were noted.

DRAFT DISCUSSION

The 3 ingredients in this report are sugar alcohols, each of which is commonly ingested in food products. Since the ingestion of these ingredients is safe, and exposure relating from ingestion of food would be far greater than exposure due to cosmetic use, the concern for systemic toxicity was mitigated.

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

CONCLUSION

To be determined.

TABLES

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

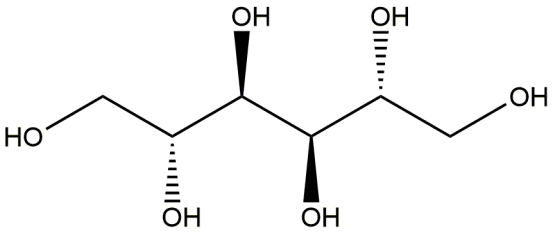
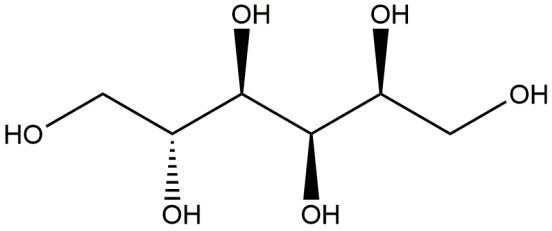
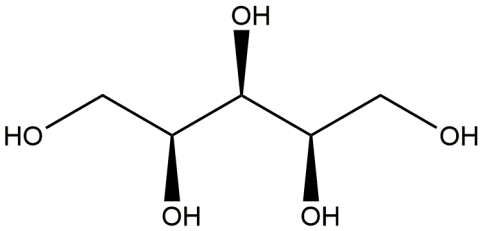
Ingredient CAS No.	Definition & Structure	Function(s)
Mannitol 69-65-8 87-78-5	Mannitol is the hexahydric alcohol that conforms to the formula: 	Binders; Flavoring Agents; Humectants; Skin-Conditioning Agents- Humectant
Sorbitol 50-70-4	Sorbitol is the hexahydric alcohol that conforms to the formula: 	Flavoring Agents, Fragrance Ingredients, Humectants; Skin-Conditioning Agents- Humectant
Xylitol 87-99-0	Xylitol is the pentahydric alcohol that conforms to the formula: 	Deodorant Agents; Flavoring Agents; Humectants; Skin-Conditioning Agents- Humectant

Table 2. Chemical Properties of Mannitol, Sorbitol, and Xylitol

Property	Value	Reference
Mannitol		
Physical Form	crystalline powder or free-flowing granules	9
Color	white	9
Odor	odorless	9
Molecular Weight (g/mol)	182.172	9
Density/Specific Gravity (@ 20 ºC)	1.52	9
Melting Point (ºC)	168	9
Boiling Point (ºC)	290 - 295	9
Water Solubility (g/L @ 25 ºC)	216	9
log K_{ow}	-3.10	9
Disassociation constants (pKa) (@ 25 ºC)	13.50	9
Sorbitol		
Physical Form	crystalline powder, granules	10
Color	white	10
Molecular Weight (g/mol)	182.172	10
Density/Specific Gravity (@ 20 ºC)	1.489	10
Vapor Pressure (mmHg@ 25 ºC)	9.9×10^{-9}	10
Melting Point (ºC)	111	10
Boiling Point (ºC)	295	10
Water Solubility (g/L @ 25 ºC)	2750	10
log K_{ow}	-2.20	10
Disassociation constants (pKa) (@ 25 ºC)	13.6	10

Table 2. Chemical Properties of Mannitol, Sorbitol, and Xylitol

Property	Value	Reference
Xylitol		
Physical Form	crystalline powder	[8]
Color	white	[8]
Molecular weight (g/mol)	152.146	[8]
Vapor Pressure (mmHg @ 25 ºC)	2.47×10^{-3}	[8]
Melting Point (ºC)	93.5	[8]
Boiling Point (ºC)	216	[8]
Water Solubility (g/L @ 20 ºC)	642	[8]
log K_{ow}	-2.56	[8]

Table 3. Frequency (2019) and Concentration (2018) of Use

	# of Uses[17]	Max Conc of Use (%)[18]	# of Uses[17]	Max Conc of Use (%)[18]	# of Uses[17]	Max Conc of Use (%)[18]
	Mannitol		**Sorbitol**		**Xylitol**	
Totals*	404	0.000063 – 60.5	1976	0.00007 – 70	472	0.013 – 14
Duration of Use						
Leave-On	337	0.000063 – 60.5	1177	0.0005 – 20	290	0.013 – 2
Rinse-Off	66	0.023 – 20	783	0.00007 – 70	181	0.05 – 14
Diluted for (Bath) Use	1	NR	16	0.02 – 2.5	1	NR
Exposure Type						
Eye Area	46	0.00008 – 0.1	139	0.00044 – 4.9	27	NR
Incidental Ingestion	5	0.4 – 4.1	105	1.1 – 70	113	0.06 – 14
Incidental Inhalation-Spray	117[a]; 101[b]	0.9[b]	8; 343[a]; 454[b]	1.8 – 3.5[a]; 0.0012 – 32[b]	1; 103[a]; 109[b]	0.15[b]
Incidental Inhalation-Powder	6; 117[a]	0.2; 0.1 – 2.3[c]	2; 343[a]; 4[c]	2.3 – 3.6; 1.8 – 3.50[a]; 0.006 – 20[c]	103[a]; 2[c]	0.042 – 2[c]
Dermal Contact	372	0.000063 – 60.5	1532	0.00044 – 31.9	330	0.013 – 2
Deodorant (underarm)	3[b]	0.12	3[b]	0.0005 – 1.1	27[b]	0.09; 0.013[b]
Hair - Non-Coloring	11	0.023 – 12.5	309	0.00007 – 10.9	28	0.15 – 0.24
Hair-Coloring	1	NR	11	0.006 – 5	NR	0.05
Nail	14	0.015 – 0.03	5	3.5 – 7	NR	NR
Mucous Membrane	17	0.051 – 4.1	337	0.02 – 70	128	0.06 - 14
Baby Products	NR	NR	9	1.4 – 14	7	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays...
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – no reported use

Table 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
			ORAL			
Mannitol	Mice	5/sex/group	distilled water	0.3, 0.6, 1.2, 2.5, or 5 g/kg via gavage	> 5 g/kg/bw	35
Mannitol	Mice	NR	NR	NR	22 g/kg/bw	34
Mannitol	Rats	5/sex/group	distilled water	0.3, 0.6, 1.2, 2.5, or 5 g/kg via gavage	> 5 g/kg/bw	35
Mannitol	Rats	NR	NR	NR	13.5 g/kg/bw	34
Mannitol	Rats	10/group	NR	NR	17.3 g/kg/bw	29
Sorbitol	Mouse (male)	NR	NR	NR	23.2 g/kg/bw	36
Sorbitol	Mouse (female)	NR	NR	NR	25.7 g/kg/bw	36
Sorbitol	Rat (male)	NR	NR	NR	17.5 g/kg/bw	36
Sorbitol	Rat (female)	NR	NR	NR	15.9 g/kg/bw	36
Xylitol	Mouse	NR	NR	NR	25.7 g/kg/bw	37
Xylitol	Mouse	NR	NR	NR	12.5 g/kg/bw	37
Xylitol	Mouse	NR	NR	NR	22 g/kg/bw	37
Xylitol	Rat	10/group	5% gum acacia solution	up to 4 g/kg/bw; gavage	> 4 g/kg/bw	32
Xylitol	Rat	NR	NR	NR	14.1 g/kg/bw	37
Xylitol	Rat	NR	NR	NR	17.3 g/kg/bw	37
Xylitol	Rabbit	NR	NR	NR	25 g/kg/bw	37
			INHALATION			
Mannitol	Rats	10/group	NR	≤ 98 mg/kg; observation for 14 days after 1 h exposure	No deaths. Over the 14-day observation period, there was a reduction of body weight gain (42% lower than controls, 24% lung/bronchi weight decrease, arterial mural mineralization in the lung/bronchi(4/10), inflammatory cells in nasal turbinates (4/10), loss of cilia in trachea (6/10). These effects were seen at 98 mg/kg/d.	34
Xylitol	Mice	6	Water	Mice were exposed to aerosolized Xylitol (5%) for 150 min in an exposure chamber	Well tolerated by mice with no significant effects on the airway physiology or composition of airway inflammatory cells	38

Table 5. Repeated Dose Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
				DERMAL		
Sorbitol	4 groups of 5 female albino rabbits	30 days	water and propylene glycol	30%; a dose of 0.5 mL was applied to shaved skin and covered with an occlusive patch	No macroscopic changes were noted. Microscopic evaluation after 10 days of treatment displayed moderate acanthosis with cellular vacuolization and a thinning out of collagen fibers of the superficial portions of the dermis.	[39]
				ORAL		
Mannitol	B6C3F1 Mice (5/sex)	14 days	Feed	0.6, 1.25, 2.5, 5 or 10%	All animals survived the study and no compound-related effects were observed.	[35]
Mannitol	B6C3F1 Mice (10/sex)	13 wks	Feed	0, 0.3, 0.6, 1.2, 2.5 or 5%	Mean body weight gain was higher than controls in all dose groups except for males given 5.0% Mannitol. All animals survived the duration of the study and no compound-related effects were observed.	[35]
Mannitol	F344/N Rats (5/sex)	14 days	Feed	0.6, 1.25, 2.5, 5, 10%	Necropsies were performed on all animals. No animals died, and all groups had similar increases in body weight. Females fed diets containing 10% Mannitol gained less weight than females fed a lower concentration. Two out of 5 of the male rats given 10% Mannitol had diarrhea on days 4 to 6. No gross lesions were observed	[35]
Mannitol	F344/N Rats (10/sex)	13 wks	Feed	0, 0.3, 0.6, 1.25, 5%	Mean body weight gains of the top-dose group males were depressed by 9.6% relative to the controls. Mean body weight gains in all other groups were similar to the control group. All animals survived the study and no compound-related clinical signs were observed.	[35]
Mannitol	Wistar-derived SPF albino Rats (# of animals not provided)	94 wks	Feed	0, 1, 5, 10%	Body weights were generally decreased by 5-7% in the medium and high dose male rats. A low incidence of benign thymomas was present in female rats (2 thymic tumors in female controls, 6 in each of the 1 and 5% Mannitol group, and 10 in the 10% Mannitol group). No significant difference in thymomas between treated and control groups were observed in male rats.	[29]
Mannitol	Female Sprague Dawley Rats (# of animals not provided)	27 mos	Feed	0, 1, 5, 10%	The mortality rate of the rats receiving 10% Mannitol was 68%. No other Mannitol-induced effects were reported. The mortality rate of control rats was not stated. The authors of the study did not attribute deaths to Mannitol exposure.	[29]
Sorbitol	Mongrel Dogs (1 male, 1 female)	3 days	Water	0.675, 1.35 g/kg bw (90% w/vol); doses given via stomach tube	At the highest dose, the stomach appeared hyperemic.	[36]
Sorbitol	Wistar Rats (15 males)	17 mos	Diet	10 or 15%	No evidence of deleterious effect on weight gain, reproduction, or histopathological appearances of the main organs. Slight diarrhea was apparent in treated animals.	[36]
Xylitol	Sprague-Dawley Rats (20 rats/sex/dose)	2, 5, or 14 days (gavage)	NR	0, 1.25 then 10 g/kg/d, 2.5 g/kg/d only, or 5 g/kg/d only	No evidence of hepatotoxicity was reported. Serum levels of all parameters measured (glucose, bilirubin, free fatty acids, total lipids, triglycerides, cholesterol, alkaline phosphatases, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, glucose 6-phosphate dehydrogenase) were within normal limits.	[40]
Xylitol	Rats (# of animals not provided)	NR	Feed	10 or 30%	No effect on weight gain, fertility, or histology of the liver, kidneys, or heart.	[37]

Table 5. Repeated Dose Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
Xylitol	8 CD rats/sex/group	13 wks	Feed	0, 5, 10, 20 g/kg/d	At study completion, mean body weights of male and female rats fed Xylitol at 20 g/kg/d and 10 g/kg/d were significantly less than control groups. A slight increase in brain, liver, kidney, heart, spleen, and testes weight was observed in the same groups when expressed as a percent body weight. The test substance was considered to be tolerated well. Slightly reduced weight gains and transient diarrhea were observed at the highest dose levels.	32,37
Xylitol	Rats (# of animals not provided)	90 days (gavage)	NR	0.5 or 1.73 g/kg	Reduced sleep and activity of rats was recorded after treatment with 1.73 g/kg. At the 0.5 g/kg dose level, no changes were recorded.	37
Xylitol	Monkeys (# of animals not provided)	13 wks (gavage)	NR	1, 3, 5 g/kg/d	Transient diarrhea and soft stools were initially present in the high dose group. No effects relating to behavior, appetite, body weight, organ weight, gross pathology, or microscopic pathology were observed.	61
Xylitol	Beagle Dogs (8/sex/dose)	2 years	Feed	0, 2, 5, 10, 20%	Treated animals gained weight more rapidly than controls. Urinary, hematological, and biochemical investigations yielded results within the usual biological range. However, during the first year of treatment, a slightly elevated serum alkaline phosphatase and serum protein values was observed in the 20% Xylitol group. Dogs in the 20% Xylitol group had slightly heavier livers than in other groups. No degenerative changes were reported.	42
INHALATION						
Mannitol	Sprague-Dawley Rats (5/sex/dose)	7 days	Air	5 or 9 mg of Mannitol/L of air (exposure of 120-240 minutes/day)	The estimated achieved dose of Mannitol was 573 and 979 mg/kg/d for the low dose and high dose groups, respectively. No treatment-related effects were reported.	6
Mannitol	CD-1 Rats (10/sex/dose)	2 wks	Air	0, 0.9, 2.5, and 6.9 mg/kg	No significant treatment related effects were observed. An NOAEL of 6.9 mg/kg/d was determined.	6
Mannitol	Beagle Dogs (3/sex/group)	2 wks	Air	0, 25, 100, 197 mg/kg/d	Coughing occurred during and after dosing in all treated groups. Spongy (4/6) and froth-filled lung (3/6) were reported in the animals dosed with 197 mg/kg of Mannitol. Lung congestion/hemorrhage was apparent in 2/6 high-dose animals, and pigment in the submandicular lymph node was seen in 3/6 high-dose animals. Peribronchiolar infiltration and foamy alveolar macrophages was observed in all dosed animals. Inflammatory foci and focal hyperplasia were seen in 1/3 high dose female animals.	6
Mannitol	Beagle Dogs (4/sex/dose)	26 wks	Air	0, 43, 178 mg/kg/d (0, 0.20, 8.7 mg/L) (120 minutes exposure/day)	Coughing occurred during and after dosing in the high dose group, but only in the first week in the low dose group. Minimal laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node were observed in the high-dose group. No other treatment related effects were noted.	6
Mannitol	Dogs (number of animals and strain not reported)	26 wks	Air	up to 834 mg/kg/d	Coughing primarily occurred early in the treatment phase, and then reduced down to a minimum. Salivation and emesis were also observed. Enlargements of the mandibular lymph nodes were observed in 2 out of the 4 treated animals. One out of four treated females given 716 mg/kg Mannitol per day displayed erythrophagocytosis or lymphadenitis, however, this effect was not present in male dogs.	34
Xylitol	Beagle Dogs (3/sex/group)	14 days	Water	4 mg/L of either saline (control) or aerosolized Xylitol for 15, 30, or 60 minutes/day	All animals survived to their scheduled sacrifice and no statistically significant difference among exposed and control groups were observed in body weights or food consumption. Additionally, there was no exposure-related change in organ weight, gross pathology lesions, or microscopic lesions.	41

Table 6. Carcinogenicity studies

Ingredient	Animal (#/group)	Vehicle	Procedure	Results	Reference
Mannitol	50 F344/N rats/sex and 50 B6C3F1 mice/sex	Diet	A diet containing D-Mannitol was given to animals for 103 wks at concentrations of 0, 2.5, or 5%.	Survival and mean body weights of dosed and control male rats and of dosed and control mice of both sexes were similar. High-dose female rats had a statistically significant higher ($P < 0.05$) survival rate than low-dose female rats; however, neither the survival of the low-dose group nor that of the high-dose group was significantly different than that of the controls. Mean body weight gain of treated rats was depressed (<10%) compared to that of the controls. Dilation of the gastric fundal gland was observed in increased in dosed female rats compared to that of the controls. Retinopathy and cataracts were apparent in high-dose male rats and low- and high-dose female rats. Mild nephrosis characterized by focal vacuolization of the renal tubular epithelium was seen in increased incidence in dosed mice of each sex. The test substance was considered to be non-carcinogenic.	[14,35]
Mannitol	50 Wistar rats/group/sex	Diet	In a study examining the toxic potential of erythritol, a control group of animals given diets containing 10% Mannitol for 104 - 107 wks was used.	No significant increase in tumor incidence noted. Treatments were well-tolerated without diarrhea or other side effects. Body weights were significantly below control levels. Survival of the animals was not adversely affected by treatment. In male and female rats, pelvic nephrocalcinosis, which in females was directly associated with pelvic hyperplasia, was noted.	[52]
Mannitol	Wistar-derived SPF albino rats (# of rats not stated)	Diet	Animals were fed a diet containing 0, 1, 5, or 10% Mannitol for 94 wks.	A low incidence of benign thymomas was observed.	[29]
Mannitol	Female Wistar rats (100/group)	Diet	Animals were fed a diet containing 0, 1, 5, or 10% Mannitol for 30 mos.	Slightly increased incidences of tissues masses in the cervix and/or uterus was noted in the treated groups compared to the control. This was considered of no biological importance because of their low overall incidence. Histopathological evaluations of the thymus did not reveal any abnormalities. Overall body weight gain differences between the control and treated groups were slight, and not statistically significant. Evaluation of mortality, behavior, food consumption, urinary chemistry, organ and body weights, and subcutaneous tissue masses were similar to controls.	[29]
Mannitol	Female Fischer rats (100 animals/group)	Diet	Rats were given 0, 1, 5, or 10% Mannitol in the diet for 30 mos.	Slightly increased incidences of tissue masses in the anogenital area, cervix and uterus were noted in the high dosed group compared to the control group. The incidence of uterine masses was well within the expected spontaneous incidence rate for this strain of rats. Focal medullary hyperplasia and medullary pheochromocytoma was higher in the high-dose group compared to the control group, however, no clear dose response was seen. The mean body weights of rats receiving 5 or 10% Mannitol were slightly lower than control rats.	[29]

Table 6. Carcinogenicity studies

Ingredient	Animal (#/group)	Vehicle	Procedure	Results	Reference
Sorbitol	75 Sprague-Dawley rats/sex/dose	Diet	Animals were given Sorbitol (0 or 20%) in the diet for 78 wks.	Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly for males and females receiving Sorbitol.	[36]
Xylitol	100 mice/sex (strain not stated)	Diet	Mice were fed a diet containing up to 20% Xylitol for their entire life-span.	An increased incidence of crystalline calculi in the urinary bladder was apparent in male mice treated with 10 and 20% Xylitol. A small number of tumors, both benign and malignant, were found in the transitional epithelium in high-dose male mice. All Xylitol-treated animals showed fewer renal tumors than control animals. Hepatocellular tumors were observed in both sexes in all experimental groups, but were more frequent in males; However, male mice treated with Xylitol showed a lower incidence of hepatocellular tumor than control mice. Male mice in the highest Xylitol dosage group displayed an increase in centrilobular degenerative changes in the liver compared to the control group.	[62]
Xylitol	75 rats/sex (strain not stated)	Diet	Rats were fed a diet containing up to 20% Xylitol for the majority of the animals' lifespan.	Unilateral or bilateral pheochromocytomas were observed in a proportion of rats from all groups, including controls. A statistically significant increase in the number of pheochromocytomas was observed in male rats treated with 20% Xylitol ($p < 0.05$) compared to the controls. The total number of tumor-bearing rats was similar between treated and control groups.	[63]

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2019 FDA Frequency of Use Data

Xylitol: 472 total

01A - Baby Shampoos	XYLITOL	1
01B - Baby Lotions, Oils, Powders, and Creams	XYLITOL	2
01C - Other Baby Products	XYLITOL	4
02A - Bath Oils, Tablets, and Salts	XYLITOL	1
03D - Eye Lotion	XYLITOL	11
03E - Eye Makeup Remover	XYLITOL	8
03F - Mascara	XYLITOL	1
03G - Other Eye Makeup Preparations	XYLITOL	7
04E - Other Fragrance Preparation	XYLITOL	1
05A - Hair Conditioner	XYLITOL	4
05C - Hair Straighteners	XYLITOL	2
05F - Shampoos (non-coloring)	XYLITOL	14
05G - Tonics, Dressings, and Other Hair Grooming Aids	XYLITOL	2
05I - Other Hair Preparations	XYLITOL	5
07C - Foundations	XYLITOL	8
07F - Makeup Bases	XYLITOL	3
07I - Other Makeup Preparations	XYLITOL	6
09A - Dentifrices	XYLITOL	52
09B - Mouthwashes and Breath Fresheners	XYLITOL	22
09C - Other Oral Hygiene Products	XYLITOL	39
10A - Bath Soaps and Detergents	XYLITOL	6
10B - Deodorants (underarm)	XYLITOL	27
10E - Other Personal Cleanliness Products	XYLITOL	8
11A - Aftershave Lotion	XYLITOL	1
11E - Shaving Cream	XYLITOL	1

12A - Cleansing	XYLITOL	21
12C - Face and Neck (exc shave)	XYLITOL	82
12D - Body and Hand (exc shave)	XYLITOL	21
12F - Moisturizing	XYLITOL	76
12G - Night	XYLITOL	6
12H - Paste Masks (mud packs)	XYLITOL	3
12I - Skin Fresheners	XYLITOL	1
12J - Other Skin Care Preps	XYLITOL	24
13B - Indoor Tanning Preparations	XYLITOL	1
13C - Other Suntan Preparations	XYLITOL	1

Mannitol: 404 total

02A - Bath Oils, Tablets, and Salts	MANNITOL	1
03B - Eyeliner	MANNITOL	1
03C - Eye Shadow	MANNITOL	8
03D - Eye Lotion	MANNITOL	8
03E - Eye Makeup Remover	MANNITOL	8
03F - Mascara	MANNITOL	1
03G - Other Eye Makeup Preparations	MANNITOL	20
05A - Hair Conditioner	MANNITOL	1
05E - Rinses (non-coloring)	MANNITOL	1
05F - Shampoos (non-coloring)	MANNITOL	6
05I - Other Hair Preparations	MANNITOL	3
06G - Hair Bleaches	MANNITOL	1
07A - Blushers (all types)	MANNITOL	6
07B - Face Powders	MANNITOL	6
07C - Foundations	MANNITOL	12
07F - Makeup Bases	MANNITOL	3
07I - Other Makeup Preparations	MANNITOL	2

08A - Basecoats and Undercoats	MANNITOL	1
08B - Cuticle Softeners	MANNITOL	1
08E - Nail Polish and Enamel	MANNITOL	11
08G - Other Manicuring Preparations	MANNITOL	1
09A - Dentifrices	MANNITOL	5
10A - Bath Soaps and Detergents	MANNITOL	11
10B - Deodorants (underarm)	MANNITOL	3
11A - Aftershave Lotion	MANNITOL	1
11G - Other Shaving Preparation Products	MANNITOL	1
12A - Cleansing	MANNITOL	22
12C - Face and Neck (exc shave)	MANNITOL	104
12D - Body and Hand (exc shave)	MANNITOL	12
12E - Foot Powders and Sprays	MANNITOL	1
12F - Moisturizing	MANNITOL	81
12G - Night	MANNITOL	11
12H - Paste Masks (mud packs)	MANNITOL	10
12I - Skin Fresheners	MANNITOL	6
12J - Other Skin Care Preps	MANNITOL	31
13B - Indoor Tanning Preparations	MANNITOL	1
13C - Other Suntan Preparations	MANNITOL	2

Sorbitol: 1976 total

01B - Baby Lotions, Oils, Powders, and Creams	SORBITOL	4
01C - Other Baby Products	SORBITOL	5
02A - Bath Oils, Tablets, and Salts	SORBITOL	9
02B - Bubble Baths	SORBITOL	6
02D - Other Bath Preparations	SORBITOL	1
03A - Eyebrow Pencil	SORBITOL	1
03B - Eyeliner	SORBITOL	25

03C - Eye Shadow	SORBITOL	8
03D - Eye Lotion	SORBITOL	42
03E - Eye Makeup Remover	SORBITOL	4
03F - Mascara	SORBITOL	14
03G - Other Eye Makeup Preparations	SORBITOL	45
04A - Cologne and Toilet waters	SORBITOL	1
04B - Perfumes	SORBITOL	1
04E - Other Fragrance Preparation	SORBITOL	1
05A - Hair Conditioner	SORBITOL	53
05B - Hair Spray (aerosol fixatives)	SORBITOL	5
05C - Hair Straighteners	SORBITOL	13
05E - Rinses (non-coloring)	SORBITOL	2
05F - Shampoos (non-coloring)	SORBITOL	70
05G - Tonics, Dressings, and Other Hair Grooming Aids	SORBITOL	94
05H - Wave Sets	SORBITOL	7
05I - Other Hair Preparations	SORBITOL	65
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	SORBITOL	4
06C - Hair Rinses (coloring)	SORBITOL	1
06D - Hair Shampoos (coloring)	SORBITOL	1
06G - Hair Bleaches	SORBITOL	1
06H - Other Hair Coloring Preparation	SORBITOL	4
07B - Face Powders	SORBITOL	2
07C - Foundations	SORBITOL	30
07D - Leg and Body Paints	SORBITOL	1
07E - Lipstick	SORBITOL	3
07F - Makeup Bases	SORBITOL	5
07G - Rouges	SORBITOL	1
07H - Makeup Fixatives	SORBITOL	1
07I - Other Makeup Preparations	SORBITOL	25
08B - Cuticle Softeners	SORBITOL	3

08C - Nail Creams and Lotions	SORBITOL	1
08G - Other Manicuring Preparations	SORBITOL	1
09A - Dentifrices	SORBITOL	65
09B - Mouthwashes and Breath Fresheners	SORBITOL	15
09C - Other Oral Hygiene Products	SORBITOL	22
10A - Bath Soaps and Detergents	SORBITOL	205
10B - Deodorants (underarm)	SORBITOL	3
10E - Other Personal Cleanliness Products	SORBITOL	11
11A - Aftershave Lotion	SORBITOL	15
11D - Preshave Lotions (all types)	SORBITOL	1
11E - Shaving Cream	SORBITOL	23
11F - Shaving Soap	SORBITOL	8
11G - Other Shaving Preparation Products	SORBITOL	42
12A - Cleansing	SORBITOL	175
12B - Depilatories	SORBITOL	5
12C - Face and Neck (exc shave)	SORBITOL	217
12D - Body and Hand (exc shave)	SORBITOL	122
12E - Foot Powders and Sprays	SORBITOL	4
12F - Moisturizing	SORBITOL	269
12G - Night	SORBITOL	44
12H - Paste Masks (mud packs)	SORBITOL	51
12I - Skin Fresheners	SORBITOL	14
12J - Other Skin Care Preps	SORBITOL	87
13A - Suntan Gels, Creams, and Liquids	SORBITOL	4
13B - Indoor Tanning Preparations	SORBITOL	13
13C - Other Suntan Preparations	SORBITOL	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: June 19, 2019

SUBJECT: Mannitol and Disodium Adenosine Triphosphate

Anonymous. 2019. Summary of studies of a trade name mixture containing: 15% Mannitol and 15% Disodium Adenosine Triphosphate.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

June 2019

Summary of Studies of a Trade Name Mixture Containing: 15% Mannitol and 15% Disodium Adenosine Triphosphate

Phototoxicity

A phototoxicity study (completed in 1993) was conducted with the trade name mixture (10% aqueous solution of the mixture [1.5% Mannitol, 1.5% Disodium Adenosine Triphosphate]) in 10 volunteers. The test item (0.2 ml) was applied under occlusive conditions to two different areas of the forearm, one designated as non-irradiated, the other as the irradiated test site. After a 24-hour exposure, one treated site was irradiated with UVA light (320-400 nm) for 15 minutes. The other site served as the non-irradiated control. Skin reactions were scored immediately after light exposure as well as 24 and 48 hours later.

Results: No reactions were noted on either the irradiated or non-irradiated test material contact site in any subject.

Skin Sensitization

Guinea Pig Maximization Test

In a study completed in 1992, a test according to the Magnusson Kligman method was completed with the trade name mixture in male and female albino guinea pigs (strain Pirbright white). Concentrations were 0.5% (w/w) (0.075% Mannitol and 0.075% Disodium Adenosine Triphosphate) in adjuvant and water, and 10% in water (w/v) (1.5% Mannitol, 1.5% Disodium Adenosine Triphosphate) for the intracutaneous induction, and epicutaneous induction and challenge, respectively.

Results: No signs of irritation and skin reactions indicative of an immune response were seen at the readings 24 and 48 hours after removal of the challenge patch

Human Repeated Insult Patch Test

In a study completed in 1992, a 10% aqueous solution of the trade name material (1.5% Mannitol, 1.5% Disodium Adenosine Triphosphate) was repeatedly applied (total of 9 applications within 3 weeks) for 24 hours under occlusive conditions to the backs of 52 volunteers during the induction phase. The challenge took place two weeks later with the same concentration and the same area as well as a naïve site of the back. Readings were taken 24 hours after removal of the patches during induction, as well as 48 and 96 hours after removal of the challenge patches.

Results: Among the 50 volunteers completing the study, no skin reactions were noted during both induction and challenge.

Photosensitization

A photosensitization test (completed in 1994) with the trade name mixture (2% solution in water [0.3% Mannitol, 0.3% Disodium Adenosine Triphosphate]) was conducted on 36 volunteers. For 3 weeks, 6 induction patches with the test item were applied in duplicate to the same site of the skin for 24 hours each time, one site subsequently irradiated with UV light (260-400 nm) for 15 minutes each session,

while the other site was left non-irradiated. After two weeks, the challenge patch was applied at virgin sites with and without irradiation.

Results: At the challenge phase, no skin reactions were exhibited on either the irradiated or the non-irradiated test material contact site. No reactions were observed on the irradiated or non-irradiated control site of the 34 individuals completing the study.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 30, 2019

SUBJECT: Xylitol

TKL Research, Inc. 2018. Human repeat insult patch test with body lotion containing 3% Xylitol.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

TKL RESEARCH

HUMAN REPEAT INSULT PATCH TEST

with body lotion containing 3% xylitol

TKL STUDY NO. [redacted]

[redacted]

CONDUCTED FOR:

[redacted]

DATE OF FINAL REPORT:

December 7, 2018

TABLE OF CONTENTS

APPENDICES

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

Jonathan S. Dosik Digitally signed by Jonathan S. Dosik Date: 2018.12.07 09:06:18 -05'00' December 7, 2018

Jonathan S. Dosik, MD
Dermatologist
Principal Investigator

Date

Tina LaRosa Digitally signed by Tina LaRosa Date: 2018.12.07 09:06:28 -05'00' December 7, 2018

Tina LaRosa
Director, Dermatologic Safety Operations

Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY
Human Repeat Insult Patch Test

SPONSOR
[redacted]

STUDY MATERIAL
[redacted] Lotion [redacted] body lotion containing 3% xylitol

DATE STUDY INITIATED
August 20, 2018

DATE STUDY COMPLETED
October 5, 2018

DATE OF FINAL REPORT
December 7, 2018

INVESTIGATIVE PERSONNEL
Jonathan S. Dosik, MD – Board Certified Dermatologist
Principal Investigator

Tina La Rosa
Director, Dermatologic Safety Operations

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SUMMARY

a body lotion containing 3% xylitol

One (1) product, [redacted], was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with self-assessed sensitive skin using a semi-occlusive repeated insult patch study. One hundred ten (110) subjects completed the study.

The Dermatologist was present at final grading.

Under the conditions employed in this study, there was no evidence of sensitization to [redacted].

1.0 OBJECTIVE

The objective of this study was to confirm that a test substance will not produce evidence of delayed contact sensitization following external contact with the skin by means of a repeated patch application procedure.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were to be enrolled to provide 100 completed subjects. Subjects were given a screener and questionnaire. Based on the responses from these 2 documents, subjects were categorized as having self-perceived sensitive skin. 100% of the subjects had self-perceived sensitive skin. In the absence of any sensitization reactions in this sample size (100 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 3.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 years of age or older (no more than 20% over the age of 65), in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Had self-perceived sensitive skin (determined by Sensitive Skin Questionnaire [Appendix I, of the protocol Appendix IV] provided by the Sponsor);
4. Were of race providing the skin pigmentation that allowed discernment of erythema;
5. Had completed a medical screening procedure; and
6. Had read, understood and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;
2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2]

Following the ninth evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). The Dermatologist was present at the final grading. Re-challenge was performed whenever there was evidence of possible sensitization.

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

Due to the holiday occurring on Monday, September 3, 2018 subjects from both [redacted] and [redacted] were instructed to return to the facility on Tuesday, September 4, 2018.

3.2.2 Definitions Used for Grading Responses

The symbols found in the data listings accompanying this report were used to express the response observed at the time of examination:

SYMBOL AND RESPONSE

- = No reaction

? = Minimal or doubtful response, slightly different from surrounding normal skin

\+ = Definite erythema, no edema

++ = Definite erythema, definite edema

+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema

S = Spreading of reaction beyond patch site (ie. reaction where material did not contact skin)

p = Papular response > 50%

pv = Papulovesicular response > 50%

D = Damage to epidermis: oozing, crusting and/or superficial erosions

I = Itching

X = Subject absent

PD = Patch dislodged

NA = Not applied

NP = Not patched (due to reaction achieved)

N9G = No ninth grading

3.2.3 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS body lotion containing 3% xylitol

Identification : [redacted] Lotion [redacted]
Amount Applied : 0.15mL
Special Instructions : The study material was applied to patch immediately prior to patch application.

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material were discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

Study material was applied to the patch as instructed. The patch was applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater at the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to Rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 PROTOCOL

See Protocol - Appendix IV.

7.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) are designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 20 years from completion of the study. Storage is maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provides a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of TKL.

8.0 RESULTS AND DISCUSSION

One hundred nineteen (119) subjects between the ages of 18 and 70 were enrolled and 110 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition:

Number enrolled:		119
Number discontinued:		9
Lost to follow-up:	8	
Voluntary withdrawal:	1	
Number completed:		110

Source: Table 1, Appendix I

There were no adverse events (AEs) reported on the study.

The Dermatologist was present at final grading.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

9.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to [redacted] a body lotion containing 3% xylitol

10.0 REFERENCES

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Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

APPENDIX I

SUMMARY TABLES

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	57
Subjects completed induction phase	56 (98.2)
Subjects completed all phases	56 (98.2)
Total subjects discontinued	1 (1.8)
Voluntary withdrawal	1 (1.8)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	13 (22.8)
N (%) 45 to 65	37 (64.9)
N (%) 66 and up	7 (12.3)
Mean (SD)	51.9 (12.2)
Median	54.6
Range	20.4 to 70.8
Sex	
N (%) Male	12 (21.1)
N (%) Female	45 (78.9)
Race	
Asian	1 (1.8)
Black	3 (5.3)
Caucasian	53 (93.0)
Ethnicity	
Hispanic/Latino	2 (3.5)
Not Hispanic/Not Latino	55 (96.5)

See data listing 2 for further detail.

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[redacted]
TKL Study No. [redacted]

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = [redacted] REF# [redacted]

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	55	55	51	55	55	56	56	56	55	2	56	56	
Total evaluable	55	55	51	55	55	56	56	56	55	2	56	56	
Number absent	2	2	5	1	1	0	0	0	1		0	0	
Number discontinued	0	0	1	1	1	1	1	1	1		1	1	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N= 56)

Response	n(%) Subjects
-	56 (100.0%)

Maximum Elicited Response During Challenge
All Subjects Completing Challenge (N= 56)

Response	n(%) Subjects
-	56 (100.0%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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TKL Study No. [redacted]

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	62
Subjects completed induction phase	56 (90.3)
Subjects completed all phases	54 (87.1)
Total subjects discontinued	8 (12.9)
Lost to follow-up	8 (12.9)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	21 (33.9)
N (%) 45 to 65	32 (51.6)
N (%) 66 and up	9 (14.5)
Mean (SD)	49.0 (15.3)
Median	51.3
Range	18.3 to 69.7
Sex	
N (%) Male	12 (19.4)
N (%) Female	50 (80.6)
Race	
Amer Ind	1 (1.6)
Asian	1 (1.6)
Black	30 (48.4)
Caucasian	30 (48.4)
Ethnicity	
Hispanic/Latino	4 (6.5)
Not Hispanic/Not Latino	58 (93.5)

See data listing 2 for further detail.

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[redacted]
TKL Study No. [redacted]

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = [redacted] REF# [redacted]

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	58	59	54	56	55	55	56	55	55	4	53	53	
?	0	0	0	1	1	1	0	0	0	0	1	1	
Total evaluable	58	59	54	57	56	56	56	55	55	4	54	54	
Number absent	1	0	3	0	1	1	0	1	1		0	0	
Number discontinued	3	3	5	5	5	5	6	6	6		8	8	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N= 56)

Response	n(%) Subjects
-	55 (98.2%)
?	1 (1.8%)

Maximum Elicited Response During Challenge
All Subjects Completing Challenge (N= 54)

Response	n(%) Subjects
-	53 (98.1%)
?	1 (1.9%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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TKL Study No. [redacted]

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

APPENDIX II

DATA LISTINGS

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
002	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
003	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
004	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
005	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
006	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
007	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
008	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
009	08/20/18	08/20/18	--	08/24/18	I2	S	5
010	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
011	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
012	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
013	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
014	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
015	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
016	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
017	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
018	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
019	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
020	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
021	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
022	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
023	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
024	08/20/18	08/20/18	09/25/18	09/28/18	C	C	40
025	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
026	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
027	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
028	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
029	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
030	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
031	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
033	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
034	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
035	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
036	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
037	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
038	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
039	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
040	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
041	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
042	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
043	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
044	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
045	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
046	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
047	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
048	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
049	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
050	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
051	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
052	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
053	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
054	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
055	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
056	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36
057	08/24/18	08/24/18	09/25/18	09/28/18	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
001	41.1	Male	Not Hispanic/Not Latino	Caucasian
002	58.2	Female	Not Hispanic/Not Latino	Caucasian
003	54.6	Female	Hispanic/Latino	Caucasian
004	47.3	Female	Not Hispanic/Not Latino	Caucasian
005	62.0	Female	Not Hispanic/Not Latino	Caucasian
006	21.9	Male	Not Hispanic/Not Latino	Caucasian
007	54.6	Female	Not Hispanic/Not Latino	Caucasian
008	54.8	Female	Not Hispanic/Not Latino	Caucasian
009	50.6	Female	Not Hispanic/Not Latino	Caucasian
010	41.4	Female	Not Hispanic/Not Latino	Caucasian
011	62.1	Female	Not Hispanic/Not Latino	Caucasian
012	66.5	Female	Not Hispanic/Not Latino	Caucasian
013	33.0	Female	Not Hispanic/Not Latino	Caucasian
014	58.0	Female	Not Hispanic/Not Latino	Black
015	46.7	Female	Not Hispanic/Not Latino	Caucasian
016	26.4	Female	Not Hispanic/Not Latino	Caucasian
017	52.4	Female	Not Hispanic/Not Latino	Caucasian
018	43.5	Female	Not Hispanic/Not Latino	Caucasian
019	46.8	Female	Not Hispanic/Not Latino	Caucasian
020	68.2	Female	Not Hispanic/Not Latino	Caucasian
021	33.7	Female	Not Hispanic/Not Latino	Caucasian
022	56.2	Male	Not Hispanic/Not Latino	Caucasian
023	46.9	Female	Not Hispanic/Not Latino	Caucasian
024	47.0	Female	Not Hispanic/Not Latino	Black
025	66.9	Male	Not Hispanic/Not Latino	Caucasian
026	45.7	Female	Not Hispanic/Not Latino	Caucasian
027	63.6	Female	Not Hispanic/Not Latino	Caucasian
028	63.5	Female	Not Hispanic/Not Latino	Caucasian
029	57.7	Female	Not Hispanic/Not Latino	Caucasian
030	25.2	Male	Not Hispanic/Not Latino	Caucasian
031	66.2	Male	Not Hispanic/Not Latino	Caucasian
032	55.3	Female	Not Hispanic/Not Latino	Caucasian
033	40.9	Female	Not Hispanic/Not Latino	Black
034	63.7	Male	Not Hispanic/Not Latino	Caucasian
035	34.5	Female	Not Hispanic/Not Latino	Caucasian
036	55.8	Female	Hispanic/Latino	Caucasian
037	58.2	Male	Not Hispanic/Not Latino	Caucasian

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
038	55.0	Female	Not Hispanic/Not Latino	Caucasian
039	66.1	Female	Not Hispanic/Not Latino	Caucasian
040	66.9	Male	Not Hispanic/Not Latino	Caucasian
041	70.8	Female	Not Hispanic/Not Latino	Caucasian
042	58.3	Female	Not Hispanic/Not Latino	Caucasian
043	46.3	Female	Not Hispanic/Not Latino	Caucasian
044	58.6	Female	Not Hispanic/Not Latino	Caucasian
045	39.3	Female	Not Hispanic/Not Latino	Caucasian
046	41.2	Female	Not Hispanic/Not Latino	Caucasian
047	63.3	Female	Not Hispanic/Not Latino	Caucasian
048	20.4	Female	Not Hispanic/Not Latino	Caucasian
049	64.6	Male	Not Hispanic/Not Latino	Caucasian
050	48.8	Female	Not Hispanic/Not Latino	Caucasian
051	53.2	Female	Not Hispanic/Not Latino	Caucasian
052	62.4	Female	Not Hispanic/Not Latino	Caucasian
053	50.0	Female	Not Hispanic/Not Latino	Caucasian
054	47.2	Male	Not Hispanic/Not Latino	Caucasian
055	57.4	Female	Not Hispanic/Not Latino	Caucasian
056	64.4	Female	Not Hispanic/Not Latino	Asian
057	50.8	Male	Not Hispanic/Not Latino	Caucasian

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Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted] REF# [redacted]

Subject No.	Induction Reading 1	2	3	4	5	6	7	8	9	MU	Challenge Phase 48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	-	-	-	-	N9G		-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	-	-	-	-	-	-	-	-	-		-	-	
007	-	-	-	-	-	-	-	-	-		-	-	
008	-	-	-	-	-	-	-	-	-		-	-	
009	-	-	X	X	X	X	X	X	X		X	X	
010	-	-	X	-	-	-	-	-	-	N9G	-	-	
011	-	-	-	-	-	-	-	-	-		-	-	
012	-	-	-	-	-	-	-	-	-		-	-	
013	-	-	-	-	-	-	-	-	-		-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	X	-	-	-	-	-	-	-	-	-	-	-	
016	-	-	-	-	-	-	-	-	-		-	-	
017	-	-	-	-	-	-	-	-	-		-	-	
018	-	-	-	-	-	-	-	-	-		-	-	
019	-	-	-	-	-	-	-	-	-		-	-	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	-	-	-	-	-	-	-	-		-	-	
023	-	-	-	-	X	-	-	-	-	-	-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required
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[redacted]
TKL Study No. [redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted] REF# [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	-	X	-	-	-	-	-	-	N9G	-	-	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	-	-	-	-	-	-	-	-	-		-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	-	-	-	-	-		-	-	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	X	-	-	-	-	-	-	N9G	-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	X	-	-	-	-	-	-	-	-	N9G	-	-	

(*) When required
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Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted] REF# [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	-	-	-	-	-		-	-	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	X	-	-	-	-	-	-	N9G	-	-	
052	-	X	-	-	-	-	-	-	-	N9G	-	-	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	-	-	-	X	-	-	-	-	-	N9G	-	-	
056	-	X	-	-	-	-	-	-	-	N9G	-	-	
057	-	-	X	-	-	-	-	-	-	N9G	-	-	

(*) When required
Generated on 10/10/18:11:33 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
002	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
003	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
004	08/27/18	08/27/18	--	08/31/18	I0	L	5
005	08/27/18	08/27/18	--	08/31/18	I0	L	5
006	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
007	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
008	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
009	08/27/18	08/27/18	--	09/05/18	I2	L	10
010	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
011	08/27/18	08/27/18	--	09/05/18	I2	L	10
012	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
013	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
014	08/27/18	08/27/18	10/02/18	10/05/18	C	C	40
015	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
016	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
017	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
018	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
019	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
020	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
021	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
022	08/31/18	08/31/18	--	10/02/18	I9	L	33
023	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
024	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
025	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
026	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
027	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
028	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
029	08/31/18	08/31/18	--	09/05/18	I0	L	6
030	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
031	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
033	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
034	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
035	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
036	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
037	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
038	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
039	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
040	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
041	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
042	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
043	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
044	08/31/18	08/31/18	--	09/19/18	I6	L	20
045	08/31/18	08/31/18	--	10/02/18	I9	L	33
046	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
047	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
048	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
049	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
050	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
051	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
052	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
053	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
054	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
055	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
056	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
057	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
058	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
059	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
060	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
061	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36
062	08/31/18	08/31/18	10/02/18	10/05/18	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
001	63.3	Female	Not Hispanic/Not Latino	Black
002	60.8	Male	Not Hispanic/Not Latino	Black
003	67.5	Female	Not Hispanic/Not Latino	Black
004	18.3	Female	Hispanic/Latino	Black
005	37.5	Female	Not Hispanic/Not Latino	Black
006	62.9	Female	Not Hispanic/Not Latino	Caucasian
007	33.0	Female	Not Hispanic/Not Latino	Black
008	19.2	Female	Not Hispanic/Not Latino	Caucasian
009	44.3	Female	Not Hispanic/Not Latino	Caucasian
010	49.5	Female	Not Hispanic/Not Latino	Black
011	50.8	Female	Not Hispanic/Not Latino	Caucasian
012	54.8	Female	Not Hispanic/Not Latino	Caucasian
013	31.6	Female	Not Hispanic/Not Latino	Black
014	50.6	Female	Not Hispanic/Not Latino	Caucasian
015	67.4	Female	Not Hispanic/Not Latino	Black
016	63.3	Female	Not Hispanic/Not Latino	Caucasian
017	56.1	Female	Not Hispanic/Not Latino	Caucasian
018	65.1	Female	Not Hispanic/Not Latino	Caucasian
019	56.7	Female	Not Hispanic/Not Latino	Caucasian
020	58.3	Female	Not Hispanic/Not Latino	Caucasian
021	54.4	Female	Not Hispanic/Not Latino	Black
022	62.0	Female	Not Hispanic/Not Latino	Caucasian
023	65.5	Female	Not Hispanic/Not Latino	Caucasian
024	69.7	Female	Not Hispanic/Not Latino	Caucasian
025	67.1	Male	Not Hispanic/Not Latino	Caucasian
026	48.5	Female	Not Hispanic/Not Latino	Amer Ind
027	48.1	Male	Not Hispanic/Not Latino	Black
028	54.1	Female	Not Hispanic/Not Latino	Black
029	39.1	Female	Not Hispanic/Not Latino	Black
030	50.9	Female	Not Hispanic/Not Latino	Black
031	61.5	Female	Not Hispanic/Not Latino	Caucasian
032	67.5	Female	Not Hispanic/Not Latino	Caucasian
033	58.4	Female	Not Hispanic/Not Latino	Black
034	21.2	Male	Not Hispanic/Not Latino	Black
035	29.3	Female	Not Hispanic/Not Latino	Black
036	67.6	Female	Not Hispanic/Not Latino	Black
037	42.8	Female	Not Hispanic/Not Latino	Caucasian

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
038	27.0	Female	Not Hispanic/Not Latino	Black
039	64.0	Female	Not Hispanic/Not Latino	Caucasian
040	53.4	Female	Not Hispanic/Not Latino	Black
041	30.6	Female	Not Hispanic/Not Latino	Black
042	33.1	Female	Not Hispanic/Not Latino	Caucasian
043	24.2	Female	Hispanic/Latino	Black
044	48.5	Male	Not Hispanic/Not Latino	Caucasian
045	50.6	Female	Not Hispanic/Not Latino	Black
046	42.8	Female	Hispanic/Latino	Caucasian
047	30.7	Male	Not Hispanic/Not Latino	Black
048	63.5	Male	Not Hispanic/Not Latino	Caucasian
049	67.7	Female	Not Hispanic/Not Latino	Black
050	67.4	Male	Not Hispanic/Not Latino	Caucasian
051	27.6	Male	Not Hispanic/Not Latino	Black
052	35.2	Female	Not Hispanic/Not Latino	Black
053	46.8	Female	Not Hispanic/Not Latino	Caucasian
054	53.7	Female	Not Hispanic/Not Latino	Caucasian
055	54.4	Female	Not Hispanic/Not Latino	Black
056	57.1	Female	Hispanic/Latino	Caucasian
057	50.8	Female	Not Hispanic/Not Latino	Caucasian
058	67.0	Male	Not Hispanic/Not Latino	Caucasian
059	51.6	Male	Not Hispanic/Not Latino	Black
060	23.2	Female	Not Hispanic/Not Latino	Asian
061	23.2	Male	Not Hispanic/Not Latino	Caucasian
062	22.5	Female	Not Hispanic/Not Latino	Black

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[redacted]
TKL Study No. [redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted] REF# [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	X	-	-	-	-	-	-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	X	X	X	X	X	X	X	X	X		X	X	
005	X	X	X	X	X	X	X	X	X		X	X	
006	-	-	-	-	-	-	-	-	-		-	-	
007	-	-	-	-	-	-	-	-	-		-	-	
008	-	-	-	-	-	-	-	X	-	-	-	-	
009	-	-	X	X	X	X	X	X	X		X	X	
010	-	-	-	-	-	-	-	-	-		-	-	
011	-	-	X	X	X	X	X	X	X		X	X	
012	-	-	X	-	-	-	-	-	-	-	-	-	
013	-	-	X	-	-	-	-	-	-	-	-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	-	-	-	-	X	-	-	-	N9G	-	-	
017	-	-	-	-	-	-	-	-	-		-	-	
018	-	-	-	-	-	-	-	-	-		-	-	
019	-	-	-	-	-	-	-	-	-		-	-	
020	-	-	-	-	-	-	-	-	-		?	?	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	-	-	-	-	-	-	-	-		X	X	
023	-	-	-	-	-	-	-	-	-		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required
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[redacted]
TKL Study No. [redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted] REF# [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	-	-	-	-	-	-	-	-		-	-	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	X	X	X	X	X	X	X	X	X		X	X	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	?	?	?	-	-	-		-	-	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	X	-	-	-	-	-	-	N9G	-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	-	-	-	-	-	-	-		-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	N9G		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	-	-	X	X	X		X	X	
045	-	-	-	-	-	-	-	-	-		X	X	
046	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
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Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted] REF# [redacted]

Subject No.	Induction Reading 1	2	3	4	5	6	7	8	9	MU	Challenge Phase 48hr	72hr	96hr(*)
047	-	-	-	-	-	-	-	-	-		-	-	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	-	-	-	-	-	-	-		-	-	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	X	-	-	-	-	-	-	-	-	N9G	-	-	
056	-	-	-	-	-	-	-	-	-		-	-	
057	-	-	-	-	-	-	-	-	-		-	-	
058	-	-	-	-	-	-	-	-	-		-	-	
059	-	-	-	-	-	-	-	-	-		-	-	
060	-	-	-	-	-	-	-	-	-		-	-	
061	-	-	-	-	-	-	-	-	-		-	-	
062	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 27, 2019

SUBJECT: Draft Report: Safety Assessment of Hexa/Penta-Hydric Alcohols as Used in Cosmetics (draft prepared for the April 8-9, 2019 CIR Expert Panel meeting)

The Personal Care Products Council respectfully submits the following comments on the draft report, Safety Assessment of Hexa/Penta-Hydric Alcohols as Used in Cosmetics.

Key Issues

Introduction - The statement that the primary focus of the safety assessment is topical exposure should be deleted from the Introduction as most of the information in the report concerns oral and inhalation exposure. As these ingredients are used in oral products, e.g., dentifrices, the oral exposure information is important for assessing the safety of these ingredients as they are used in cosmetic products.

The NTP also completed a single dose study in rats (no deaths) that is not yet included in the CIR report (the rat study should be added to Table 4 and the Acute Toxicity section).

Genotoxicity, Summary - A number of genotoxicity studies on Mannitol are cited to the NTP testing status page. This page provides references that likely include more detailed information. For example the mouse lymphoma cell assay is in:

> Myhr, B. and Caspary, W. Chemical mutagenesis at the TK locus in L5178Y mouse lymphoma cells. I. Results for 31 coded compounds in the National Toxicology Program. *Environ. Molec. Mutagen.* Vol. 18 (1991) 51-83.

It is not appropriate to indicate "doses not stated" when the studies are not cited to the reference where more information may be found.

Additional Considerations

Introduction - The NTP technical report (reference 2) should not be included among the references that are secondary sources. This report should be considered a primary reference as it includes detailed information on the endpoints that were examined. A secondary reference is one that summarizes other studies such as industry sponsored studies that are not readily available. For example, in addition to the ECHA and the

WHO Food Additive Series documents, the FDA NDA review (reference 40) should be considered a secondary reference.

Method of Manufacture - The is no special manufacturing process used to make Mannitol, Sorbitol and Xylitol for cosmetics relative to making these ingredients for other purposes. Please delete: "no methods specific to cosmetic ingredient manufacture were found in the literature or submitted as unpublished data".

Non-Cosmetic - It should also be noted that 21CFR180.25 defines methods of manufacture for Mannitol used in food, and indicates that it must meet *Food Chemical Codex* specifications.

Dermal Penetration, Mannitol - Reference 31 also looked at dermal penetration in young compared to older rats. Were any effects observed?

ADME, Human, Oral, Mannitol - Please correct "flor" to "flora"

Acute, Animal, Oral; Summary - It is not appropriate to state that the "lowest" LD_{50} was greater than 5 g/kg (Mannitol in mice) and greater than 4 g/kg (Xylitol in rats). Stating that an LD_{50} is greater than a value means that at the highest dose tested more than 50% of the animals survived (no LD_{50} could be determined). For Mannitol in the NTP single dose studies, all rats and mice treated with 5 mg Mannitol/kg survived. This information would be more useful to the reader than just stating that the LD_{50} was greater than the highest dose tested. It would be more appropriate to state that the only LD_{50} for Mannitol in mice was 22 mg/kg. The lowest LD_{50} for Xylitol in rats was 14.1 g/kg. As there was only one LD_{50} for Xylitol in rabbits, it is not appropriate to call it the "lowest".

Short-term, Oral - Please revise: "No animals died the duration of the study..."

Short-term, Inhalation; Chronic, Inhalation - Either the duration of each exposure should be stated (e.g., 15, 30 or 60 minutes as stated for the beagle study [reference 41]), or there should be an introductory sentence to indicate that these studies were completed to support safety of the drug use of inhaled Mannitol.

Subchronic, Oral - It would be helpful to state the endpoints examined in the NTP 13-week studies in rats and mice. Currently the results of the mouse study states: "No other adverse effects were observed". The results of the rat study states: "no compound-related clinical signs were observed". The difference in the presentation of the results of these studies suggests that perhaps different endpoints were examined.

Chronic, Oral - Please state that the NTP chronic studies of Mannitol are presented in the Carcinogenicity section.

Chronic, Oral; Table 5 - Stating that: "No other Mannitol-induced effects were reported" for the 27-month oral study of Mannitol in rats is misleading and suggests that the reported mortality rate was attributed to Mannitol. As stated in Table 5, the mortality rate was not attributed to Mannitol. Twenty-seven months is a long duration for a rat study. Look at the survival curves for the NTP Mannitol study. For example, in the NTP study, a study that was at least 2 week shorter, 36% of the control male rats were dead before the end of study. For the 27-month study, the CIR report should clearly state that "No Mannitol-induced effects were reported."

DART - Please spell the same word consistently throughout the report (the DART section has "Cecal" and "Caecal").

Genotoxicity, In Vivo, Xylitol - It should be stated that the mice in the mammalian erythrocyte micronucleus test were treated twice, 30 hours and 6 hours before sacrifice.

Carcinogenicity, Xylitol - As the study was completed in rats, "species not stated" should be corrected to "strain not stated".

Deposition in Bronchoalveolar Fluid - The studies described in this section should be moved to the ADME section, as the are examining deposition of Mannitol in the lungs following inhalation exposure.

Clinical Studies, Metabolism - The studies described in this section should be moved to the ADME section.

Summary - Please revise: "Fifty percent Humans administered..." The endpoints examined but not found to be affected should also be stated.

The duration (time/day) of the inhalation exposure studies should be stated.

Table 4 - Since the dose is provided as ≤98 mg/kg/d and it states that the effects were seen at 98 mg/kg/d, please also state the lower dose that caused no adverse effects.

Table 5 - In the 13-week dietary study of Xylitol in rats (cited to references 6 and 42), what compound was tested? The Ingredient column says Xylitol, while the results column says "Xylitol-containing compound". If something other than Xylitol was tested, it should be clearly identified.

References - The WHO Food Additive Series document on Xylitol is in the reference section multiple times (references 5, 43, 58, 59, 60 and 61).

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: May 16, 2019

SUBJECT: Photoxicity Potential of Xylitol

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to comment on the phototoxicity potential of Xylitol.

Based on the structure of Xylitol, it should not absorb UV light to a great extent.

A review of the guinea pig phototoxicity study[1] cited in the CIR report indicated that it was not completed under a standard protocol. For example, the UVA challenge was at 200 J/cm^2 which is higher than the ICH guidance of 5-20 J/cm^2. The authors note that: "the irradiation is 100 times higher than the dose that a person could be exposed to on a summer day at noon" – thus the relevance of the exposure is questionable. Other weaknesses of this study include that the time between the application of the test material and UV exposure was not stated, and details on the strength of the reaction were not stated.

The dose of Xylitol per unit area used in the phototoxicity study was also high – 33.3 mg/cm^2 compared to 12.5-25.0 mg/cm^2 tested in the dermal irritation study. For comparison, Xylitol at 10% in a leave-on face cream would have a dose per unit area of 0.3 mg/cm^2.

Therefore, based on the limitations of the phototoxicity study, the lack of structural alerts, and reported use concentrations in leave-on products of 2% and less, we believe that phototoxicity potential of Xylitol should not be a concern.

[1] Ferreira AS, Barbosa NR, and Silva SS. In Vivo Xylitol Primary Dermal Irritation and Phototoxicity Evaluation. *Latin American Journal of Pharmacy*. 2009;28(2):192-195