Safety Assessment of Polyol Phosphates as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: May 11, 2018
Panel Date: June 4-5, 2018

The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 11, 2018
Subject: Draft Tentative Report on Polyol Phosphates

An Insufficient Data Announcement (IDA) with the following data requests was issued at the March 5-6, 2018 CIR Expert Panel meeting.

- Method of manufacture and impurities data on Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate
- Chemical characterization data on Xylityl Phosphate
- Absorption, distribution, metabolism, and excretion (ADME) data on Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate
- Skin sensitization data (animal or human) on Phytic Acid at the highest maximum use concentration of 2% or on a cosmetic product containing 2% Phytic Acid

Data were received in response to the request for sensitization data, but not the other data types, and the following data were received from the Personal Care Products Council (Council):

1) HRIPT (occlusive patches) on a leave-on product containing 0.1% Sodium Phytate (irritation and allergenicity evaluated);
2) HRIPTs (occlusive patches) on 2 rinse-off products containing 0.05% Sodium Phytate (both, 1% dilution yielding effective test concentration = 0.0005%) (dermal sensitization evaluated);
3) HRIPT (semi-occlusive patches) on a leave-on product containing 0.05% Sodium Phytate (dermal sensitization evaluated) (*phytic062018data1*, file for items 1, 2, and 3);
4) HRIPT (occlusive patches) on a moisturizer containing 5% Phytic Acid (dermal sensitization evaluated) (*phytic062018data2*);
5) Maximization test on a face gel containing 0.25% Phytic Acid and a clear liquid containing 1% Sodium Phytate;
6) Single (24-h) insult patch test on a product containing 0.25% Phytic Acid;
7) Human photosensitization test on a clear liquid containing 1% Sodium Phytate; and
8) EpiOcular™ viability assay for ocular irritation potential on a product containing 50% Sodium Phytate (in 49% water, 1% alcohol) (*phytic062018data3*, file for times 5-8).

These data are attached for the Panel's review and are highlighted in the text of the Draft Tentative Report on Polyol Phosphates. A determination as to whether the data received satisfy the Panel's request for skin sensitization data will need to be made.

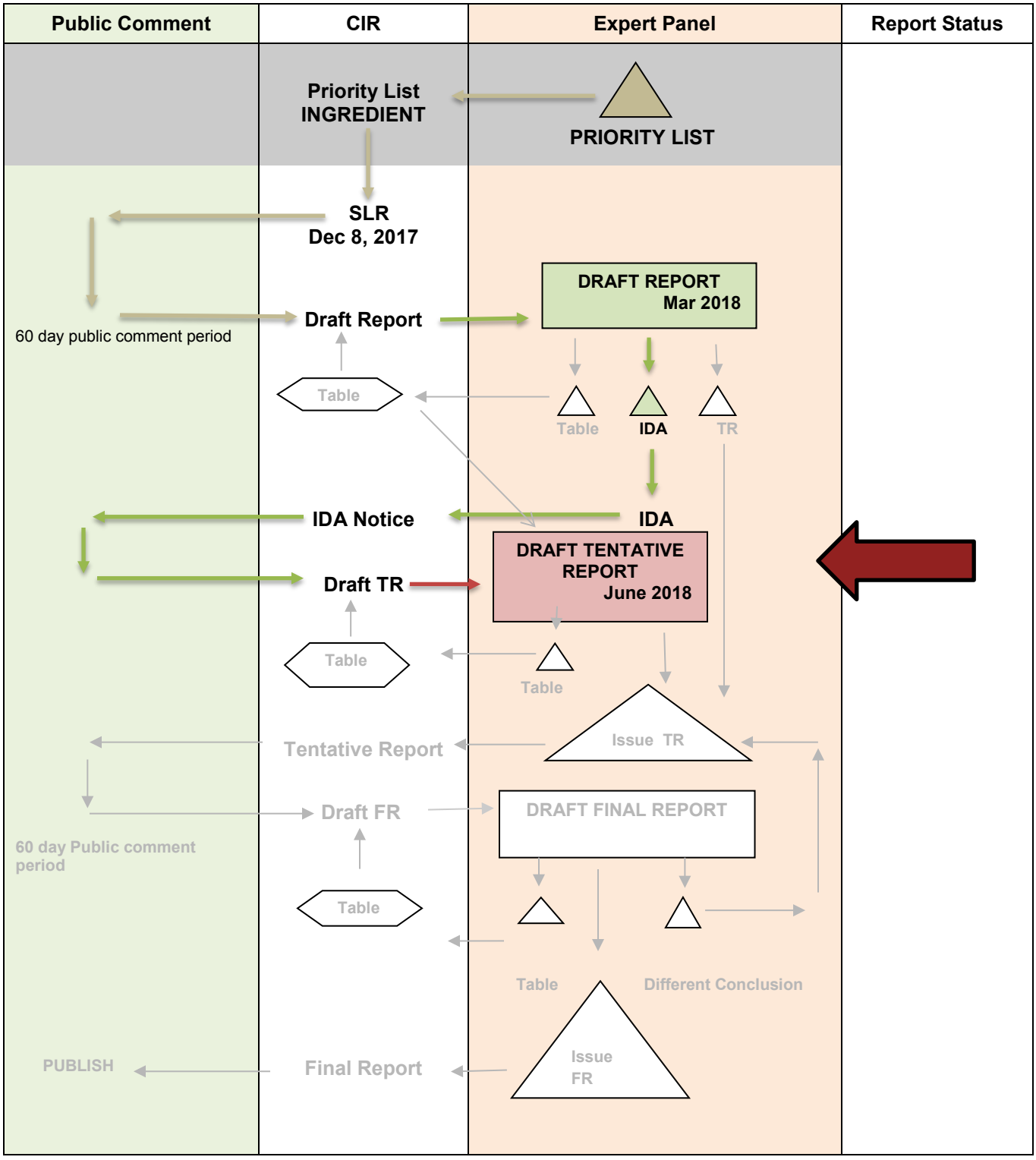
Also included in this package for your review are the Draft Tentative Report (*phytic062018rep)*, the CIR report history (*phytic062018hist*), flow chart (*phytic062018flow*), literature search strategy (*phytic062018strat*), ingredient data profile (*phytic062018prof*), 2018 FDA VCRP data (*phytic062018FDA*), and minutes from the March 5-6, 2018 CIR Expert Panel meeting (*phytic062018min*).

In that all of the data requested by the Panel have not been received, the Panel may consider issuing a Tentative Report with an insufficient data conclusion. The Panel also has the option of issuing a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, if deemed appropriate after further review of the available data.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Polyol Phosphates

MEETING June 2018



CIR History of:

Polyol Phosphates

A Scientific Literature Review (SLR) on Polyol Phosphates was issued on December 8, 2017.

Draft Report, Teams/Panel: March 5-6, 2018

The draft report contains use concentration data on the Polyol Phosphates, skin (human) irritation and ocular (*in vitro*) irritation data on a cream containing 0.48956% Sodium Phytate, and data on the production method, impurities, and skin/ocular irritation potential *in vitro* relating to Phytic Acid (50%) that were received from the Council. Report comments that were received from the Council have been addressed.

The Panel issued an Insufficient Data Announcement (IDA) with the following data requests on the polyol phosphates:

- Method of manufacture and impurities data on Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate
- Chemical characterization data on Xylityl Phosphate
- Absorption, distribution, metabolism, and excretion (ADME) data on Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate
- Skin sensitization data (animal or human) on Phytic Acid at the highest maximum use concentration of 2% or on a cosmetic product containing 2% Phytic Acid

The involvement of monosaccharides (i.e., glucose, fructose, mannose, and xylose) in redox reactions was considered by the Panel prior to determining the need for ADME data on the 6 sugar-phosphates (e.g., Trisodium Fructose Diphosphate).

Draft Tentative Report, Teams/Panel: June 4-5, 2018

The following HRIPT data were received in response to the IDA that was issued at the March 2018 Panel meeting, and have been added to the draft tentative report: 1) HRIPT (occlusive patches) on a leave-on product containing 0.1% Sodium Phytate (irritation and allergenicity evaluated); 2) HRIPTs (occlusive patches) on 2 rinse-off products containing 0.05% Sodium Phytate (both, 1% dilution yielding effective test concentration = 0.0005%) (dermal sensitization evaluated); 3) HRIPT (semi-occlusive patches) on a leave-on product containing 0.05% Sodium Phytate (dermal sensitization evaluated); 4) HRIPT (occlusive patches) on a moisturizer containing 5% phytic acid; and 5) maximization tests on a face gel containing 0.25% Phytic Acid and a clear liquid containing 1% Sodium Phytate, single (24-h) insult patch test on a product containing 0.25% Phytic Acid, human photosensitization test on a clear liquid containing 1% Sodium Phytate, and Epiocular viability assay for ocular irritation potential on a product containing 50% Sodium Phytate (in 49% water, 1% alcohol).

Data Profile on Polyol Phosphates June 4th-5th, 2018 Panel – Wilbur Johnson

	Dermal Penetration			Nail Penetration	Penetration Enhancement	ADME					Acute Toxicity			Short-Term Toxicity	Sub-Chronic Toxicity	Chronic Toxicity	DART		Genotoxicity	Carcinogenicity	Other Relevant Studies		Dermal Irritation*	Dermal Sensitization /Photosensitization		Ocular Irritation *		Clinical Studies	Case Reports		Epidemiology Studies
	In Vivo -Animal	In Vitro-Human	In Vivo-Human	In Vitro-Human	In Vitro-Animal	In Vitro-Human Dermal	Animal-Dermal	Animal-Oral	Animal-Inhalation	Human-Oral	Animal-Dermal	Animal-Oral	Animal-Inhalation	Animal	Animal	Animal	In Vitro	In Vivo	In Vitro/In Vivo	In Vivo	In Vitro	In Vivo-Animal	Animal/Human/In vitro	Animal	Human/In Vitro	In Vitro	Animal/In vitro	Human-Oral/injection	Human-Dermal	Human-Inhalation	Human
Sodium Phytate	X		X							X				X						X		X	X		X	X	X				
Phytic Acid								X		X		X		X	X			X	X	X			X		X		X	X			
Disodium Glucose Phosphate																															
Manganese Fructose Diphosphate																															
Phytin	X									X									X												
Sodium Mannose Phosphate																	X											X			
Trisodium Fructose Diphosphate																															
Trisodium Inositol Triphosphate																															
Xylityl Phosphate																															
Zinc Fructose Diphosphate																															

X = data

[Polyol Phosphates (7/7/17; 10/2-3/17; 1/18/18)]

Ingredient	CAS #	Info-Base	Sci-Finder	Pub-Med	TOX-NET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NIC-NAS	NTIS	NTP	WHO	FAO	FEMA	ECETOC
Sodium Phytate	14306-25-3; 34367-89-0	1/1	1062	17/179	9/70	0	0	0	0	0	0	0	0	0	0	0		0
Phytic Acid	83-86-3	1/1	14,627	64/723	7/117	0	0	0	0	0	0	0	0	0	0	0		0
Disodium Glucose Phosphate	59-56-3	1/1	4	1/331	0/109	0	0	0	0	0	0	0	0	0	0	0		0
Manganese Fructose Diphosphate		1/1	10	1/59	0/3	0	0	0	0	0	0	0	0	0	0	0		0
Phytin	3615-82-5	1/1	1834	19/132	2/42	0	0	0	0	0	0	0	0	0	0	0		0
Sodium Mannose Phosphate	70442-25-0	1/1	3	14/559	0/0	0	0	0	0	0	0	0	0	0	0	0		0
Trisodium Fructose Diphosphate	81028-91-3	1/1	7	0/2	0/0	0	0	0	0	0	0	0	0	0	0	0		0
Trisodium Inositol Triphosphate		1/1	1	0/1	0/0	0	0	0	0	0	0	0	0	0	0	0		0
Xylityl Phosphate	1224593-11-6	1/1	1	7/371	0/0	0	0	0	0	0	0	0	0	0	0	0		0
Zinc Fructose Diphosphate		1/1	5	2/27	0/0	0	0	0	0	0	0	0	0	0	0	0		0

Search Strategy

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

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

LINKS

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

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

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

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

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

Day 1 of the March 5-6, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

Polyol Phosphates

DR. BELSITO: Okay. We're moving on to the polyol phosphates. This is the first time we're seeing the report. We got stuff in Wave two. In vitro genotox. In vitro irritation sensitization. In vitro ocular. What do we think of this first pass draft?

DR. LIEBLER: I thought it was insufficient for method of manufacture and impurities for the non-phytic ingredients.

DR. BELSITO: Okay before we get to that, can we ask you the big question, Dan? Are you okay with the grouping?

DR. LIEBLER: Yes.

DR. BELSITO: Okay. And what about the report name?

DR. LIEBLER: Yeah.

DR. BELSITO: I can delete that comment. Yeah, we can talk about those later. I think you've got the tables screwed up here because the toxicokinetics, Table 6, was the ADME and not toxicokinetics. And the toxicokinetics were in Table 7 through, I think, 9. You see what I'm talking about? If you go to Page 11, it says toxicokinetic studies. And then you're talking about topical application and absorption metabolism.

DR. LIEBLER: Page 11?

MR. JOHNSON: Page 11. That's the beginning of the toxicokinetic studies, which are presented in Table 5.

DR. LIEBLER: Do you mean, Don, that the numbering of the tables is out of order?

DR. BELSITO: Yeah.

DR. LIEBLER: Rather than relative to where they appear in the report?

DR. BELSITO: Right. Because Table 5 is absorption, right? Table 5 is absorption.

MR. JOHNSON: Absorption. Yeah. It's entitled toxicokinetic studies.

DR. BELSITO: But is absorption toxicokinetic studies? Because then Table 6 is acute toxicity. Table 7 is short term.

DR. LIEBLER: Yeah, I think that's okay. So, absorption is part of toxicokinetics, right. And that's Table 5, and that's referred to at the bottom of PDF 11.

DR. BELSITO: Okay.

DR. LIEBLER: And then you bring in the acute tox on PDF 13 at the top, and that's Table 6. I think we're okay.

DR. BELSITO: Okay. But then do we need a heading for that section, absorption, distribution, metabolism or not? Because there's no heading. It just starts toxicokinetic studies. And then below that dermal penetration.

MR. JOHNSON: Should that be changed to absorption, distribution, metabolism?

DR. BELSITO: Don't we usually have a subheading for that?

DR. LIEBLER: Yeah. And you do have it. It's on Page 12. PDF 12. And about a third of the way down, it's got absorption, distribution, metabolism, excretion.

MR. JOHNSON: Yeah. Because that's the main heading, toxicokinetic.

DR. LIEBLER: Animal and human. Yeah. So, ADME is a subheading. I think that's the way we normally do it.

DR. BELSITO: Okay. But then I guess I was just confused because it starts off with Table 5. Toxicokinetic studies summarized below are presented in Table 5. And then it says dermal penetration and then it says absorption, distribution, metabolism and excretion. Shouldn't that heading occur at the top before we refer to Table 5? Do you see what I'm saying? Because when I read that I thought all of the toxicity studies are going to be in Table 5.

DR. SNYDER: No.

DR. BELSITO: I looked, and it was just absorption.

DR. SNYDER: Yeah. It's TK data, yeah.

DR. LIEBLER: You could just essentially cut and paste and move the ADME part above the dermal penetration part.

MR. JOHNSON: Okay.

DR. BELSITO: But then you should also bring that sentence above, below. Because it says the

toxicokinetic studies summarized below are in Table 5. And not all of the toxicokinetic studies summarized below are in Table 5.

DR. SNYDER: And there's an ADME study in Table 5.

DR. BELSITO: It's the ADME which is in Table 5.

DR. SNYDER: Yeah. Because you have a subheading here on the Table.

MR. JOHNSON: Okay.

DR. BELSITO: I would just put toxicokinetic studies, ADME. The toxicokinetic studies on absorption, distribution and metabolism are presented in Table 5. Because then you say the acute toxicity is Table 6. The short term is Table 7.

I mean, it's just confusing. When I saw that, I immediately went to Table 5 and thought I was going to see all the tox studies, and I didn't. You see what I'm saying?

DR. LIEBLER: Yeah. Toxicokinetics is different than tox.

DR. BELSITO: I understand.

DR. LIEBLER: Okay.

DR. KLAASSEN: Actually, this is a little confusing the way we do it, not just on this report, but all of them. What toxicokinetics really is, is the quantitation of ADME.

DR. LIEBLER: For a toxicant.

DR. KLAASSEN: For a toxicant. And for us to kind of separate these two, maybe is confusing. Maybe we should say, as a heading, ADME and toxicokinetics or something. Because it's not a different area. It's not like the difference between carcinogenicity and reproduction. It's the absorption, metabolism and distribution, excretion data, in more of a quantitative fashion.

DR. SNYDER: But he is following what the other reports have. All of the reports have TK studies. Then it's followed by dermal penetration, penetration enhancement, ADME.

DR. LIEBLER: That's our template. At one point we thought that that was the way to do it and we spent three meetings talking about it.

MR. JOHNSON: And all of those are in the table, to all of those studies.

DR. LIEBLER: You could have ADME instead of toxicokinetics. It's just that we decided on a boilerplate a while ago -- a template a while ago.

DR. BELSITO: Well, just figure out how it makes sense. Dan and I are both going to think it's insufficient. Dan, you go first since you started out with that originally.

DR. LIEBLER: Right. Method of manufacture and impurities for the non-phytic ingredients, which are also the ones that are apparently not used. Also need sensitization. And then a discussion point is all of these are dietary constituents and are metabolized to common metabolic intermediates. These are all in my notes, Wilbur.

MR. JOHNSON: Okay.

DR. LIEBLER: Probably will be safe to use when formulated to be nonirritating. Except for those that might end up being insufficient. That's where I come out, safe as used and formulated to be nonirritating. And I'm okay with the two read across materials that you have listed in Table 2. That's it for me.

DR. BELSITO: I had a question about that. Okay. You're okay with those?

DR. LIEBLER: Yes.

MR. JOHNSON: For the sensitization data request, that request is for which ingredients? Is that for the non-phytic as well, or all of the ingredients?

DR. SNYDER: The 2 percent max use one.

DR. LIEBLER: For the non-phytic ingredients.

MR. JOHNSON: Sensitization data --

DR. LIEBLER: Oh, sensitization. No. No, that's up to Don.

DR. SNYDER: That's the max used, 2 percent.

DR. BELSITO: The 2 percent was phytic acid. And while I can see that in formulation it's not going to be pure acid, if they are concerned about effects of irritation, or whatever, at 2 percent phytic acid, then they could use whatever that formulation is that reports 2 percent phytic acid into an HRIPT on the whole formulation with 2 percent phytic.

But we don't have sensitization cleared at all. I mean all we have is a KeratinoSens on the sodium salt. We don't even come close to in vitro data to clear this in terms of sensitization.

MR. JOHNSON: Just on the phytic acid?

DR. BELSITO: Well, the 2 percent, the highest is reported in phytic acid in a leave on. Either 2 percent phytic acid or an HRIPT on the product that reportedly contains 2 percent phytic acid.

I have a note here, what did you guys think of the tumor promotion study? Is that just chronic irritation?

DR. SNYDER: Yeah.

DR. BELSITO: This is 29 of the PDF.

DR. SNYDER: Yeah. That's at 2 percent in the diet, four weeks, tendency for increase papillomas. I had question mark, question mark, the language they used. But I think it's probably --

DR. LIEBLER: Brought about a tendency. That's even mushy enough for social science.

DR. SNYDER: It's like feely. That's touchy feely too.

DR. LIEBLER: Brought about a tendency.

DR. BELSITO: You're not moved by the "brought about a tendency"?

DR. LIEBLER: I'm not moved. Not at all.

DR. SNYDER: Neither was I.

DR. BELSITO: We don't even need to discuss this.

DR. LIEBLER: Is that language from --

DR. SNYDER: The actual report.

MR. JOHNSON: Yes. It is.

DR. LIEBLER: Okay. I mean, either it increases papillomas or no.

DR. KLAASSEN: If we're going to use those words, we probably should put parentheses around them.

DR. LIEBLER: When interviewed, the animals indicated that they were seriously considering growing papillomas.

MR. JOHNSON: But it says that the study results confirmed promoting activity.

DR. BELSITO: Yes. This material clearly gets through skin. So, we're happy with all the tox data? It's clean?

DR. LIEBLER: I didn't see anything that had any alarms to me. Let me go back and look.

DR. BELSITO: I just said, absorbs, so we need clean tox data.

Our conclusions are method of manufacture and impurities for the non-phytic ingredients. And so, it's insufficient for that. Insufficient for sensitization of phytic acid at 2 percent. Also, do we need a UV spectrum or photo data?

DR. LIEBLER: No.

DR. BELSITO: No, why?

DR. LIEBLER: Not going to absorb.

DR. BELSITO: Dan says it's not going to absorb.

DR. BELSITO: Okay.

DR. LIEBLER: There's no bonds in that ring so it's not going to absorb. No double bonds.

DR. BELSITO: Okay. That, at least, can go in the discussion, that we didn't feel we needed photo data because --

DR. LIEBLER: Lack of UV absorption.

DR. BELSITO: Okay. And then I said we need irritation, but you said formulate not to be irritating.

DR. SNYDER: We got some negative irritation in the Wave 2.

DR. BELSITO: Yeah, I know.

DR. LIEBLER: Wasn't there some positive irritation though with --

MR. JOHNSON: Phytic acid at --

DR. LIEBLER: Phytic acid. I mean, that's what you would expect with this kind of a -- basically it's an acidic chemical that can be perfectly buffered in a formulation and it should be fine. It just depends on how it's applied and what else is mixed in with it.

MR. JOHNSON: Would there be a need to establish a threshold for skin irritation?

DR. LIEBLER: No.

DR. BELSITO: We're not asking for irritation, but we will say formulated to be nonirritating?

DR. LIEBLER: Yeah. I mean, that's just how I interpret it. When you have some data that suggests it can be irritating, under some circumstances at some concentrations; and others it says it's not. Don't we usually, when we have that situation, say formulated to be nonirritating?

DR. BELSITO: Yeah.

DR. LIEBLER: I mean, even something that's dietary GRAS could be irritating when applied to the skin in pure form, which is -- what was that one study where it was irritating.

DR. BELSITO: Okay. We won't ask for any additional irritation data, just formulated to be nonirritating will be in the conclusion.

MR. JOHNSON: And that's for all of the ingredients?

DR. LIEBLER: Sure.

DR. BELSITO: Basically, we're asking for method of manufacturer for the non-phytic ingredients and sensitization for phytic acid at 2 percent.

DR. LIEBLER: Yeah. And these are all phosphoric acid testers.

DR. BELSITO: Okay. Any other comments on polyol?

Day 1 of the March 5-6, 2018 CIR Expert Panel Meeting – Dr. Marks'Team

Polyol Phosphates

DR. MARKS: The next set of ingredients are the polyol phosphates. This is again a draft report on these ingredients, so it's the first review. I'll go to page 5. Ron Hill, I know you used another page, but I kind of like this page that --

DR. HILL: It doesn't matter because I thought they were -- I think I thought they were all fine.

DR. MARKS: Tom? Ron? Ingredients, do you like all these ingredients?

DR. HILL: Let me see, what did I think? No, I didn't. I wanted to see all the sugar phosphates salts removed.

DR. SLAGA: Take the sugar phosphates out?

DR. HILL: Take the sugar phosphates out, and I was equivocal about the xylitol, but I thought it could probably stay.

DR. MARKS: So, the glucose, the fructose, the mannose, fructose -- that leaves -- let me go here. So, that will leave sodium phytate, phytic acid, phytin. Would you include the trisodium down there? Inositol? Or is that going to be deleted too?

DR. HILL: No, that stays. I actually had flagged it, but then looking at how that relates to everything else, that ought to stay.

DR. MARKS: How about the next one, xylitol? Is that how you say that?

DR. HILL: Yes.

DR. MARKS: That stays too?

DR. HILL: I was debating with myself quite a bit but then decided, after reading the report, that I thought it should stay.

DR. MARKS: Does that mean we have five ingredients then?

DR. BERGFELD: Are you keeping the zinc fructose?

DR. HILL: No, that's gone because it's a sugar.

DR. MARKS: Yes, the fructose.

DR. HILL: I count five.

DR. MARKS: Yes, okay. Tom? Do you like that?

DR. SLAGA: Yeah. I agree with that.

DR. MARKS: And the reason you eliminated the others? Just because chemically you thought they were --

DR. HILL: Yes. Sugars do redox chemistry and then they have equilibria between ring-open and ring-closed form; whereas the inositol and the phytates -- including phytic acid -- are pseudo sugars. They're not really sugars. They're heavily hydroxylated cyclohexenes.

The only one that stands out as being different is xylitol because it's open chain. But yes, I couldn't come up with -- it's not a sugar, so then I couldn't come up with any reason to ditch it. Chemically, other than not being in a ring, it should be quite similar to those others. Biologically, maybe not so much.

And then the uses, I think we're fairly -- let's see. Okay. The only other complication I would raise, while we're talking about ingredients, is we do have this complication, the xylitol phosphate has anti-acne and anti-dandruff use, which is of course not us, which is not true of the phytates.

DR. BERGFELD: It looks like an exfoliative.

DR. HILL: Yes, it says that too. So, is that a reason to throw it out? I didn't think so.

DR. HELDRETH: We simply just don't review them for those purposes.

DR. HILL: Yeah. That was what I thought.

DR. BERGFELD: Interesting.

DR. HELDRETH: We've often looked at ingredients like this, like the benzophenones where we don't look at it as a sunscreen because that's a drug of course; but we do look at it as something that can protect the product, and it isn't advertised as a sunscreen.

DR. MARKS: Tom? You like those, eliminate the sugars and phosphates. Okay. Needs. What needs -- so, we're eliminating to these five ingredients. What needs to we have with them?

DR. BERGFELD: A question I had, if you don't mind.

DR. MARKS: Sure.

DR. BERGFELD: It's made from corn maize so it makes it into a plant. Hydrolysis of kernels

of rice -- rice husks, excuse me, not corn, rice.

DR. MARKS: That's page 10. I had that also under the method of manufacture. But do we have the impurities?

DR. HILL: Could you repeat what you just said?

DR. BERGFELD: This is not just a chemical, these are plant derived.

DR. HILL: Right.

DR. BERGFELD: I was looking at it as a botanical actually in some manner, that you need your impurities and you need to know a little bit more about the composition.

DR. HILL: I wrote, first of all, we don't know that food grade specs are pertinent with respect to cosmetic ingredients. So, we're given food grade specs, but nothing to go on. We note the production is from rice brand. There is no crystallization or other cleanup evident that would remove things like pesticide and herbicide residues. We see that bleaching is involved, so what is being bleached and what happens to it. Then we only have info for phytic acid and nothing else.

DR. MARKS: So, we can take care of the pesticides. We would like to see whether there is residual, but with a pesticide boilerplate also.

From that, Ron Hill, I get mainly impurities. Is that what you want to see? Or do you want more method of manufacture or composition? Which?

DR. HILL: I was puzzling because the comment I wrote here is before I thought we should take those sugars out. Because I wrote, we have production processes for only the phytate. So, other than the inositol phosphate, production processes for the others are expected to be disparate. But I think I was thinking of the sugars and the xylitol actually, the xylitol phosphate.

I'm kind of curious what might be known about that complex mixtures of esters things, but then in the end I don't know that it matters. But if we could get information about what's known about that mixture for xylitol phosphate, that would be useful for making a robust report. For me, I wrote, it just goes to help ensure that we provide an accurate picture of the chemistry of the compounds. If we don't remove the sugars, then something else happens.

DR. MARKS: So, basically impurities? Is that what you want to see?

DR. HILL: Yes, impurities and -- or really, we've talked about this before. When we ask impurities and method of manufacture, we're really trying to get at the same concerns from one direction or the other. If we had good characterization of impurities, we might not need anything about the production process. The reason we typically ask for both is so that we capture what else might be in there of concern that we're concerned might affect the safety.

DR. MARKS: Okay. Method of manufacture for all of them?

DR. HILL: Well, we have it. I'd like it for the xylitol.

DR. MARKS: And impurities?

DR. HILL: Or impurities.

DR. MARKS: And just for the xylitol? The rest you feel are okay or we can read across?

DR. HILL: I feel like we'd like to know that the inositol production is comparable to the phytate production. We don't have that. I think we should ask for it and see what we get.

MR. JOHNSON: So, impurities data just on xylitol compound and none of the others?

DR. HILL: No, no, because what I wrote is, we don't know that the food grade specs are pertinent to the cosmetic ingredients. Production is from rice brand with no crystallization or other cleanups. So, no, we definitely need information about what else might be in there with the phytates. The impurities.

MR. JOHNSON: For all of the ingredients.

DR. HILL: Impurities for all the ones that we keep.

DR. MARKS: Okay. Any other needs? Ron or Tom?

DR. SLAGA: I don't have any others.

DR. MARKS: You don't have any others. I want to see sensitization on sodium -- the sodium phytate that's used in a lot of ingredients at a 0.5 percent. We have in wave two that an in vitro luciferase test was okay. I don't know the parameters of that test. I'm not familiar with it; and I went online to try and look it up and I couldn't find anything, and there wasn't much detail. I would prefer to see other sensitization studies, either animal or human, to confirm the safety. I'd put that in needs.

MR. JOHNSON: On all the ingredients or just that one?

DR. MARKS: Well, that one primarily. But you could ask for it for all, but that one is the one that has the most uses. The one with the highest concentration is that phytic acid at 2 percent. That has 69 uses. Sensitization.

DR. HILL: It's interesting because looking at the structures of these and the physical chemical properties I thought, well, these won't be absorbed. But then we have toxicokinetic information to suggest otherwise, so that I found fascinating.

DR. MARKS: Okay. So, tomorrow I'll be seconding a motion. Presumably it's going to be issue an insufficient data announcement. Our team would like more method of manufacture and impurities, assuming we agree -- the two teams -- on the five ingredients that we discussed earlier. The pesticides boilerplate will go on no matter what since there is a plant derivation of these ingredients and light sensitization data on them. I think that's the needs.

Let me see what Ron Shank says. He wanted skin sensitization for sodium phytate and phytic acid. We talked about that. Or safe when formulated to be non-irritating and non-sensitizing. I don't like that conclusion when we have specific ingredients.

He, in parenthesis says, these are normal constituents of foods; there are almost no tox data on the sugar phosphates and they are not currently used in cosmetics, so drop them from the report. And in wave two, the luciferase test for sensitization was negative. Is this sufficient? My feeling was, no.

DR. HELDRETH: Just one last clarification for Wilbur's sake. We proposed a read across justification table and we just wanted to get the panel's input. Does that seem acceptable?

DR. MARKS: Yes.

DR. HELDRETH: Thank you.

DR. HILL: You're talking about the one you put in here, in the draft?

DR. HELDRETH: Yes, Table 2.

DR. HILL: I was happy with those.

DR. HELDRETH: Good, great.

Day 2 of the March 5-6, 2018 CIR Expert Panel Meeting - Full Panel

Polyol Phosphates

DR. BELSITO: Yes. This is the first time we're looking at this group of ingredients, and we received data both initially and in Wave two. First and foremost, our group felt that we could include all of the ingredients that were listed; there were none that we wanted to exclude.

And then having looked at the data for them, we felt that currently it was insufficient. That we wanted method of manufacture and impurities for the nonphytic ingredients. It was insufficient for sensitization of phytic acid at 2 percent, realizing that in formulation it may not be present simply as phytic acid. So, we would take a cosmetic preparation that add 2 percent phytic acid and look at data for that in preparation.

I think that was it, right? So, method of manufacture, impurities and sensitization at maximum concentration of use, which was 2 percent phytic acid. And the method of manufacture and impurities was for the nonphytic ingredient.

DR. BERGFELD: Jim?

DR. MARKS: We had --

DR. BERGFELD: Is that a motion? Excuse me. Is that a motion?

DR. BELSITO: That was a motion.

DR. MARKS: We had a similar -- it would become an insufficient data announcement. Our team felt we wanted to eliminate the sugar phosphates, so that would leave just five ingredients.

And then, Ron Hill, do you want to mention that? And then the other thing, I'll let Ron Hill mention, in a minute, why eliminating this sugar phosphates -- do we need to mention this in vitro luciferase test? I wanted sensitization also, but there was a suggestion with that test, whatever it is --

DR. BELSITO: Well, it's the KeratinoSens test that we heard about at the last meeting. It looks at step two of the adverse outcome pathway for sensitization. It's a way of looking at in vitro sensitization, but it's far from adequate. We don't have a direct peptide reactivity and we have no indication or macrophage activity. It just indicates whether the KeratinoSens is activated.

Yeah, I mean, we need sensitization, that's why I asked for it.

DR. MARKS: Right. Do you want to, Ron Hill, mention about the sugar phosphates, why you wanted to eliminate those? Because obviously, it's a difference in the approach with the teams.

DR. HILL: Actually, I wasn't the only one, but I don't remember what Ron Shank wrote.

DR. SLAGA: He wanted them eliminated.

DR. HILL: Yeah. I think the three of the four of us thought that those didn't belong. I just wrote that sugars do redox chemistry, biologically they're different than the pseudo sugars; the inositol and basically the polyhydroxy cyclohexane is the backbone of inositol and the phytates, so they're different.

With the sugars, we have the possibility of ring-open, ring-close conversions. The biological processing of those would be expected to be, at least, somewhat different and we thought that they didn't belong.

I wanted to make clear that it wasn't because we really have no data on them, it was because they should be in a different group. If we want to review them, put them in a different group and then go forward.

DR. MARKS: Ron Shank said there is almost no tox data on the sugar phosphates. They are not currently used in cosmetics, so drop them from the report. So, his was more an operational issue, I think, not a chemistry issue. Ron Hill, you didn't like them from a chemical point.

DR. HILL: From a chemical point of view, and a biochemical point of view, I thought they didn't belong here.

DR. BERGFELD: Dan?

DR. LIEBLER: Yeah. I acknowledged the differences in chemistry, but I didn't feel that they were enough to overcome the similarities in function in cosmetic ingredients. There are some differences, certainly, but there are also some very clear unifying factors. These are essentially small polyhydroxy molecules with phosphates on them, in many cases, multiple phosphates.

The metabolites of these, after phosphatase, is essentially endogenous nutrients or endogenous metabolic intermediates and carbon metabolism.

Those are things that mitigated my concern. Many of these, I realize, aren't used, and we may not get data on them; but I'd rather have a problem with them for insufficient data rather than simply excluding them. They're in the INCI dictionary and they fall into this group. My default is to start with them. I didn't feel there was enough reason to exclude them.

DR. BERGFELD: Ron Hill, you want to respond?

DR. HILL: I would be okay with leaving them in, but they're going to be insufficient until I see data giving some idea of what would go on with them. Because I agree that they're endogenous molecules, but I know of no endogenous sugar phosphates. I've never seen sugars with phosphates.

If it's oral exposure, are they cleaved in the gut? If it's dermal exposure, I would have looked at the physical/chemical properties of these phosphates, and these heavily hydrophilic phosphates, and thought there would be no dermal absorption, but it's clear that's not the case.

I'm puzzled, but we have no information. I would not be able to come to a sufficient conclusion unless I have a good bit more information on those molecules.

DR. LIEBLER: My point is that we can ask for the data. And when the data aren't forthcoming, then we can decide that it's insufficient. Rather than just eliminating them off the top. That's my distinction.

DR. MARKS: Our team would concur with that, let's move forward including them. I'm sure Ron Shank will read these minutes, and he will give his opinion again at the next meeting when we look at these ingredients.

DR. BERGFELD: No, we've had a motion, but we haven't had a second. So, are you seconding?

DR. MARKS: Yeah. I'll second the motion after our discussion. And actually, the motion's insufficient data announcement, so actually it's what data are we going to ask for. It's going to be for everything, not just the five we mentioned.

DR. BERGFELD: Shall we just call for the vote and then we'll go to the discussion points that we need. All those in favor of moving forward with an insufficient data announcement? Thank you. Unanimous.

Now, what do we need.

DR. MARKS: I think Don outlined that earlier.

DR. BERGFELD: Do you want to outline it again, please?

DR. BELSITO: Sure.

DR. MARKS: I think it was method of manufacture, impurities --

DR. BELSITO: Method of manufacture and impurities for the nonphytic ingredients, and insufficient for sensitization of 2 percent phytic acid.

DR. BERGFELD: What about these sugars?

DR. BELSITO: Well, that would be method of manufacture and impurities.

DR. BERGFELD: Okay.

MR. JOHNSON: One question. Dr. Belsito, is the data request for human data or animal data?

DR. BELSITO: It's a request for data and then we can assess it, maybe.

MR. JOHNSON: So, it doesn't matter. Okay.

DR. BELSITO: I think that there's the potential that 2 percent phytic acid could be irritating. You know what I mean? If there's a product out there that contains 2 percent phytic acid, hopefully, there's an HRIPT on it in formulation and that will satisfy me.

DR. HILL: I would like to see ADME data on notably the sugars, any of the sugars, for all potential cosmetic groups of exposure. And also, I would like to know more about the chemistry of the xylitol phosphate. It's a complex mixture. I think due diligence to know what we're approving the safety of, we deserve to know more about the chemistry, whatever might be known of that.

DR. BERGFELD: Okay. That's agreeable. Do we have all the needs written down? Anyone need to have them clarified? Wilbur, you're okay?

MR. JOHNSON: Yes, I am. Thank you.

DR. BERGFELD: All right. We're going to move on then. Thank you very much.

Safety Assessment of Polyol Phosphates as Used in Cosmetics

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The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of polyol phosphates, which function as chelating agents, oral care agents, and skin conditioning agents in cosmetic products. The Panel reviewed relevant data relating to the safety of these ingredients under the intended conditions of use in cosmetic formulations, and the issuance of a conclusion is expected.

INTRODUCTION

The safety of the following 10 polyol phosphate ingredients in cosmetics is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment.

Inositol Phosphates
Sodium Phytate
Phytic Acid
Phytin
Trisodium Inositol Triphosphate

Saccharide Phosphates
Disodium Glucose Phosphate
Manganese Fructose Diphosphate
Sodium Mannose Phosphate
Trisodium Fructose Diphosphate
Xylityl Phosphate
Zinc Fructose Diphosphate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Sodium Phytate, Phytic Acid, and Trisodium Inositol Triphosphate are reported to function as chelating agents in cosmetic products.[1] Sodium Phytate and Phytic Acid are also reported to function as oral care agents, and, Trisodium Fructose Diphosphate, as an antioxidant in cosmetic products (Table 1). The remaining ingredients have the skin conditioning agent function in common, except for Xylityl Phosphate, which functions as an antiacne agent, antidandruff agent, deodorant agent, and exfoliant. Functioning as an antiacne or antidandruff agent is not considered a cosmetic function in the United States and, therefore, the CIR Expert Panel (Panel) will not evaluate safety in relation to either of those uses.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

The following data on chemicals that are not cosmetic ingredients are included in this safety assessment, and are being used for read across (see Table 2): human dermal penetration data on Potassium Phytate (potential read-across for Sodium Phytate, Phytic Acid, and Phytin) and tumor promotion data on phytic acid hexamagnesium salt *n*-hydrate (potential read-across for Phytin (the calcium and magnesium salt of Phytic Acid)).

CHEMISTRY

Definition and General Characterization

The ingredients in this report are each the phosphate(s) of a carbohydrate (e.g., inositol or, a monosaccharide or "sugar alcohol") or a salt thereof. One example of these polyol phosphate salts is Disodium Glucose Phosphate (Figure 1). Some of these ingredients may exist in open chain, furanose and/or pyranose forms, like many sugars do. Some of these ingredients are naturally occurring. Indeed, Phytic Acid and other particular inositol phosphates (Figure 2) are present in practically all mammalian cells.[2] The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.

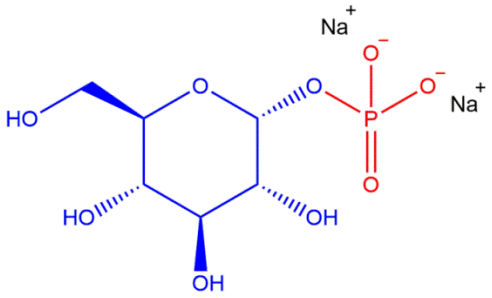


Figure 1. Disodium Glucose Phosphate, example of a saccharide phosphate

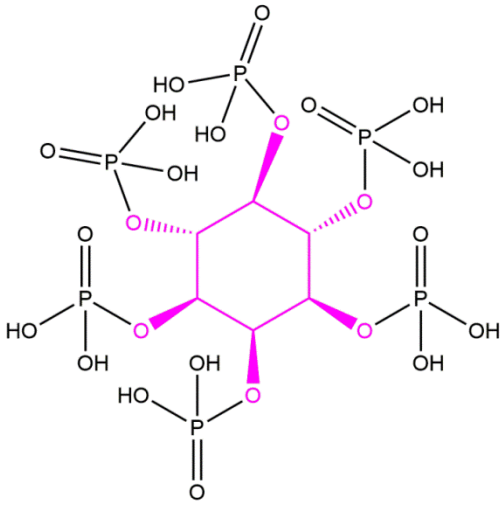


Figure 2. Phytic Acid, example of an inositol phosphate

Chemical and Physical Properties

Properties of polyol phosphates are presented in Table 3.[3,4,5,6,7] Sodium Phytate is soluble in water and Phytic Acid is soluble in water containing alcohol-ether mixtures.[3] Phytin is poorly soluble in water.

Method of Manufacture

Phytic Acid

According to one source, an aqueous solution of Phytic Acid (50% aqueous) for use in foods is obtained by acid hydrolysis of maize seed (kernels), rice bran, or rice husks (hulls).[8] The initial hydrolysis is followed by multiple processing steps that include: centrifugation, filtration, neutralization, dilution, decolorization, further hydrolysis and pH adjustment, ion-exchange, and concentration.

According to one foods manufacturer, the production of Phytic Acid (50% solution) involves the addition of diluted sulfuric acid to defatted food-grade rice bran to dissociate phytate from iron and protein complexes.[9] The solution then undergoes centrifugation, filtration to remove impurities, neutralization with sodium hydroxide, and dilution with water. Also, the diluted solution is decolorized, and sulfuric acid is added to dissociate the bound minerals from phytate to release Phytic Acid. The Phytic Acid-containing solution undergoes pH adjustment, ion-exchange, decolorization, and vacuum concentration to achieve a 50% concentration. Because rice bran is the source of Phytic Acid in this production method, it should be noted that one source indicates that the content of Phytic Acid in rice bran ranges from 0.22% to 2.22%.[10]

Another reported method for the production of Phytic Acid begins with the hydrochloric acid leaching of bran, which is followed by filtration, neutralization with sodium hydroxide, and water scrubbing.[11] The resulting paste phytin is acidified and then subjected to positive ion exchange, condensation, and decolorization, yielding Phytic Acid.

Composition

Phytic Acid

According to a company's food-grade chemical specification for Phytic Acid (50% solution), 48% to 52% is the range for Phytic Acid content and for water content.[9]

Impurities

Phytic Acid

According to the United States Pharmacopeial Convention's (USP) Food Ingredients Expert Committee, the acceptance criteria for Phytic Acid (aqueous solution) include: arsenic (not more than 3 mg/kg), calcium (not more than 0.02%), chloride (not more than 0.02%), inorganic phosphorus (not more than 0.2%), lead (not more than 1 mg/kg) and sulfate (not more than 0.02%).[8]

Specifications for one manufacturer's food-grade Phytic Acid (50% solution; as described above in Method of Manufacture) include: heavy metals (as Pb) (< 20 ppm), lead (< 1 ppm), arsenic (< 2 ppm), total phosphorus (13.5 % to 14.6%), inorganic phosphorus (not more than 1%), chloride (not more than 0.04%),and sulfate (not more than 0.071%).[9] Furthermore, because the raw material that is used in the production of Phytic Acid (50% solution) is defatted rice bran, there is the potential for presence of residual pesticides and herbicides.

An impurities analysis of 50% Phytic Acid (vehicle not stated) was provided.[12] Results indicated that the levels of the following heavy metals were below the detection limits (≤ 400 ppb to ≤ 100 ppb): mercury, cadmium, zinc, cobalt, copper, nickel, and lead. Determination of the level of arsenic was not possible because the 50% Phytic Acid preparation appeared to strongly interfere with the assay reagents. As expected, the negative control (distilled water) tested negative for arsenic.

USE

Cosmetic

The safety of the polyol phosphates is evaluated based on data received from the United States (U.S.) FDA and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[13] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[14]

According to 2018 VCRP data, the greatest use frequency is reported for Sodium Phytate, which is reported to be used in 412 cosmetic products (259 leave-on, 146 rinse-off, and 7 diluted for bath use).[13] The results of a concentration of use survey conducted in 2016-2017 indicate that Phytic Acid is being used at concentrations up to 2% in leave-on products (body and hand products [not spray]), which is the greatest use concentration that is being reported for the polyol phosphates reviewed in this safety assessment.[14] Further use frequency and concentration of use data are presented in Table 4.

According to VCRP and Council survey data, the following 7 polyol phosphates are not currently being used in cosmetic products in the U.S.: Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Phytin, Trisodium Fructose Diphosphate, Trisodium Inositol Triphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate.

Cosmetic products containing polyol phosphates may be applied to the skin and hair or, incidentally, may come in contact with the eyes (at maximum use concentrations up to 0.05% for Sodium Phytate and Phytic Acid in eye makeup removers and eye lotions, respectively) and mucous membranes (at maximum use concentrations up to 0.5% Sodium Phytate in lipstick). Ingredient use in lipstick products may result in incidental ingestion. Products containing polyol phosphates may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Sodium Phytate is reported in the VCRP as being used in a perfume formulation, which may result in incidental inhalation exposure. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[15,16,17,18] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited

in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[15,16]

The polyol phosphates reviewed in this safety assessment are not included on the European Union's list of substances that are restricted or list of substances that are prohibited in cosmetic products.[19]

Noncosmetic

Sodium Phytate

Sodium Phytate is used as a complexing agent for the removal of traces of heavy metal ions.[3] It is also used as the starting material in the manufacture of inositol.

Phytic Acid

After reviewing a GRAS exemption claim, the U.S. Food and Drug Administration (FDA) issued the following statement: "Based on the information provided … as well as other information available to FDA, the agency has no questions at this time regarding … [the submitted] conclusion that Phytic Acid is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of Phytic Acid."[20]

Reportedly, Phytic Acid (2% to 4%) has proven to be efficient in the treatment of epidermal melasma, especially when associated with glycolic acid or retinoic acid.[21] Furthermore, the Phytic Acid combination peel has been described as a proprietary peel that is a mixture of glycolic acid, lactic acid, mandelic acid, and Phytic Acid.

Phytic Acid is used in the chelation of heavy metals in processing of animal fats and vegetables, as a rust inhibitor, in the preparation of phytate salts, in metal cleaning, and in the treatment of hard water.[4]

TOXICOKINETIC STUDIES

The toxicokinetic studies summarized below are presented in Table 5.

Dermal Penetration

Animal

Sodium Phytate and Phytin

Over a period of 16 days, groups of 6 female Wistar rats consumed a synthetic purified diet that resulted in undetectable urinary Phytic Acid.[22] The rats were then treated topically (once per day for 14 days) with 4 g of a standard moisturizing cream supplemented with Sodium Phytate (0.4%, 1.2%, or 2%) or 2.0% Phytin. The treated area of dorsal skin was ~50 cm^2. Samples of 24 h urine were collected at days 0, 7, and 14. Sodium Phytate was absorbed at significantly higher amounts than Phytin. When the topical cream contained 2% Sodium Phytate, the value for urinary Phytic Acid was 66.35 ± 5.49 mg/l on day 30. When topical application was discontinued after day 30 (~day 35), the mean value for urinary Phytic Acid was ~2 mg/l on day 55. When the topical cream contained 2% Phytin, the value for urinary Phytic Acid was 16.02 ± 2.61 mg/l on day 30. When topical application was discontinued, the mean value for urinary Phytic Acid was ~1 mg/l on day 45. Thus, Phytic Acid was absorbed through the skin layers (having crossed the epidermis and dermis), entered the bloodstream, and urinary excretion was increased.

Human

Potassium Phytate (read-across for Sodium Phytate, Phytic Acid, and Phytin)

In a study involving 20 healthy volunteers on a Phytic Acid-poor diet, the urinary excretion of Phytic Acid increased by 54% following topical treatment with a standard moisturizing gel containing 4% potassium phytate. Thus, the test substance was absorbed through the epidermis and dermis, entered the blood, and the urinary excretion of Phytic Acid was increased. Urine samples were collected at day 7 of treatment.[23]

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Phytic Acid

When [^{14}C]-Phytic Acid was administered orally (in distilled water, by gastric tube) to groups of 5 male Sprague-Dawley rats, ~6% of the administered dose was recovered in the feces at 48 h post-dosing.[24] Following the oral administration of [^{3}H]-Phytic Acid (by stomach tube) to 9 male Fisher 344 rats, absorption (79.0 ± 10.0% of total radioactivity) was described as rapid and, at 24 h, much of the radioactivity was distributed in the liver, kidneys, muscle, and skin. Also, at 24 h, the total radioactivity recovered in the feces was 14.1 ± 8.7% of the administered dose, and the overall radioactivity in the urine collected was 2.4 ± 1.6% (most due to presence of the metabolite, inositol (the core, non-phosphorylated carbohydrate of Phytic Acid), concentration not stated) of the total administered dose.[25]

Groups of 12 female Wistar rats were fed Phytic Acid in the diet at doses of 11.6 g/kg dry matter (DM) and 9 g/kg DM for 12 weeks; the highest Phytic Acid concentrations were detected in the brain (5.89×10^{-2} mg/g DM), and concentrations detected in other organs were 10-fold less.[26] In another study, C.B-17 SCID female mice (specific pathogen-free, bearing MDA-MB-231 breast cancer xenografts; number not stated) were dosed orally with 0.01 ml/g [^{14}C]-Phytic Acid and unlabeled Phytic Acid so that each mouse received 20 mg/kg Phytic Acid and 0.150 mCi/kg in phosphate-buffered saline. The % of the administered dose that was excreted in the urine as inositol was 0.3% , and ~10% of the administered dose was present in the feces, primarily as inositol.[27]

Human

Oral

Phytic Acid

In human subjects (number not stated), 1% to 3% of the total amount of Phytic Acid administered (oral dosing method unknown) was excreted in the urine as Phytic Acid.[28] The results of another study indicated that 1% to 10% of the total amount of Phytic Acid ingested was excreted in the urine.[29]

Sodium Phytate, Phytic Acid, and Phytin

In a study in which 7 volunteers received Phytic Acid, Sodium Phytate, or Phytin in the diet, urinary levels of Phytic Acid increased continuously until normal values were reached and the amount of Phytic Acid excreted was not affected by the type of Phytic Acid salt that was administered.[30] Because normal values for urinary Phytic Acid are not stated in this publication it should be noted that, according to another source, the common Phytic Acid amount present in human urine is 0.4 g/l.[29]

Phytate (cation not declared; read-across for Sodium Phytate, Phytic Acid, and Phytin)

Healthy women (15 young and 14 elderly) consumed low-phytate diets (young women: 682 mg phytate/day; elderly women: 782 mg phytate/day) or a high-phytate diet (young women: 1587 mg phytate/day; elderly women: 1723 mg phytate /day) for a period of 10 days.[31] Study results indicated that phytate degradation in the gastrointestinal tract was substantial and more variable in young women than in elderly women. In a similar study, Healthy women (14 young and 14 elderly) consumed low-phytate diets (young women: 681 mg phytate /day; elderly women: 782 mg phytate/day) or a high-phytate diet (young women: 1584 mg phytate /day; elderly women: 1723 mg phytate/day) for a period of 10 days. A considerable amount of dietary phytate was degraded in the human gut.[32] The degradation rate of dietary phytate was approximately 77% for young women, which was significantly lower than that reported for elderly women (86 %) ($P < 0.05$). Results relating to toxicity in these 2 oral feeding studies are included in the Other Clinical Reports section of this safety assessment.

The extent of dietary phytate degradation has been reported to vary from 40 to 75% in humans, and may occur throughout the whole gut.[33,34] Phytate degradation may result from the activities of dietary phytase, intestinal mucosal phytase, or phytase that is produced by the small intestinal microflora.[31] Mucosal phytase in the human small intestine seems to play a minor role when compared to dietary phytase for phytate hydrolysis.[35] Phytate degradation is also thought to occur in the colon, due to the action of microbial phytase originating from colonic bacteria.[34]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute toxicity studies summarized below are presented in Table 6.

Oral

Phytic Acid

In an acute oral toxicity study involving Jcl:ICR mice (number not stated), LD_{50} values of 1150 mg/kg (females) and 900 mg/kg (males) were reported.[9,36] LD_{50} values of 480 mg/kg (females) and 400 to 500 mg/kg (males) were reported in an acute oral toxicity study involving F344 rats (number not stated).[9,37]

Intravenous

Sodium Phytate

The intravenous (i.v.) administration of Sodium Phytate to groups of 10 NMRI mice at doses up to 0.56 mg/g (range of doses administered within 7 minutes) yielded an LD_{50} of ~0.5 mg/g, and there were no detectable effects from infusion when the rate was not more than 0.02 mg/g/minute. When Sodium Phytate was administered i.v. to rats at lower doses of 0.035 and 0.07 mg/g, there were no detectable signs when doses were administered at a rate requiring 40 minutes for administration of the total dose. Different infusion rates were used in this study, and whether or not mortalities were observed was dependent on the infusion rate.[38]

Short-Term Toxicity Studies

The short-term toxicity studies summarized below are presented in Table 7.

Oral

Sodium Phytate

Groups of 5 male Wistar rats were fed Sodium Phytate at dietary concentrations ranging from 0.02% to 10% (in high-sucrose diet) for 14 to 15 days.[39] Statistically significant depression of food intake and growth was observed at dietary concentrations of 5% and 10% Sodium Phytate, but not at lower concentrations. There were no significant differences in food intake, body weight, and organ weights among groups of 10 diabetic KK mice fed Sodium Phytate in the diet (0.5% or 1%) for 8 weeks.[40]

Phytic Acid

Three different concentrations of 50% Phytic Acid solution (equivalent to doses of 80, 155, or 315 mg/kg/day) were administered orally to groups of 21 to 24 pregnant female JcI:ICR mice on gestation days 7 to 15. There were no maternal mortalities in the control or 80 mg/kg/day group. Two of 22 dams in the 155 mg/kg/day group and 15 of 24 dams in the 315 mg/kg/day group died during the study. Statistically significant changes in organ weights were observed in all dose groups; however, there was no significant dose-response relationship for these findings and no statistically significant macroscopic findings were observed.[9,41] Other study results are included in the section on Developmental and Reproductive Toxicity. Groups of 8 male Wistar rats were fed dietary concentrations of 0.1% to 1% Phytic Acid for 20 days. No effects on organ weight were noted, but the concentration of triiodothyronine (T_3) in the serum was statistically significantly lower at all administered Phytic Acid concentrations.[42] In another study, dosing with Phytic Acid (2% in distilled water) was well tolerated in 10 female wild-type mice (C7BL/6J strain) treated for 70 days.[43]

In a 12-week dose range-finding study (for 108-week oral carcinogenicity study), groups of 20 male and female F344 rats received Phytic Acid at concentrations up to 10% in drinking water.[44] All rats that received 10% Phytic Acid and all males and 1 female that received 5% Phytic Acid died before the end of the experiment. The 108-week oral carcinogenicity study is summarized in that section of this safety assessment.

Chronic Toxicity Study

In a chronic study, 8 female Tg2576 mice and 10 C7BL/6J mice received Phytic Acid at a concentration of 2% in distilled water for 6 months. Seven control Tg2576 mice and 12 control C7BL/6J mice received distilled drinking water for the same duration. Phytic Acid was well-tolerated, as indicated by the observation that average weekly body weights (an indirect measurement of toxicity) were similar for vehicle and Phytic Acid-treated animals.[43]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

The developmental and reproductive toxicity studies summarized below are presented in Table 8.

Animal

Oral

Phytic Acid

Three different concentrations of 50% Phytic Acid solution (equivalent to doses of 80, 155, or 315 mg/kg/day) were administered orally to groups of 21 to 24 pregnant JcI:ICR mice on gestation days 7 to 18. No significant effects on the incidence of external or skeletal malformations were observed at any dose of Phytic Acid. There were also no significant effects on the following: number of live fetuses, number of corpora lutea per litter, number of implantations per litter, incidence of early resorptions, or number of live fetuses per litter.[41] The treatment of groups of 30 male albino rats (*Rattus norvegicus*) with Phytic Acid had an ameliorative effect on the pathological and hormonal alterations induced by aflatoxin B1 injection. Specifically, treatment with Phytic Acid had a marked regenerative effect upon the aflatoxin B1-induced histopathological changes in the seminiferous tubules (i.e., degeneration with absence of spermatozoa) and resulted in statistically significant ($P < 0.05$) amelioration of the reduced testosterone concentration induced by aflatoxin B1injection.[45]

GENOTOXICITY STUDIES

The genotoxicity studies summarized below are presented in Table 9.

In Vitro

Sodium Phytate

The genotoxicity of a Sodium Phytate (concentration not stated) trade name material consisting of 50% water and 1% ethanol was evaluated in the Ames test using the following *Salmonella typh*imurium strains: TA 97a, TA 98, TA 100, TA 102, and TA 1535.[46] The test material, in deionized water, was evaluated at doses up to 4995 µg/plate with and without metabolic activation. Results were negative for genotoxicity. A second experiment (pre-incubation method, modification of Ames test) was performed to confirm the results of the first. The test material was evaluated at doses up to 5013 µg/plate, with and without metabolic activation. There were no signs of genotoxicity.

Phytic Acid

Phytic Acid (50% solution) was non-genotoxic in the Ames test, with or without metabolic activation, when tested at doses up to 10 mg/plate.[47] In the L5178Y TK+/- mouse lymphoma assay, Phytic Acid was non-genotoxic at concentrations up to 5000 µg/ml with or without metabolic activation.[48] Also, Phytic Acid (2 mg/ml) was non-genotoxic to Chinese hamster ovary cells in the chromosomal aberrations assay.[47] However, Phytic Acid (an unknown high concentration) was genotoxic in the chromosomal aberrations assay.[9]

In Vivo

Phytic Acid

In the micronucleus test involving bone marrow cells from ddY mice, Phytic Acid was non-genotoxic at an administered intraperitoneal (i.p.) dose of 30 mg/kg or 60 mg/kg.[9]

CARCINOGENICITY STUDIES

The carcinogenicity studies summarized below are presented in Table 10.

Phytic Acid

Phytic Acid was administered at a concentration of 1.25% or 2.5% in drinking water to groups of 60 male and 60 female F344 rats for 108 weeks.[44] Renal papillomas (related to calcification and necrosis of renal papillae) were observed in 3 male and 4 female rats treated with 2.5% Phytic Acid, respectively, and in 3 female rats treated with 1.25% Phytic Acid. Many tumors developed in all groups, including the control group, and the organ distribution of tumor types (other than the renal tumors observed) did not differ significantly from those known to occur spontaneously in the F344 strain.

Tumor Promotion

Phytic Acid and Sodium Phytate; also Hexamagnesium Phytate Hydrate (read-across for Phytin)

Sodium Phytate (2% in diet) was classified as a promoter of urinary bladder carcinogenesis, after initiation by exposure to 0.05% *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine, in a study involving groups of 15 to 16 male F344 rats. Sodium Phytate significantly increased the development of preneoplastic and neoplastic lesions of the urinary bladder. Potassium phytate brought about a tendency for increase in papillomas, whereas hexamagnesium phytate hydrate and Phytic Acid were without effect.[49]

ANTICARCINOGENICITY STUDIES

The anticarcinogenicity studies summarized below are presented in Table 11.

Dermal

Phytic Acid

In a 30-week study involving groups of 15 female Swiss albino mice, Phytic Acid (0.1 mg, 1 mg, or 5 mg) was applied to the skin weekly after application of 7,12- dimethylbenz[a]anthracene (DMBA). Skin tumor development was inhibited in a dose-dependent manner.[50] When 8 female Crl:SKH1- *hr* hairless mice were treated with 4% Phytic Acid cream (100 mg applied to dorsum), followed by UVB irradiation, topical application of the 4% cream was found to decrease tumor incidence (monitored for 32 weeks) and multiplicity when compared to application of the cream without Phytic Acid.[51]

Oral

Sodium Phytate

Sodium Phytate (0.1% or 1% in drinking water) was administered to groups of 20, 30, or 50 male F344 rats for 44 weeks after azoxymethane injection, and was found to be antineoplastic (reduction in tumor prevalence, frequency, and size) for large intestinal cancer in a dose-dependent manner.[52]

Phytic Acid

In a study involving groups of 15 to 16 female Sprague-Dawley rats, feeding with 2% dietary Phytic Acid after dosing with DMBA resulted in significant reduction in the size of palpable mammary tumors, when compared to the control group, at the end of week 18.[53] In a 22-week study involving groups of 20 female ICR mice that received 2% Phytic Acid in drinking water, the animals were initiated with DMBA and then exposed to the tumor promoter 12-*O*-tetradecanoyl phorbol - 13-acetate (TPA). Mice that ingested Phytic Acid during initiation had a 50% reduction in mean number of skin papillomas, but such inhibition was not observed when Phytic Acid was given during the promotion period or throughout both initiation and promotion phases.[54] Phytic Acid (2% in drinking water) was administered to 15 female Crl:SKH1- *hr* hairless mice prior to UVB exposure, and another group of 15 received UVB exposure only. Tumor formation monitored until week 31, and Phytic Acid + UVB exposure caused a statistically significant decrease in the skin tumor incidence, an antiphotocarcinogenic effect.[55]

OTHER RELEVANT STUDIES

Anti-Inflammatory Activity

Phytic Acid

The anti-inflammatory activity of Phytic Acid in adult Swiss albino rats (groups of 6) was evaluated using the carrageenan-induced rat paw edema model.[56] The animals received oral doses (in water, given *ad libitum*) of Phytic Acid ranging from 30 to 150 mg/kg, and control animals were dosed with distilled water. At 1 h post dosing, the animals received a subplantar injection (left hind paw) of 1% carrageenan solution. The development of edema was the index of acute inflammatory changes, and differences in paw volume determined immediately after carrageenan injection versus 3 h post-injection were reported. Dosing with Phytic Acid caused a dose-dependent reduction in carrageenan-induced paw edema. The reduction in edema volume was statistically significant ($p < 0.05$) at doses ranging from 60 to 150 mg/kg, but not at a dose of 30 mg/kg. The maximum anti-inflammatory activity of Phytic Acid was observed at an oral dose of 150 mg/kg.

Cytotoxicity

Phytic Acid

The effect of Phytic Acid on cell growth was evaluated using a colorimetric assay for the quantification of cell proliferation and viability based on the cleavage of the WST-1 tetrazolium salt by mitochondrial dehydrogenases in viable cells.[57] The following cell lines were used: HL60 human promyelocytic leukemia cell line, chronic myelogenous leukemia cell lines K562, AR23, and RWLeu4, and the KG1 progenitor leukemia cell line. The WST-1 tetrazolium salt (10 µl) was added to well culture plates containing 100 µl of cell suspension. The plates were evaluated after 4-h of incubation. Phytic Acid had a clear cytotoxic effect on all of the tested cell lines, with an IC_{50} of 5 mmol/l after 72 h of culture.

Phytic Acid extracted from rice bran induced marked growth inhibition in ovary, breast, and liver cancer cells, with 50% growth inhibition concentration (IC_{50}) values of 3.45, 3.78 and 1.66 mM, respectively.50 Phytic Acid exhibited no sensitivity towards a normal cell line (BALB/c 3T3 cells).

Effect on Nutrient Absorption

Phytate (cation not declared; read-across for Sodium Phytate, Phytic Acid, and Phytin)

In a study involving 717 pregnant women in rural Bangladesh, the mean dietary intake of phytate was found to be ~695.1 mg/day.[58] Phytate inhibited iron absorption from the diet in all of the women, inhibited calcium absorption in 52% of the women, and inhibited zinc absorption in 12% of the women.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The skin irritation and sensitization studies summarized below are presented in detail in Table 1.

Irritation

In Vitro

Sodium Phytate

The skin corrosion potential of a Sodium Phytate trade name material consisting of 50% water and 1% ethanol was evaluated in an *in vitro* skin model (reconstructed human epidermis) test for skin corrosion.[46] The concentration of Sodium Phytate in the trade name material was not stated. Prior to testing, the trade name material was dried, yielding 0.1% to 10% residual water. After 3 minutes of treatment with the test material, the mean value of relative tissue viability was reduced to 80.6%, above the threshold for corrosion potential (50%). After 1 h of treatment, the mean value of relative tissue viability was reduced to 86.9%. The test material was classified as non-corrosive to the skin. Using the same skin model, the same test material was evaluated for skin irritation potential. At the end of the 60-minute application period, the mean value for relative tissue viability was reduced to 84.7%, above the threshold for skin irritation potential (50%). The test material was classified as non-irritating to the skin.

Phytic Acid

The skin irritation potential of 50% Phytic Acid (vehicle not stated) was evaluated using the EpiDerm™ skin model in vitro toxicity testing system.[59] The model consisted of normal, human-derived epidermal keratinocytes cultured to form a multilayered, highly differentiated model of the human epidermis. A semi-log scale was used to plot the % viabilities versus the dosing times. By interpolation, the time at which the % viability would be 50% (ET_{50}) was estimated. Phytic Acid (50%)

elicited an ET_{50} that was significantly less than 1 h. This value may be compared with the ET_{50} for concentrated nitric acid (ET_{50} = <0.5 h, severe irritation [probably corrosive]). The authors concluded that 50% Phytic Acid has an expected in vivo dermal irritancy potential in the severely irritating to possibly corrosive range.

Human

Sodium Phytate

The skin irritation potential of a cream containing 0.489956% Sodium Phytate was evaluated in a 48-h patch test (semi-occlusive patches) involving 22 subjects. The dose per cm^2 and other study details are not included in this study summary. The conclusion for this study is stated as "no to negligible dermal irritation potential."[60]

Phytic Acid

A product (mineral treatment, undiluted) containing 0.25% Phytic Acid was evaluated for skin irritation potential in a single-insult (24 h) occlusive patch test involving 21 subjects.[61] Test results were negative.

Sensitization

In Vitro

Sodium Phytate

The skin sensitization potential of a dried Sodium Phytate trade name material (defined in preceding section) was evaluated in the *in vitro* ArE-Nrf2 Luciferase test (OECD 442d protocol, 2 experiments) for skin sensitization.[46] The dried test material was tested at concentrations ranging from 54 µg/ml to 333 µg/ml in the first experiment, and at concentrations ranging from 54 µg/ml to 278 µg/ml in the second experiment. It was concluded that the dried test material had no sensitization potential.

Human

Sodium Phytate

A rinse-off product containing 0.05% Sodium Phytate (1% dilution; effective test concentration = 0.0005%) produced negative results in an occlusive HRIPT involving 111 subjects.[62] HRIPT results were also negative for another rinse-off product containing 0.05% Sodium Phytate (1% dilution; effective test concentration = 0.0005%) in a study involving 111 subjects. The following other negative HRIPT results for products containing Sodium Phytate have been reported: a leave-on product containing 0.05% Sodium Phytate (undiluted, 111 subjects),[62] a leave-on product containing 0.1% Sodium Phytate (undiluted, 112 subjects), [62] and a topical coded product containing 1% Sodium Phytate (maximization test, 25 subjects) [63]

Phytic Acid

A moisturizer containing 5% Phytic Acid was classified as a non-sensitizer in an HRIPT involving 110 subjects.[64] In a maximization test involving 25 subjects, a face gel containing 0.25 % Phytic Acid produced negative results. [65]

Photosensitization/Phototoxicity

A photosensitization test (HRIPT) on a clear liquid containing 1% Sodium Phytate was performed using 25 subjects (21 females and 4 males).[66] During induction, the test substance (~ 40 mg) was applied for 24 h, under an occlusive patch, to a 2 cm x 2 cm area on the lower back. After patch removal, the test site was irradiated with 3 minimal erythemal doses (MEDs) from a xenon arc solar simulator. This procedure was repeated for a total of 6 induction exposures over a 3-week period. The induction phase was followed by a 10- to 14-day non-treatment period. During the challenge phase, the test substance (~ 40 mg) was applied, in duplicate, for 24 h to new sites (2 x 2 cm) on the opposite side of the lower back. The sites were then irradiated with ½ an MED + 4 J/cm2 of UVA. Reactions were scored at 48 h and 72 h after UV irradiation. No reactions suggestive of photocontact allergy were observed in any of the subjects tested.

OCULAR IRRITATION STUDIES

The ocular irritation studies summarized below are presented in more detail in Table 2.

In Vitro

Phytic Acid

Phytic Acid (50%) (vehicle not stated) was evaluated for ocular irritation potential using the EpiOcular™ tissue model *in vitro* toxicity testing system.[67] The ET_{50} for Phytic Acid (50%) was ~ 9 minutes (estimated Draize ocular irritation score of > 25 (moderately irritating)).

Sodium Phytate

In the EpiOcular™ eye irritation test, negative results were reported for a cream containing 0.48956% Sodium Phytate[60] and for a coded product containing 50% Sodium Phytate.[68] In a bovine corneal opacity and permeability test, results were negative for a dried Sodium Phytate (unknown concentration) trade name material and the same material at a concentration of 2% aqueous.[46] In the reconstructed human cornea-like epithelium (RhCE) test, the same dried Sodium Phytatetrade name material was classified as non-irritating,[46] and a Sodium Phytate (concentration not stated) trade name material consisting of 50% water and 1% ethanol was classified as slightly irritating in the *in vitro* hen's egg chorioallantoic membrane test (HET-CAM).[69]

CLINICAL STUDIES

Other Clinical Reports

Phytate (cation not declared; read-across for Sodium Phytate, Phytic Acid, and Phytin)

Healthy women (15 young and 14 elderly) consumed low-phytate diets (young women: 682 mg phytate/day; elderly women: 782 mg phytate/day) or a high-phytate diet (young women: 1587 mg phytate/day; elderly women: 1723 mg phytate /day) for a period of 10 days.[31] Overt signs of toxicity were not reported in the study results. In a similar study, healthy women (14 young and 14 elderly) consumed low-phytate diets (young women: 681 mg phytate /day; elderly women: 782 mg phytate/day) or a high-phytate diet (young women: 1584 mg phytate /day; elderly women: 1723 mg phytate/day) for a period of 10 days. Again, overt signs of toxicity were not reported in the study results.[32]

SUMMARY

The safety of 10 polyol phosphates as used in cosmetics is reviewed in this safety assessment: According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Sodium Phytate, Phytic Acid, and Trisodium Inositol Triphosphate are reported to function as chelating agents in cosmetic products. Sodium Phytate and Phytic Acid are also reported to function as oral care agents, and Trisodium Fructose Diphosphate as an antioxidant, in cosmetic products. The remaining ingredients have the skin conditioning agent function in common, except for Xylityl Phosphate, which is reported to function as an antiacne agent, antidandruff agent, deodorant agent, and exfoliant. Functioning as an antiacne or antidandruff agent is not a cosmetic use and, therefore, the Panel will not evaluate safety in relation to those uses.

An aqueous solution of Phytic Acid is obtained by acid hydrolysis of maize seed (kernels), rice bran, or rice husks (hulls). The production of Phytic Acid (50% solution) involves the addition of diluted sulfuric acid to defatted food-grade rice bran to dissociate phytate from iron and protein complexes.

According to the United States Pharmacopeial Convention's (USP) Food Ingredients Expert Committee, the acceptance criteria for Phytic Acid solution (aqueous solution) include: arsenic (not more than 3 mg/kg), calcium (not more than 0.02%), chloride (not more than 0.02%), inorganic phosphorus (not more than 0.2%), lead (not more than 1 mg/kg) and sulfate (not more than 0.02%). The results of an impurities analysis on 50% Phytic Acid (vehicle not stated) indicated that the levels of heavy metals were lower than the detection level provided by the assay. Detection of a level of arsenic was not possible due to a problem with the assay that was described as strong interference of 50% Phytic Acid with the assay reagents.

According to 2018 VCRP data, the greatest use frequency is reported for Sodium Phytate, which is reported to be used in 412 cosmetic products (259 leave-on, 146 rinse-off, and 7 diluted for bath use). The results of a concentration of use survey conducted in 2016-2017 indicate that Phytic Acid is being used at concentrations up to2% in leave-on products (body

and hand products [not spray]), which is the greatest use concentration that is being reported for the polyol phosphates reviewed in this safety assessment.

Following the topical treatment of Wistar rats with a cream supplemented with Sodium Phytate (up to 2%) or 2% Phytin, Phytic Acid was detected in the urine. Phytic Acid was also detected in the urine of human subjects on a Phytic Acid-poor diet after application of a moisturizing gel containing 4% potassium phytate.

Phytic Acid concentrations were detected in the brains of Wistar rats fed Phytic Acid in the diet for 12 weeks; concentrations detected in other organs were 10-fold less. When [^{14}C]-Phytic Acid was administered orally to Sprague-Dawley rats, much of the radioactivity was distributed in the liver, kidneys, muscle, and skin at 24 h. Most of the radioactivity in the urine was due to the presence of inositol. In human subjects, 1% to 10% of administered Phytic Acid ingested was excreted in the urine. The feeding of Phytic Acid, Sodium Phytate, or Phytin in the diet resulted in a continuous increase in urinary levels of Phytic Acid until normal values were reached.

LD_{50} values of 480 mg/kg (females) and 400 to 500 mg/kg (males) were reported in an acute oral toxicity study involving F344 rats. In an acute oral toxicity study involving male and female Jcl:ICR mice, LD_{50} values of 1150 mg/kg (females) and 400 to 900 mg/kg (males) were reported.

There was no significant dose-response relationship regarding changes in organ weights and no statistically significant macroscopic findings in pregnant female JcI:ICR mice that received oral doses up to 315 mg/kg/day on gestation days 7 to 15. Groups of 10 male diabetic KK mice were fed dietary concentrations of 0.5 % or 1% Sodium Phytate for 8 weeks. Concentrations of fasting and random blood glucose levels were statistically significantly lower ($p < 0.05$) only in the group fed 1% Sodium Phytate. Groups of 8 male Wistar rats were fed dietary concentrations of 0.1% to 1% Phytic Acid for 20 days. No effects on organ weight were noted, but the concentration of T_3 in the serum was statistically significantly lower at all administered Phytic Acid concentrations. Dosing with Phytic Acid (2% in distilled water) was well-tolerated in female C7BL/6J mice treated for 70 days.

In a 12-week dose range-finding study, groups of 20 male and female F344 rats received Phytic Acid at concentrations up to 10% in drinking water. All rats that received 10% Phytic Acid and all males and 1 female that received 5% Phytic Acid died before the end of the experiment. There were no consistent differences in results for control versus test animals in a study in which 8 female Tg2576 mice and 10 C7BL/6J mice received Phytic Acid at a concentration of 2% in distilled water for 6 months.

Three different concentrations of 50% Phytic Acid solution (equivalent to doses of 80, 155, or 315 mg/kg/day) were administered orally to groups of pregnant female 21 to 24 JcI:ICR mice on gestation days 7 to 15. No significant effects on the incidence of external or skeletal malformations were observed at any dose of Phytic Acid. The treatment of groups of 30 male albino rats (*Rattus norvegicus*) with Phytic Acid had an ameliorative effect on the pathological and hormonal alterations induced by aflatoxin B1 injection.

In *in vitro* assays, Phytic Acid was non-genotoxic in the Ames test and L5178Y mouse lymphoma assay, but was genotoxic (at an unknown high concentration) in the chromosomal aberrations assay involving Chinese hamster ovary cells. Phytic Acid was also non-genotoxic in the *in vivo* micronucleus test involving bone marrow cells from mice that received i.p. doses of 30 mg/kg or 60 mg/kg.

The genotoxicity of a Sodium Phytate (concentration not stated) trade name material consisting of 50% water and 1% ethanol was evaluated in the Ames test using the following *Salmonella typh*imurium strains: TA 97a, TA 98, TA 100, TA 102, and TA 1535. The test material, in deionized water, was evaluated at doses up to 4995 µg/plate with and without metabolic activation, and results were negative. A second experiment (pre-incubation method, modification of Ames test) was performed to confirm the results of the first. The test material was evaluated at doses up to 5013 µg/plate, with and without metabolic activation, and results were negative.

Renal papillomas (related to calcification and necrosis of renal papillae) were observed in a very small number of male and female F344 rats in groups of 120 animals treated orally with 1.25% or 2.5% Phytic Acid in drinking water. The organ distribution of other tumor types did not differ significantly from those known to occur in F344 rats. Sodium Phytate (2% in the diet) was classified as a promoter of urinary bladder carcinogenesis. The results of animal studies indicate that Phytic Acid is antiphotocarcinogenic (2% in drinking water [mice]) as well as anticarcinogenic (doses up to 5 mg applied to skin [mice]; 4% in cream applied to skin [mice]; 2% in drinking water [mice]); 2% in diet [rats]), and that Sodium Phytate is anticarcinogenic (up to 1% in drinking water [rats]). Anti-inflammatory activity (oral dose of 150 mg/kg in rats) and cytotoxicity (IC_{50} = 5 mmol/l, leukemia cell lines) have also been associated with Phytic Acid treatment.

A Sodium Phytate (test concentration not stated) trade name material consisting of 50% water and 1% ethanol was evaluated in an *in vitro* skin model (reconstructed human epidermis) to determine its skin irritation and corrosive potential. Results were classified as negative for skin irritation and corrosion.

A cream containing 0.48956% Sodium Phytate was classified as having no to negligible irritation potential in a 48-h semi-occlusive patch test involving 22 subjects. Based on results from the EpiDerm™ skin model in vitro toxicity testing system, Phytic Acid (50%) (vehicle not stated) has an expected in vivo dermal irritancy potential in the severely irritating to possibly corrosive range. A product (mineral treatment, undiluted) containing 0.25% Phytic Acid was evaluated for skin irritation potential in a single-insult (24 h) occlusive patch test involving 21 subjects. Test results were negative. A leave-on product containing 0.1% Sodium Phytate (undiluted) was negative for irritation and allergenicity in an occlusive HRIPT involving 112 subjects.

The skin sensitization potential of a dried Sodium Phytate (concentration not stated) trade name material was evaluated in the *in vitro* ArE-Nrf2 Luciferase test. The test material was evaluated at concentrations ranging from 54 µg/ml to 333 µg/ml. No substantial and reproducible dose-dependent increase in luciferase induction above 1.5-fold was observed up to the maximum test concentration. The test material was classified as having no sensitizing potential.

Two rinse-off products, each containing 0.05% Sodium Phytate (1% dilution; effective test concentration = 0.0005%) were evaluated in occlusive HRIPTs involving 111 subjects. Both products were classified as non-sensitizers. In another study, a leave-on product containing 0.05% Sodium Phytate (undiluted) was evaluated in a semi-occlusive HRIPT involving 111 subjects. The product did not induce dermal sensitization. There was no evidence of delayed contact hypersensitivity in the 110 subjects evaluated in an HRIPT on a moisturizer containing 5% Phytic Acid. A product containing 1% Sodium Phytate and a face gel containing 0.25% Phytic Acid did not induce skin sensitization in groups of 25 subjects in maximization tests.

A clear liquid containing 1% Sodium Phytate did not induce photosensitization in a study involving 25 subjects.

A cream containing 0.48956% Sodium Phytate was classified as having no ocular irritation potential in the in vitro EpiOcular™ eye irritation test. A product containing 50% Sodium Phytate was classified as a minimal to non-irritant and Phytic Acid (50%) was classified as moderately irritating in this test. The ocular irritation potential of a Sodium Phytate (concentration not stated) trade name material was also evaluated in the following *in vitro* assays: bovine corneal opacity and permeability test, reconstructed human cornea-like epithelium (RhCE) test, and the hen's egg chorioallantoic membrane test (HET-CAM). Test results indicated that the trade name material was non-irritating/non-corrosive to slightly irritating.

Overt signs of toxicity were not reported in studies in which healthy women consumed a low-phytate diet (682 mg phytate/day) or a high-phytate diet (1723 mg phytate/day) for a period of 10 days.

DRAFT DISCUSSION

The Panel determined that additional data are needed for completion of the safety assessment of polyol phosphates. The complete list of data needs includes:

- Method of manufacture and impurities data on Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate
- Chemical characterization data on Xylityl Phosphate
- Absorption, distribution, metabolism, and excretion (ADME) data on Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate
- Skin sensitization data (animal or human) on Phytic Acid at the highest maximum use concentration of 2% or on a cosmetic product containing 2% Phytic Acid

The involvement of monosaccharides (i.e., glucose, fructose, mannose, and xylose) in redox reactions was considered by the Panel prior to determining the need for ADME data on the 6 sugar-phosphates (e.g., Trisodium Fructose Diphosphate).

HRIPT data on a moisturizer containing 5% Phytic Acid, as well as products containing Sodium Phytate at lower concentrations, were received. These data may satisfy the Panel's request for skin sensitization data.

The Panel discussed the issue of incidental inhalation exposure from perfumes. Sodium Phytate is reported as being used in a perfume formulation, which may result in incidental inhalation exposure. The Panel noted that 95% to 99% of the droplets/particles produced in cosmetic aerosols and loose-powder cosmetic products would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs.

In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, 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.

DRAFT CONCLUSION

The CIR Expert Panel concluded that the available data are insufficient to make a determination that the polyol phosphates (listed below) are safe under the intended conditions of use in cosmetic formulations.

Inositol Phosphates
Sodium Phytate
Phytin*
Trisodium Inositol Triphosphate*

Saccharide Phosphates
Disodium Glucose Phosphate*
Manganese Fructose Diphosphate*
Sodium Mannose Phosphate
Trisodium Fructose Diphosphate*
Xylityl Phosphate*
Zinc Fructose Diphosphate*

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

TABLES

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

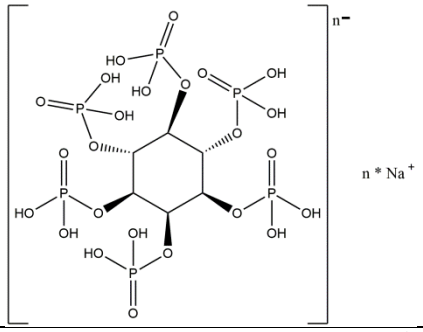
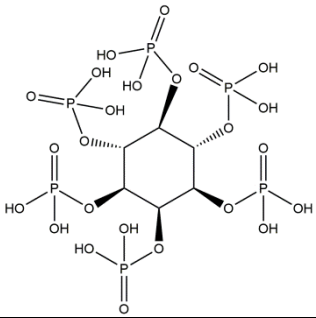
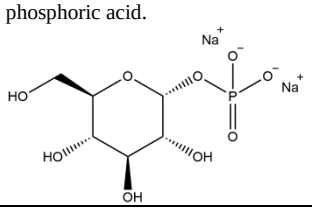
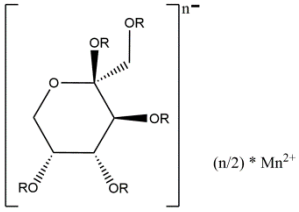
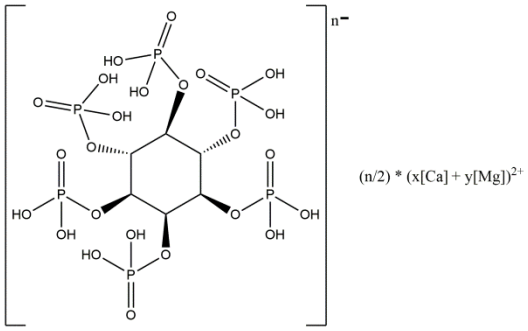
Ingredient CAS No.	Definition & Monomer Structures	Function(s)
Sodium Phytate 14306-25-3 34367-89-0	Sodium Phytate is the complex sodium salt of Phytic Acid.  	Chelating Agents; Oral Care Agents
Phytic Acid 83-86-3	Phytic Acid is the hexaphosphoric acid ester of inositol. It conforms to the formula: 	Chelating Agents; Oral Care Agents
Disodium Glucose Phosphate 59-56-3	Disodium Glucose Phosphate is the disodium salt of the monoester of glucose and phosphoric acid.  	Skin-Conditioning Agents - Emollient
Manganese Fructose Diphosphate	Manganese Fructose Diphosphate is the manganese salt of a complex mixture of esters of fructose and phosphoric acid.  [wherein R is hydrogen in 3 instances and phosphate in 2 instances]	Antioxidants; Skin-Conditioning Agents - Miscellaneous
Phytin 3615-82-5	Phytin is the calcium and magnesium salt of Phytic Acid.  	Humectants; Skin-Conditioning Agents - Emollient; Skin-Conditioning Agents - Humectant

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

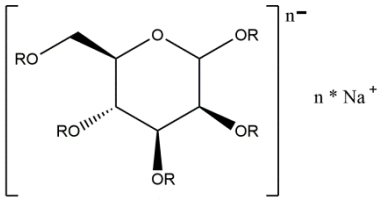
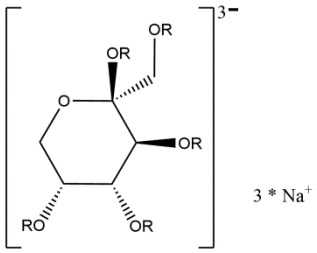
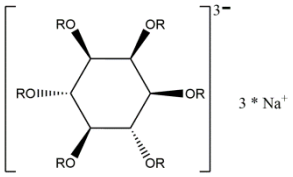
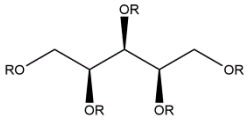
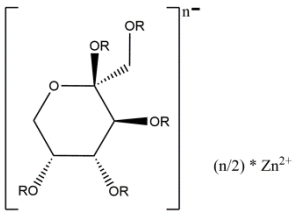
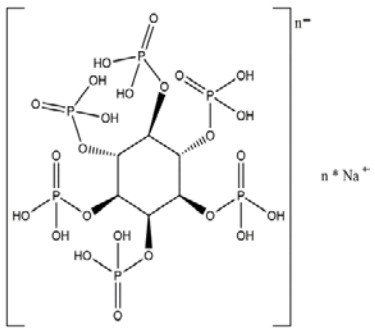
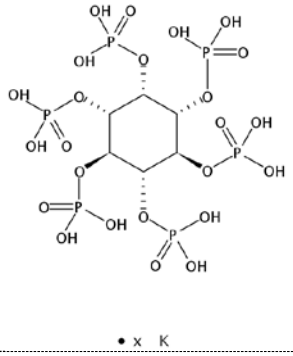
Ingredient CAS No.	Definition & Monomer Structures	Function(s)
Sodium Mannose Phosphate 70442-25-0	Sodium Mannose Phosphate is the sodium salt of a complex mixture of esters of phosphoric acid and Mannose.  [wherein R is phosphate in at least one instance and hydrogen in all other instances]	Skin-Conditioning Agents – Humectant; Skin-Conditioning Agents – Miscellaneous
Trisodium Fructose Diphosphate 81028-91-3	Trisodium Fructose Diphosphate is a trisodium salt of a complex mixture of esters of fructose and phosphoric acid.  [wherein R is hydrogen in 3 instances and phosphate in 2 instances]	Antioxidants; Chelating Agents
Trisodium Inositol Triphosphate	Trisodium Inositol Triphosphate is the trisodium salt of the complex mixture of esters of phosphoric acid and inositol.  [wherein R is hydrogen in 3 instances and phosphate in 3 instances]	Skin-Conditioning Agents - Miscellaneous
Xylityl Phosphate 1224593-11-6	Xylityl Phosphate is the complex mixture of esters formed between xylitol and phosphoric acid.  [wherein R is the residue of phosphoric acid in at least one instance, and hydrogen in all other instances]	Antiacne Agents; Antidandruff Agents; Deodorant Agents; Exfoliants
Zinc Fructose Diphosphate	Zinc Fructose Diphosphate is the zinc salt of a complex mixture of esters of fructose and phosphoric acid.  [wherein R is hydrogen in 3 instances and phosphate in 2 instances]	Antioxidants; Skin-Conditioning Agents - Miscellaneous

Table 2. Read-across Justifications

	Target Material(s)	Read-Across Material
Name	***Sodium Phytate (also Phytic Acid & Phytin)***	***potassium phytate***
CAS No(s).	14306-25-3; 34367-89-0	33705-24-7
Structure		
read-across endpoints	• dermal penetration	
justification	chemical properties, physical properties and metabolism are expected to be similar for these two salts of Phytic Acid	
Examples:		
Formula weight (Da)	877.86 (nonasodium)[3]	1117.12 (dodecapotassium)[70]
log K_{ow} (estimated)	-6.54. [5]	-26.31 ref EPI Suite

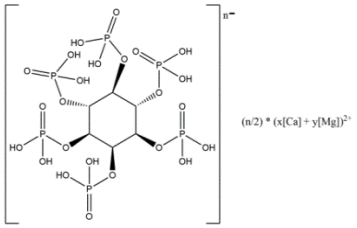
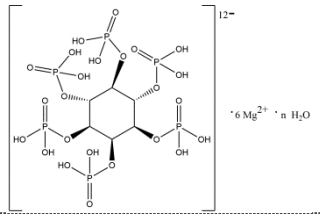
Name	***Phytin***	Phytic acid hexamagnesium salt n-hydrate
CAS No(s).	3615-82-5	
Structure		
read-across endpoints	• tumor promotion	
justification	Because Phytin is defined as the calcium and magnesium salt of Phytic Acid, data on phytic acid hexamagnesium salt *n*-hydrate may be useful in the safety assessment of Phytin.	
Examples:		
Formula weight (Da)	841 (est. for tri-calcium tri-magnesium) 720.38 (mono-calcium mono-magnesium)	812 (est. for hexamagnesium mono-hydrate)

Table 3. Physical and Chemical Properties of Polyol Phosphates

Property	Value	Reference
Sodium Phytate		
Physical form and/or color	Hygroscopic powder	4
Formula weight (Da)	877.86 (nonasodium)	3
Solubility	Soluble in water, with neutral reaction	3
log K_{ow}	-6.54 (est.)	5
Phytic Acid		
Physical form and/or color	Syrupy, straw-colored liquid	3
Molecular weight (Da)	660	6
Solubility	Soluble in water containing alcohol-ether mixtures; very slightly soluble in absolute alcohol and methanol; practically insoluble in anhydrous ether, benzene, and chloroform	3
Miscibility	Miscible with water, 95% alcohol, and glycerol	3
Density (g/l)	1.58	4
log K_{ow}	-1.6	6
pH (10% aqueous solution)	0.86	3
Disodium Glucose Phosphate		
Formula weight (Da)	304.10	7
log K_{ow}	-3.79 (est.)	5
Manganese Fructose Diphosphate		
Formula weight (Da)	393.04	7
log K_{ow}	-3.12 (est.)	5
Phytin		
Physical form and/or color	White, odorless powder	3
Solubility	Poor solubility in water; soluble in dilute acids	3
Formula weight (Da)	720.38 (mono-calcium mono-magnesium)	7
log K_{ow}	-10.11 (est.)	5
Sodium Mannose Phosphate		
Formula weight (Da)	282.12 (mono-sodium mono-phosphate)	7
log K_{ow}	-6.38 (est.)	5
Trisodium Fructose Diphosphate		
Formula weight (Da)	406.06	7
log K_{ow}	-9.99 (est.)	5
Trisodium Inositol Triphosphate		
Formula weight (Da)	486.04	7
log K_{ow}	-12.77 (est.)	5
Xylityl Phosphate		
Molecular weight (Da)	232.12 (monophosphate)	7
log K_{ow}	-3.23 (est.)	5
Zinc Fructose Diphosphate		
Formula weight (Da)	403.48 (monozinc)	7
log K_{ow}	-4.80 (est.)	5

Table 4. Frequency and Concentration of Use According to Duration and Type of Exposure.[13,14]

	Sodium Phytate		Phytic Acid		Sodium Mannose Phosphate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	412	0.0099-0.5	115	0.003-2	33	0.1
Duration of Use						
Leave-On	259	0.0099-0.5	88	0.003-2	30	0.1
Rinse off	146	0.025-0.3	27	0.005-0.3	3	NR
Diluted for (bath) Use	7	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	18	0.025-0.05	5	0.025-0.05	3	NR
Incidental Ingestion	2	0.5	NR	0.3	NR	NR
Incidental Inhalation- Sprays	4;121[a]	0.05-0.3[a]	27[a]	0.005-0.05[a]	12*	NR
Incidental Inhalation- Powders	1[b]	NR	NR	NR	NR	0.1[b]
Dermal Contact	352	0.0099-0.3	75	0.003-2	33	0.1
Deodorant (underarm)	NR	NR	1	NR	NR	NR
Hair - Non-Coloring	58	0.05-0.3	22	0.005	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	43	0.3-0.5	NR	0.3	NR	NR
Baby Products	2	NR	NR	NR	NR	NR

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

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

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

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

Table 5. Absorption, Distribution, Metabolism, and Excretion Studies

Ingredient	Animals or Subjects/Protocol	Results
Dermal Penetration		
Animal Study		
Phytic Acid or Phytin (in moisturizing cream)	Groups of 6 female Wistar rats. After consuming a purified synthetic diet for 16 days, during which urinary Phytic Acid became undetectable, rats treated topically (50 cm^2 area of dorsal skin, applied once per day) with 4 g of standard cream (pH of 4 to 4.5) supplemented with Sodium Phytate (0.4%, 1.2%, or 2%) or 2.0% Phytin. Samples of 24 h urine were collected at days 0, 7, and 14. Animals treated with Sodium Phytate (0.4% and 1.2%) cream killed at day 14. Treatment of animals with 2% Sodium Phytate cream or 2% Phytin cream maintained until day 34, i.e., when urinary Phytic Acid concentrations became constant.	Sodium Phytate was absorbed at significantly higher amounts than Phytin. Phytic Acid urinary concentrations were observed at approximately 14 days after 2% Phytic Acid (as salt) topical cream application. When the topical cream contained 2% Sodium Phytate, the value for urinary Phytic Acid was 66.35 ± 5.49 mg/l. When the topical cream contained 2% Phytin, the value for urinary Phytic Acid was 16.02 ± 2.61 mg/l. When application of the cream was stopped, a dramatic decrease in the urinary excretion of Phytic Acid was observed during a period of 10 days.[22]
Human Study		
Moisturizing gel containing 4% potassium phytate (read-across for Sodium Phytate)	20 healthy volunteers (7 males and 13 females). In phase 1, all subjects received Phytic Acid-poor diet for 15 days and urine samples provided. Urine samples were collected at day 7 of treatment to evaluate phytic acid excretion (2-h urine). In phase 2, subjects continued with the Phytic Acid-poor diet and treated topically (1400 cm^2 area of skin, applied twice per day) with 10 g of standard moisturizing gel containing 4% potassium phytate; urine samples provided. Six control subjects received Phytic Acid-poor diet for 15 days	Following topical application of gel, an increase in the urinary excretion of Phytic Acid (54% increase) was observed over a 2-h period. On day 0, the mean urinary excretion of phytic Acid was ~0.10 mg, and had increased to a value that was between 0.15 mg and 0.2 mg by day 7. Thus, Phytic Acid was absorbed through the epidermis and dermis, entered the blood, and increased the urinary excretion of Phytic Acid.[23]

Table 5. Absorption, Distribution, Metabolism, and Excretion Studies

Ingredient	Animals or Subjects/Protocol	Results
Absorption, Distribution, Metabolism, and Excretion Studies		
Animal Studies		
[^{14}C]-Phytic Acid	Administered orally (in distilled water, by gastric tube) to male Sprague-Dawley rats (groups of 5). Each rat received 52.7 µmoles of [^{14}C]-Phytic Acid dissolved in 2 ml of distilled water.	~6% of the administered dose recovered in feces at 48 h post-dosing. Almost complete absorption (94% of total dose) when calcium intake was low (i.e., 0.12% of the diet). High calcium intake (0.93% of the diet) resulted in decreased absorption, as indicated by increased excretion of [^{14}C]-Phytic Acid in feces (54% of the total dose).[24]
[^{3}H]-Phytic Acid	[^{3}H]-Phytic Acid (37 KBq) administered orally (gastric tube) to 9 male Fisher 344 rats total. Distribution of radioactivity evaluated at 1 h (6 animals) and 24 h (3 animals) post-dosing	Absorption described as rapid, and radioactivity distributed in stomach wall, upper small intestine, skeletal muscle, and skin at 1 h. At 24 h, much of the radioactivity distributed in liver, kidneys, muscle, and skin. Of total radioactivity, 79.0 ± 10.0% was absorbed and at least 26.6% was degraded during the 24-h period following ingestion. Total radioactivity recovered in the feces during 24-h period was 14.1 ± 8.7% of administered dose. The overall radioactivity in the urine collected during the 24-h period was 2.4 ± 1.6% of the total administered dose. Analysis of plasma and urine demonstrated that most of the radioactivity was due to inositol and small amounts of inositol monophosphate.[25]
Phytic Acid (in diet)	Groups of 12 female Wistar rats fed Phytic Acid in the diet at doses of 11.6 g/kg dry matter (DM) and 9 g/kg DM for 12 weeks	Highest Phytic Acid concentrations found in brain (5.89 x 10^{-2} (standard error (SE) 5.7 x 10-3 mg/g DM). Concentrations detected in kidneys, liver and bone were similar to each other (1.96 x 10^{-3} (SE 0.20 x 10^{-3}), 3.11 x 10^{-3} (SE 0.24 x 10-3), and 1.77 x 10^{-3} (SE 0.17 x 10^{-3}) mg/g DM, respectively), and were 10-fold less than those detected in brain.[26]
[^{14}C]-Phytic Acid	C.B-17 SCID female mice (specific pathogen-free, bearing MDA-MB-231 breast cancer xenografts; number not stated) dosed orally (gavage) with 0.01 ml/g [^{14}C]-Phytic Acid and unlabeled Phytic Acid such that each mouse received 20 mg/kg Phytic Acid and 0.150 mCi/kg in phosphate-buffered saline adjusted to pH 7.2. Two mice per time point killed up to 1440 minutes (11 time points total) after dosing.	[^{14}C]-Phytic Acid detected in liver, but only inositol detectable in other tissues. 0.3% of administered dose excreted in the urine as inositol; ~10% of administered dose present in the feces, primarily as inositol.[27] Exogenous Phytic Acid rapidly dephosphorylated to inositol.[27]
[^{14}C]-Phytic Acid	C.B-17 SCID female mice (specific pathogenfree, bearing MDA-MB-231 breast cancer xenografts dosed i.v.(tail vein) with 0.01 ml/g ^{14}C-Phytic Acid and unlabeled Phytic Acid such that each mouse received 20 mg/kg Phytic Acid and 0.150 mCi/kg in phosphate-buffered saline adjusted to pH 7.2. Three mice per time point killed up to 1380 minutes (11 time points total) after dosing.	Plasma Phytic Acid concentrations peaked at 5 minutes and were detectable until 45 minutes. Liver Phytic Acid concentrations more than 10-fold higher than plasma concentrations, whereas other normal tissue concentrations were similar to plasma. ~3% of administered dose excreted in the urine, primarily as inositol; <0.1% of administered dose excreted in feces. Exogenous Phytic Acid rapidly dephosphorylated to inositol.[27]
Human Studies		
Phytic Acid	Urine samples from subjects (number not stated) after administration (route not stated) of Phytic Acid	1% to 3% of total administered Phytic Acid excreted as Phytic Acid.[28]

Table 5. Absorption, Distribution, Metabolism, and Excretion Studies

Ingredient	Animals or Subjects/Protocol	Results
Phytic Acid	Urine samples from subjects (number not stated) after ingestion of Phytic Acid	1% to 10% of total ingested Phytic Acid excreted in the urine.[29]
Phytic Acid, Sodium Phytate, and Phytin	Seven volunteers (3 males, 4 females) were on a Phytic Acid-deficient diet during the first period (15 days) of the study. On day 7 of the first period, the subjects ingested 400 mg of Phytin (as dietary supplement). Three days later (i.e., after 3-day Phytic Acid restriction period), subjects ingested 3200 mg Phytin and 880 mg inositol (as dietary supplements). Subjects also subsequently ingested 1400 mg Sodium Phytate after being on Phytic Acid poor diet for 3 days. Urine samples were collected throughout the study. During the second period of the study, subjects were on a Phytic Acid-normal diet for 16 days to determine how long it would take for individuals to attain their normal urinary and plasma levels of Phytic Acid.	When on the Phytic Acid-deficient diet, basal levels found in plasma (0.07 ± 0.01 mg/L) were lower than those found when the Phytic Acid normal diet was consumed (0.26 ± 0.03 mg/L). After Phytic Acid restriction period, volunteers were on the Phytic Acid-normal diet; normal plasma and urinary Phytic Acid values reached in 16 days. Urinary levels of Phytic Acid increased continuously until normal values were reached. Excreted amounts were not affected by the type of Phytic Acid salt used, either Phytin or Sodium Phytate. Thus, study determined that normal plasma and urinary concentrations can be obtained either by consumption of a Phytic Acid-normal diet (taking a long time) or in a short period by taking Phytic Acid supplements.[30]

Table 6. Acute Toxicity Studies

Ingredient	Animals/Protocol	Results
Oral Studies		
Phytic Acid	Jcl:ICR mice (number not stated)	LD_{50} values of 1150 mg/kg (females) and 900 mg/kg (males).[9,36]
Phytic Acid	F344 rats (number not stated)	LD_{50} values of 480 mg/kg (females) and 400 to 500 mg/kg (males).[9,37]
Intravenous Studies		
Sodium Phytate	Groups of 10 or 20 Sprague-Dawley rats or NMRI mice received i.v. doses ranging from 0.035 to 0.56 mg/g body weight at infusion rates ranging from 2.5 to 20 minutes.	Collectively, the data for mice demonstrate that there were no detectable effects from infusion for any of the time periods studied if the infusion rate was not more than 0.02 mg/g/min, while infusion rates above 0.1 mg/g/minute were tolerated for only 2.5 minutes, and were essentially 100% fatal when continued for 5 minutes or more. When the infusion rate was varied so that a range of doses was administered (to groups of 10 mice) within a fixed time of 7 minutes, a classical mortality rate distribution with dose was observed, yielding an LD_{50} of ~0.5 mg/g. [38] The lower doses (0.035 and 0.07 mg/g) administered to rats (mostly groups of 20) caused no detectable signs at any of the 3 injection rates. The 0.28 mg/g dose showed infusion rate-related mortality similar to the mouse, with 100% mortality when infused in 3 minutes or 5 minutes, and no mortality when infused at a rate of 40 minutes. An LD_{50} was not reported. [38]

Table 7. Short-Term Toxicity Studies

Ingredient	Animals	Protocol	Results
Oral Studies			
Phytic Acid (50% solution administered as 0%, 1.6%, 3.1%, or 6.31% aqueous solution)	Groups of 21 to 24 JcI:ICR mice (in developmental and reproductive toxicity study summarized in report)	Groups received the 50% solution as oral doses (gavage) of 0%, 1.6%, 3.1%, or 6.31% concentrations (equivalent to 0, 80, 155, or 315 mg/kg body weight/day) on gestation days 7 to 15. The dose volume administered was 10 ml/kg/day.	No maternal mortalities in control or 80 mg/kg/day group. Two of 22 dams (9.1%) in the 155 mg/kg/day group and 15 of 24 dams (62.5%) in the 315 mg/kg/day group died during the study. No significant differences in rate of maternal body weight gain reported for all dose groups, compared to control group. Other maternal effects included: statistically significant decrease in absolute heart weights in the 80 mg/kg/day and 315 mg/kg/day dose groups, statistically significant increase in absolute right adrenal gland weights (in 155 mg/kg/day group), and statistically significant increase in relative adrenal gland weight (in 155 mg/kg/day and 315 mg/kg/day groups). However, there was no significant dose-response relationship for these findings, and no statistically significant macroscopic findings were observed.[9,41]
Phytic Acid (up to 10% in drinking water)	Groups of 20 (10 males, 10 females per group) F344 rats	12-week dose range-finding study (for carcinogenicity study, summarized later in report). Test substance administered daily	All rats given 10% Phytic Acid and all males and 1 female given 5% Phytic Acid died before the end of the experiment. In groups given 1.25% or 2.5% Phytic Acid, the reduction in body weight was < 10% when compared to controls.[44]
Phytic Acid (2% in distilled drinking water)	10 female wild type mice (C7BL/6J strain)	10 animals treated with Phytic Acid for 70 day period. 10 control animals received distilled drinking water	Dosing with Phytic Acid well tolerated.[43]
Phytic Acid (0.1% to 1% in diet)	Groups of 8 male Wistar rats	Animals fed Phytic Acid for 20 days. Control animals received diet only	Body weight gain and mass of liver, kidneys, adrenal glands, hypophysis, and testis unaffected in rats fed Phytic Acid in diet. Concentration of T_3 in serum statistically significantly lower ($p \leq 0.01$) at all Phytic Acid concentrations. Concentration of T_4 in serum statistically significantly lower ($p \leq 0.05$) only at 0.2% Phytic Acid. Simultaneously, statistically significantly reduced T_3/T_4 ratio only at 1% Phytic Acid. [42]
Sodium Phytate (0.02% to 10% in high-sucrose diet)	Groups of 5 male Wistar rats	Animals fed for 14 to 15 days	Significant depression of food intake and growth at 5% ($p < 0.05$) and 10% ($p < 0.01$) Sodium Phytate.[39]

Table 7. Short-Term Toxicity Studies

Ingredient	Animals	Protocol	Results
Sodium Phytate (0.5 % and 1% in diet)	Groups of 10 male diabetic KK mice	Groups received Sodium Phytate in diet for 8 weeks. Control group received diet only.	No significant differences in food intake, body weight, and organ weights among test groups. Hemoglobin A_{1c} levels were statistically significantly lower ($p < 0.05$) in both groups receiving Sodium Phytate in the diet when compared to the control group. Concentrations of fasting and random blood glucose levels were statistically significantly lower ($p < 0.05$) only in the group fed 1% Sodium Phytate. There were no significant differences in insulin levels.[40]

Table 8. Developmental and Reproductive Toxicity Studies

Ingredient	Animals or Subjects/Protocol	Results
Oral Studies		
Phytic Acid (50% solution administered as 0%, 1.6%, 3.1%, or 6.31% aqueous solution)	Groups of 21 to 24 JcI:ICR mice received the 50% solution as oral doses (gavage) of 0%, 1.6%, 3.1%, or 6.31% concentrations (equivalent to 0, 80, 155, or 315 mg/kg body weight/day) on gestation days 7 to 15. The dose volume administered was 10 ml/kg/day. Fetuses removed on gestation day 18 and examined for external and skeletal anomalies.	No significant effects on the number of live fetuses, number of corpora lutea per litter, number of implantations per litter, incidence of early resorptions, and number of live fetuses per litter. Significant increase in incidence of late resorption in 80 mg/kg/day group compared to control; however, relevance of these findings is questionable because the standard deviation for the mean incidence values was larger than the actual mean (i.e., 3.8 ± 4.2). No significant effects on late resorption observed in 155 mg/kg/day and 315 mg/kg/day groups. Fetal body weights (male offspring from dams of all dose groups) significantly decreased, in dose-dependent manner. Significant decrease in fetal body weight was reported for female offspring from dams of the 155 mg/kg/day dose group. No significant effects on incidence of external or skeletal malformations at any dose of Phytic Acid. No significant effects on incidence of external or skeletal malformations at any dose of Phytic Acid.[9,41]
Phytic Acid	Study to evaluate enhancement of aflatoxin B1-induced reproductive toxicity by Phytic Acid. Groups of 30 male albino rats (*Rattus norvegicus*): Group 1 injected with 300 µg/kg aflatoxin B1 once every 3 days for 15 days; Group 2 injected with 300 µg/kg aflatoxin B1 once every 3 days for 15 days and treated simultaneously with Phytic Acid (dose not stated) daily for another 15 days; Group 3, treated daily with Phytic Acid (40 mg/kg) for 15 days; Group 4 (control), injected with sterile phosphate buffer saline solution.	Aflatoxin B1 induced histopathological alterations in the seminiferous tubules and whole nuclei of treated-testes (degeneration in seminiferous tubules with absence of spermatozoa); testis absolute weight was significantly decreased. Treatment with Phytic Acid had marked regenerative effect upon the histopathologic features of the seminiferous tubules. Administration of Phytic Acid to aflatoxin B1-intoxicated rats induced marked ($P < 0.05$) amelioration of the reduced testosterone concentration caused by aflatoxin B1. Phytic Acid had an ameliorative effect on the pathological and hormonal alterations induced by aflatoxin B1.[45]

Table 9. Genotoxicity Studies

Ingredient	Cells/Protocol	Results
In Vitro		
Phytic Acid (50% solution; doses up to 10 mg/plate)	*Salmonella typhimurium* strains: TA92, TA94, TA98, TA100, TA1535, and TA1537. Ames test with and without metabolic activation	Non-genotoxic with or without metabolic activation.[47]
Phytic Acid (in distilled water; concentrations up to 5000 µg/ml)	L5178Y TK+/- mouse lymphoma cells. Mouse lymphoma assay with and without metabolic activation. Positive controls: 12-dimethylbenz[a]anthracene (DMBA, with metabolic activation); methyl methanesulfonate (without metabolic activation). Solvent control: distilled water	Non-genotoxic with or without metabolic activation. Positive and negative controls performed as expected. [48]
Phytic Acid (2 mg/ml)	Chinese hamster ovary cells. Chromosomal aberrations assay	Non-genotoxic.[47]
Phytic Acid (high concentration [not stated])	Chinese hamster ovary cells. Chromosomal aberrations assay	Genotoxic.[9]
Sodium Phytate (concentration not stated) trade name material containing 50% water and 1% ethanol (in deionized water, doses up to 4995 µg/plate)	*Salmonella typhimurium* strains: TA97a, TA98, TA100, TA102, and TA1535. Ames test with and without metabolic activation	No evidence of bacterial toxicity. Non-genotoxic. All positive controls (not stated) were genotoxic.[46]
Sodium Phytate (concentration not stated) trade name material containing 50% water and 1% ethanol (in deionized water, doses up to 5013 µg/plate)	*Salmonella typhimurium* strains: TA97a, TA98, TA100, TA102, and TA1535. Ames test with and without metabolic activation	No evidence of bacterial toxicity. Non-genotoxic. All positive controls (not stated) were genotoxic.[46]
In Vivo		
Phytic Acid (single dose of 60 mg/kg or 4 doses of 30 mg/kg))	Mouse bone marrow cells. Micronucleus test. ddY mice (6 per group) administered single dose or 4 doses (at 24-h intervals) i.p. pior to harvesting cells	Non-genotoxic.[9]

Table 10. Carcinogenicity Studies

Ingredient	Animals/Protocol	Results
Oral Carcinogenicity Study		
Phytic Acid (1.25% or 2.5% in drinking water)	Groups of 120 (60 males, 60 females) F344 rats treated for 108 weeks	Dose-dependent reduction in mean final body weights. Necrosis and calcification of renal papillae also reported. Renal papillomas in 3 male and 4 female rats treated with 2.5% Phytic Acid, and in 3 female rats treated with 1.25% Phytic Acid. Development of papillomas appeared to have been related to calcification and necrosis of renal papillae. Many other types of tumors developed in all groups (controls included); however, the organ distribution of the neoplasms and histological characteristics did not differ significantly from those known to occur spontaneously in the F344 strain.[44]
Tumor Promotion Study		
Phytic Acid, Sodium Phytate, potassium phytate, or hexamagnesium phytate hydrate (similar to magnesium phytate; potential read-across for Phytin). Each chemical added to diet as 2% supplement.	Male F344 rats (15 to 16 per group). Effects of dietary Phytic Acid and its salts on promotion stage of two-stage urinary bladder carcinogenesis examined. Initiation by exposure to 0.05% N-butyI-N-(4-hydroxybutyl) nitrosamine in the drinking water for 4 weeks, and then treated with basal diet containing a 2% supplement	Sodium Phytate significantly increased the development of preneoplastic and neoplastic lesions of the urinary bladder. Potassium phytate brought about tendency for increase in papillomas. Hexamagnesium phytate hydrate and Phytic Acid were without effect. Both Sodium Phytate and potassium phytate caused elevation of urinary pH, and Na^+ or K^+ concentration, respectively. Study results confirmed promoting activity of Sodium Phytate for urinary bladder carcinogenesis and indicated modulation by urinary components, as demonstrated by increases in urinary pH, and Na^+ concentration.[49]

Table 11. Anticarcinogenicity Studies

Ingredient	Animals/Protocol	Results
Dermal Studies		
Phytic Acid (0.1 mg, 1 mg, or 5 mg dose)	Groups of 15 female Swiss albino mice in 30-week study. DMBA applied to dorsal skin weekly, immediately followed by topical application of Phytic Acid. For the 3 dose groups, each topical dose per mouse applied twice weekly for 30 weeks.	Phytic Acid inhibited skin tumor development in dose-dependent manner.[50]
Phytic Acid (4% in cream)	8 female Crl:SKH1-*hr* hairless mice treated for 3 days with Phytic Acid (100 mg of 4% Phytic Acid cream applied to dorsum). 2 groups of 15 vehicle control mice treated for 3 days with topical cream without Phytic Acid (100 mg applied to dorsum). On day of whole-body UVB irradiation, cream applied 1 h in advance. Mice irradiated 3 times weekly. Tumor formation monitored for 32 weeks	Topical application of Phytic Acid, followed by UVB irradiation, decreased tumor incidence and multiplicity.[51]

Table 11. Anticarcinogenicity Studies

Ingredient	Animals/Protocol	Results
Oral Studies		
Sodium Phytate (0.1% and 1% in drinking water)	Groups of 20, 30, and 50 male F344 rats injected with azoxymethane (6 injections, at dose of 8 mg/kg/week), beginning 2 weeks after initiation of Sodium Phytate administration (administered for 44 weeks)	Sodium Phytate was antineoplastic for large intestinal cancer in dose-dependent manner. Tumor prevalence, frequency, and size were reduced.[52]
Phytic Acid (2% in diet)	Groups of 15 to 16 female Sprague-Dawley rats. Intragastric dose of DMBA, followed by placement on diet containing 2% Phytic Acid or various other diets, beginning 1-week later, for 35 weeks. The control group received basal diet after DMBA treatment.	Final incidences and multiplicities of mammary tumors not significantly different between DMBA-treated dietary groups. At the end of week 18 (i.e., when all animals were still alive), the average size of palpable mammary tumors was significantly smaller in the 2% Phytic Acid dietary group when compared to the control group.[53]
Phytic Acid (2% in drinking water)	Groups of 20 female ICR mice in 22-week study. Initiation with DMBA application to dorsal skin followed by exposure to the tumor promoter TPA. Some mice given 2% Phytic Acid (in drinking water during entire study. Other mice given 2% Phytic Acid (in drinking water) during first 3 weeks or during promotion (last 19 weeks only).	Mice that ingested Phytic Acid during initiation had 50% reduction in mean number of papillomas (in skin), and was reduction in number of tumor-bearing mice. Such inhibition not observed in mice given Phytic Acid during promotion period. Authors unable to explain why tumor suppression not achieved when Phytic Acid administered throughout both initiation and promotion phases.[54]
Phytic Acid (2% in drinking water)	Groups of 15 female Crl:SKH1- *hr* hairless mice. One group received 2% Phytic Acid in drinking water 3 days before UVB exposure (3 times per week). The other group received UVB exposure only. All mice received Phytic Acid-deficient diet. Tumor formation monitored until week 31.	Phytic Acid in drinking water significantly ($p < 0.05$) decreased incidence of skin tumors (tumor types identified: squamous cell carcinoma, cornifying epithelioma, epidermal hyperplasia, and fibroma) by 5-fold and tumor multiplicity by 4-fold. Phytic Acid had antiphotocarcinogenic effect.[55]

Table 1. Skin Irritation and Sensitization Studies on Polyol Phosphates

Test Substance	Subjects/Tissues Tested	Test Protocol	Results
Irritation (in vitro)			
Sodium Phytate trade name material consisting of 50% water and 1% ethanol (material was dried before testing)	Reconstructed human epidermis (*in vitro* skin model)	OECD 431 protocol. Sodium Phytate dried (concentration not stated, 0.1 to 10% residual water) before application. One tissue treated with 26.2 mg (3-minute incubation) and 25.8 mg (1-h incubation). Second tissue treated with 26 mg (3-minute incubation) and 26.2 mg (1-h incubation). Each dose applied with demineralized water (25 µl). Cell viability evaluated by reduction of 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) to formazan. Potassium hydroxide (8M) was positive control.	After 3 minutes of treatment, mean value for relative tissue viability reduced to 80.6%. After 1 h of treatment, mean value for relative tissue viability was reduced to 86.9%. Dried test material classified as non-corrosive to the skin. Positive control was corrosive.[46]
Dried trade name material described in preceding test	Reconstructed human epidermis (*in vitro* skin model)	OECD 439 protocol. Tissues moistened with 25 µl of Dulbecco's phosphate-buffered saline (DPBS) prior to 60-minute application of test material (dose range: 25.3 to 26.3 mg), spread on area matching tissue size (0.63 cm^2). Sodium dodecyl sulfate (5% solution) was positive control.	Mean value for relative tissue viability reduced to 84.7%. Dried test material classified as non-irritating to the skin. Positive control was skin irritant.[46]
50% Phytic Acid (vehicle not stated)	Normal, human-derived epidermal keratinocytes cultured to form a multilayered, highly differentiated model of human epidermis	Epiderm skin model *in vitro* toxicity testing system. Semi-log scale used to plot % viabilities versus dosing times. Time at which % viability would be 50% (ET_{50}) estimated.	ET_{50} for 50% Phytic Acid was significantly less than 1 h, and compared to ET_{50} for concentrated nitric acid (ET_{50} = <0.5 h, severe irritation [probably corrosive]). Phytic Acid 50% had expected *in vivo* dermal irritancy potential in severely irritating to possibly corrosive range.[59]
Irritation (Human)			
Product (mineral treatment, undiluted) containing 0.25% Phytic Acid	21 subjects	Single-insult (24 h) occlusive patch test	Skin irritation not observed in any of the subjects tested.[61]
Cream containing 0.489956% Sodium Phytate	22 subjects	48-h patch test (semi-occlusive patches). Dose per cm^2 and other study details not included.	No to negligible dermal irritation potential.[60]

Table 1. Skin Irritation and Sensitization Studies on Polyol Phosphates

Test Substance	Subjects/Tissues Tested	Test Protocol	Results
Sensitization (*In Vitro*)			
Dried Sodium Phytate trade name material described in *in vitro* irritation tests above	LuSens cell line	OECD 442d protocol. *In vitro* ArE-Nrf2 Luciferase test for skin sensitization. Test evaluates potential for test material to activate the Nrf2 transcription factor (sensitizing potential). Test material concentrations ranged from 54 µg/ml to 333 µg/ml (experiment 1) and from 54 µg/ml to 278 µg/ml (experiment 2). p-Phenylenediamine served as the positive control.	No substantial and reproducible dose-dependent increase in luciferase induction above 1.5-fold was observed in both experiments, up to the maximum test concentration. No sensitization.[46]
Sensitization (Human)			
Topical coded product containing 1% Sodium Phytate (air-dried)	25 healthy subjects (21 females and 4 males).	Maximization test. Initially, upper outer arm pretreated with SLS. Product (0.05 ml) then applied, under occlusive induction patch, to same site for 48 h (or 72 h when placed over a weekend), and site was examined for signs of irritation. After SLS pre-treatment, reapplication of product to same site. Sequence repeated for total of 5 induction exposures. Pre-treatment with SLS prior to challenge with product at new site on opposite arm. Product (0.05 ml) applied for 48 h to same site.	No evidence of contact allergy at 48 h or 72 h after challenge patch application. Product did not possess a detectable contact-sensitizing potential.[63]
Rinse-off product containing 0.05% Sodium Phytate (1% dilution; effective test concentration = 0.0005%)	111 subjects	Occlusive HRIPT. Induction phase consisted of nine 24-h induction patch applications (0.2 g of product per patch) over 3-week period. Location of patch and cm^2 area not stated. Induction followed by 2-week non-treatment period. Challenge phase involved patch application to new test site. Reactions scored at 24 h, 48 h, 72 h, and 96 h.	Two subjects had low-level reaction (± [faint, minimal erythema] or 1 [erythema]) during induction, but no reactions in any of the subjects during challenge phase. Results negative for dermal sensitization.[62]
Rinse-off product containing 0.05% Sodium Phytate (1% dilution; effective test concentration = 0.0005%)	111 subjects	Occlusive HRIPT (same procedure)	One subject had low-level reaction during induction and 2 subjects had low-level reaction during challenge phase. Results negative for dermal sensitization.[62]
Leave-on product containing 0.05% Sodium Phytate (undiluted)	111 subjects	Semi-occlusive HRIPT (same procedure)	One subject had a low-level reaction during the challenge phase, and there were no reactions in any subjects during induction. Results negative for dermal sensitization.[62]

Table 1. Skin Irritation and Sensitization Studies on Polyol Phosphates

Test Substance	Subjects/Tissues Tested	Test Protocol	Results
Moisturizer containing 5% Phytic Acid	110 subjects	Occlusive HRIPT. A 2 cm x 2 cm occlusive patch containing 0.2 g of the product was applied (application site not stated) repeatedly to each subject during the induction phase. Additional details relating to HRIPT procedure were not included. Following challenge application of the product, reactions were scored at 48 h and 96 h after patch application.	At 48 h, 1 subject had mild erythema (with 3 blemishes) at the original application site. This response (considered irritant in nature) had cleared by the 96 h evaluation, and was not observed at the alternate site. There was no evidence of delayed contact hypersensitivity in any of the subjects tested. [64]
Face gel containing 0.25 % Phytic Acid	25 healthy subjects (24 females and 1male).	Maximization test (See maximization test procedure for product containing 1% Sodium Phytate (air-dried) earlier in table). In this study, the test site was on the upper outer arm or back.	No evidence of contact allergy in any of the subjects at 48 h or 72 h after challenge patch application. The did not possess a detectable contact-sensitizing potential.[65]
Leave-on product containing 0.1% Sodium Phytate (undiluted)	112 subjects	Occlusive HRIPT. Induction phase consisted of nine 48-h induction patch applications (0.02 ml of product per patch) over 3-week period. Location of patch and cm^2 area not stated. Induction followed by 2-week non-treatment period. Challenge phase involved patch application to original test site and new test site. Reactions scored at 24 h and 48 h.	Results negative for irritation and allergenicity.[62]

Table 2. Ocular Irritation Studies

Ingredient	Cells/Protocol	Results
In Vitro		
Phytic Acid (50%) (vehicle not stated)	Epiocular tissue model *in vitro* toxicity testing system. Model consists of normal, human-derived epidermal keratinocytes that have been cultured to form a stratified, squamous epithelium that is similar to that found in the cornea. Semi-log scale used to plot % viabilities for test material versus dosing time.	By interpolation, ET_{50} determined to be ~ 9 minutes. Therefore, estimated Draize ocular irritation score is > 25 (moderately irritating).[67]
Coded product containing 50% Sodium Phytate (in 49% water, 1% alcohol)	EpiOcularTM human cell construct. Exposed to product for up to 1200 minutes. Mean percent viability for each time point used to calculate an ET_{50}.	ET_{50} of 518.4 minutes (non-irritating, minimal) reported.[68]
Cream containing 0.48956% Sodium Phytate	Epiocular eye irritation test	ET_{50} > 24 h (no ocular irritation potential).[60]
Dried Sodium Phytate (concentration not stated) trade name material	Bovine corneal opacity and permeability test (OECD 437 protocol, 3 experiments). Test material (750 µl), at a concentration of 20% in Hank's Balanced Salt Solution (HBSS), applied for 4 h to corneas of eyes that had been incubated (with cMEM [not defined] without phenol red) for 1 h. HBSS was negative control, and 20% imidazole solution was positive control. Opacity and permeability measured at the end of the incubation period.	Calculated *in vitro* irritancy scores (IVIS) were: 5.39 (1st experiment), 2.33 (2nd experiment), and 2.91 (3rd experiment). Score of ≤ 3 requires no classification for eye irritation or serious eye damage. First experiment considered insufficient for assessment because 2 of 3 replicates yielded discordant predictions from the mean value. Conclusion: no effects on corneas. Positive control caused serious eye damage.[46]
Dried Sodium Phytate trade name material (2% w/w in water)	Bovine corneal opacity and permeability test (similar procedure, stated above). Incubation period not stated. Opacity and permeability measured at end of incubation period and at 2 h post-incubation. Physiological sodium chloride was negative control, and 10% sodium hydroxide was positive control.	No effects on cornea observed, and an IVIS of -0.532 (IVIS ≥ 55.1 = corrosive or severe irritant) reported. Test substance classified as non-corrosive and/or non-severe irritant. Positive control caused severe corneal irritation.[46]

Table 2. Ocular Irritation Studies

Ingredient	Cells/Protocol	Results
Dried Sodium Phytate (concentration not stated) trade name material	Reconstructed human cornea-like epithelium (RhCE) test (OECD 492 protocol, 2 experiments). Tissues moistened with 25 µl of DPBS buffer and incubated for 30 minutes. Test material then applied (doses of 50.1 mg and 52.3 mg) for 6 h to 3-dimensional human cornea tissue model in duplicate. Tissues rinsed at end of incubation period, and cell viability was evaluated by addition of MTT, which can be reduced to formazan. Demineralized water was negative control, and methyl acetate was positive control.	Only first experiment determined to be invalid because variation between tissue replicates of the negative control too high, and, therefore, outside of range of validity. Mean value of relative tissue viability was 66.9% (in second experiment), above threshold for eye irritation potential (≤ 60%). Conclusion: test substance non-irritating to the eye. Positive control caused eye irritation, i.e., mean value of relative tissue viability was 42.2% (< 50%).[46]
Sodium Phytate trade name material (2% in 0.9% sodium chloride)	*In vitro* hen's egg chorioallantoic membrane test (HET-CAM). Test substance applied to CAM of fertilized and incubated hen's eggs at a dose of 300 µl.	Irritation value of 0 determined. Based on this value, test material can be classified as slightly irritating *in vivo*. Reference material (not identified, 5% concentration) classified as moderately irritating, demonstrating validity of test procedure.[69]

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2018 FDA VCRP Data

Sodium Phytate

01B - Baby Lotions, Oils, Powders, and Creams	1
01C - Other Baby Products	1
02B - Bubble Baths	6
02D - Other Bath Preparations	1
03B - Eyeliner	1
03C - Eye Shadow	1
03D - Eye Lotion	9
03E - Eye Makeup Remover	1
03G - Other Eye Makeup Preparations	6
04B - Perfumes	1
4E - Other Fragrance Preparation	3
05A - Hair Conditioner	21
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	25
05G - Tonics, Dressings, and Other Hair Grooming Aids	10
05I - Other Hair Preparations	1
07A - Blushers (all types)	2
07C - Foundations	6
07I - Other Makeup Preparations	1
09A - Dentifrices	1
9C - Other Oral Hygiene Products	1
10A - Bath Soaps and Detergents	27
10E - Other Personal Cleanliness Products	8
11A - Aftershave Lotion	3
11E - Shaving Cream	6
11F - Shaving Soap	3
11G - Other Shaving Preparation Products	1
12A - Cleansing	42
12C - Face and Neck (exc shave)	57
12D - Body and Hand (exc shave)	29
12F - Moisturizing	90
12G - Night	12
12H - Paste Masks (mud packs)	9
12I - Skin Fresheners	6
12J - Other Skin Care Preps	16
13B - Indoor Tanning Preparations	3
Total	**412**

Phytic Acid

03D - Eye Lotion	5
05A - Hair Conditioner	6
05F - Shampoos (non-coloring)	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
05I - Other Hair Preparations	9
07F - Makeup Bases	1

07I - Other Makeup Preparations	1
10B - Deodorants (underarm)	1
12A - Cleansing	16
12C - Face and Neck (exc shave)	30
12D - Body and Hand (exc shave)	16
12F - Moisturizing	13
12G - Night	1
12H - Paste Masks (mud packs)	2
12J - Other Skin Care Preps	7
Total	**115**

Disodium Glucose Phosphate (No FDA data)

Manganese Fructose Diphosphate (No FDA data)

Phytin (No FDA data)

Sodium Mannose Phosphate

03D - Eye Lotion	3
07C - Foundations	1
11A - Aftershave Lotion	3
12A - Cleansing	2
12C - Face and Neck (exc shave)	3
12D - Body and Hand (exc shave)	4
12F - Moisturizing	9
12G - Night	3
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	4
Total	**33**

Trisodium Fructose Diphosphate (No FDA data)

Trisodium Inositol Triphosphate (No FDA data)

Xylityl Phosphate (No FDA data)

Zinc Fructose Diphosphate (No FDA data)

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: March 6, 2018

SUBJECT: Sodium Phytate

Anonymous. 2018. Summaries of HRIPTs of Products Containing Sodium Phytate.

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

March 2018

Summaries of HRIPTs of Products Containing Sodium Phytate

Product 1

Concentration of Sodium Phytate: 0.1%
Product type: Leave-on
Patch type: Occlusive
Number of subjects completing study: 112
Did the formula produce an allergic response: No
Number of Subjects Exhibiting Low Level Reaction During Induction: 0
Number of Subjects Exhibiting High Level Reaction During Induction: 0
Number of Subjects Exhibiting Low Level Reaction During Challenge: 0
Number of Subjects Exhibiting High Level Reaction During Challenge: 0
Pass/Fail: Pass
Comments: Did not induce irritation or allergic reaction

Induction Phase Grading

Grade	Response
-	No evidence of any effect
1	Mild (pink, uniform erythema covering most of the contact site)
2	Moderate (pink-red erythema uniform in the entire contact site)
3	Marked (Bright red erythema with/without petechiae, papules, vesiculation, weeping)

Challenge Phase Grading scale

Score	Interpretation
-	Negative
?+	Doubtful reaction (slight erythema)
+	Weak (non-vesicular) reaction
++	Strong (oedematous or vesicular) reaction
+++	Extreme (bullous or ulcerative)
NT	Not tested
IR	Irritant reaction of different types

Details of Test Methodology and Results

0	panelist discontinued due to reactions
48 hrs	patch duration
9	induction patches
3	weeks induction
2	week rest period

Original and virgin site challenge Patch
24, 48 hr challenge readings

0.02 ml Amount of product applied
As is/No dilution Product dilution/concentration
Dermatologist as Co-Investigator

Grading scale Interpretation
Low Level Reactions 0 or 1
High Level Reaction 2 and above

Product 2

Concentration of Sodium Phytate: 0.05%
Product type: Rinse-off
Patch type: Occlusive
Number of subjects completing study: 111
Did the formula produce an allergic response: No
Number of Subjects Exhibiting Low Level Reaction During Induction: 2
Number of Subjects Exhibiting High Level Reaction During Induction: 0
Number of Subjects Exhibiting Low Level Reaction During Challenge: 0
Number of Subjects Exhibiting High Level Reaction During Challenge: 0
Pass/Fail: Pass
Comments: Did not induce dermal sensitzation

Product 3

Concentration of Sodium Phytate: 0.05%
Product type: Rinse-off
Patch type: Occlusive
Number of subjects completing study: 111
Did the formula produce an allergic response: No
Number of Subjects Exhibiting Low Level Reaction During Induction: 1
Number of Subjects Exhibiting High Level Reaction During Induction: 0
Number of Subjects Exhibiting Low Level Reaction During Challenge: 2
Number of Subjects Exhibiting High Level Reaction During Challenge: 0
Pass/Fail: Pass
Comments: Did not induce dermal sensitization

Study details for Products 2 and 3

ICDRG Reading scale
0 No visible reaction
± Faint, minimal erythema
1 Erythema

2	Intense erythema
3	Intense erythema, induration , vesicles
4	Severe reaction with erythema , induration, vesicles, pustules (may be weeping)
E	Edema
DR	Dryness
P	Peeling
S	Staining
^	Hyperpigmentation/Hypopigmentation
TR	Tape reaction
C	Change of test site
N9R	No 9th reading
-	No reading
X	Discontinued

Details of Test Methodology and Results

0	panelist discontinued due to reactions
24 hrs	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge
24, 48, 72, 96 hr	challenge readings
0.2 grams	Amount of product applied
1%	Product dilution
	Dermatologist as Co-Investigator

Grading Scale interpretation

Low Level Reactions	± or 1
High Level Reaction	2 and above

Product 4

Concentration of Sodium Phytate: 0.05%
Product type: Leave-on
Patch type: Semi-occlusive
Number of subjects completing study: 111
Did the formula produce an allergic response: No
Number of Subjects Exhibiting Low Level Reaction During Induction: 0
Number of Subjects Exhibiting High Level Reaction During Induction: 0
Number of Subjects Exhibiting Low Level Reaction During Challenge: 1
Number of Subjects Exhibiting High Level Reaction During Challenge: 0
Pass/Fail: Pass

Comments: Did not induce dermal sensitization

ICDRG Reading scale

0	No visible reaction
±	Faint, minimal erythema
1	Erythema
2	Intense erythema
3	Intense erythema, induration , vesicles
4	Severe reaction with erythema , induration, vesicles, pustules (may be weeping)
E	Edema
DR	Dryness
P	Peeling
S	Staining
^	Hyperpigmentation/Hypopigmentation
TR	Tape reaction
C	Change of test site
N9R	No 9th reading
-	No reading
X	Discontinued

Details of Test Methodology and Results

0	panelist discontinued due to reactions
24 hrs	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge
24, 48, 72, 96 hr	challenge readings
0.2grams	Amount of product applied
As is/No dilution	Product dilution/concentration
	Dermatologist as Co-Investigator

Grading Scale interpretation

Low Level Reactions	± or 1
High Level Reaction	2 and above

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 23, 2018

SUBJECT: Phytic Acid

Hill Top Research, Inc. 1995. Human repeat insult patch test of a moisturizer containing 5% phytic acid.

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

[redacted]

[redacted]

SUMMARY REVIEW

Test Substance: Phytic Acid (5%) in Moisturizer Cream

Type of Study: Human Repeat Insult Patch Test (HRIPT)

[redacted]

Functional Use Classification: Skin Rejuvenation

Contract Laboratory: Hill Top, Winnipeg

[redacted]

Date Report Written: 4/20/95

This is not a regulated study.

This report has been reviewed for scientific quality and is summarized as follows:

One hundred and ten subjects were treated and challenged with [redacted]. One of these subjects exhibited a response consisting of mild erythema with three blemishes on the original site at the 48-hour evaluation. This response cleared by the 96-hour evaluation and was not observed at the alternate site. This response was considered irritant in nature. There was no evidence of delayed contact hypersensitivity in any of the test subjects (0/110).

[redacted]

HUMAN REPEAT INSULT PATCH TEST

REPORT NO. [redacted]

[redacted]

[redacted]

PERFORMED BY:
Hill Top Research, Inc.
200 - 584 Pembina Hwy.
Winnipeg, Manitoba
Canada R3M 3X7

HILL TOP RESEARCH INC.
200-584 Pembina Highway · Winnipeg, Manitoba · Canada R3M 3X7
204/453-1835 · Fax 204/475-4029

Project No.: [redacted] FINAL REPORT
[redacted]

HUMAN REPEAT INSULT PATCH TEST

HILL TOP PROJECT NO.: [redacted]

SPONSOR ID #: [redacted]

CONCENTRATION: Neat

VEHICLE: NA

SUMMARY:

One hundred and ten subjects were challenged with [redacted]. One of these subjects (No. 5) exhibited a response consisting of mild erythema with three blemishes on the original site at the 48-hour evaluation. This response cleared by the 96-hour evaluation and was not observed at the alternate site. This response is considered irritant in nature.

a moisturizer with 5% phytic acid

Under the conditions of the study, [redacted] did not induce clinically identifiable evidence of induced contact hypersensitivity.

Submitted for: ***HILL TOP RESEARCH, INC.***

By: [signature] 4/20/95
Joelle Potrebka — Date
Project Leader

Approved by: [signature] 4/21/95
Leslie Lockhart — Date
Investigator

[signature] 4/21/95
Wendy Lazer — Date
Branch Manager

Project No.: [redacted] FINAL REPORT
[redacted]

PURPOSE: To determine if a test substance will produce evidence suggestive of a delayed contact hypersensitivity response under the exposure conditions of this study.

INVESTIGATIVE FACILITY: Hill Top Research, Inc.
200-584 Pembina Hwy.
Winnipeg, MB R3M 3X7

INVESTIGATOR: Leslie K. Lockhart

CONSULTING DERMATOLOGIST: Dr. J. Toole

TEST SCORER: Joelle L. Potrebka

SPONSOR AND MONITOR: [redacted]

DATES:

Induction: (Subject Nos. 1-118) 8/8/94 - 8/29/94
(Subject Nos. 119-130) 8/10/94 - 8/31/94)

Challenge: 9/12/94 - 9/16/94

NUMBER OF SUBJECTS COMPLETING THE STUDY:

110 subjects (82 females and 28 males)

PROTOCOL: (See Appendix I)

The study protocol, furnished by the study sponsor and approved by the investigator, was followed.

AMENDMENTS TO PROTOCOL:

There were no amendments affecting this sample.

DEVIATIONS FROM PROTOCOL:

Evaluation Day	Deviation
1	Subject Nos. 18 and 129 wore the patches for 48 hours.
3	Subject Nos. 37 and 66 wore the patches for 26 and 28 hours, respectively.
4	Subject No. 67 wore the patches for 31 hours.
5	Subject No. 111 wore the patches for 26 hours. Subject Nos. 26, 33 and 130 had their patch moved without reaching a move score, due to open sores in the patch site. Subject Nos. 29, 34, 35 and 111 had their patch moved due to sores and scabbing in the patch area. Subject No. 114 had the patch moved due to a cat scratch in the patch area.
6	Subject Nos. 42, 43, 45, 50, 108 and 127 had their patch moved without reaching move scores, due to open sores in the patch area.
7	Subject Nos. 5, 9, 41, 91 and 123 had their patch moved without reaching move scores, due to open sores in the patch area. Scores were not recorded for Subject No. 32; the subject was patched.
8	Subject Nos. 13, 40 and 124 had their patch moved without reaching move scores, due to open sores in the patch area.
9	Subject Nos. 42, 45, 46 and 86 had their patch moved without reaching move scores, due to open sores in the patch area. Subject No. 44 wore the patches for 27 hours.
Challenge	Subject Nos. 27, 40, 46, 50 and 75 were patched on the first move site due to scabbing on the original site.

DEVIATIONS FROM PROTOCOL: (continued)

There were no deviations which, in the opinion of the investigator, impacted the outcome of the study.

SUBJECT INFORMATION:

Number of subjects screened and excluded at initial interview:

9 (See Appendix II for reasons)

Number of subjects starting study:

130 (94 females and 36 males)

Number of subjects who withdrew:

20 (See Appendix III for reasons)

Information Concerning Unusual Responses at Patch Sites:

Unusual patch site responses were observed during the induction period in about 35% of the study population (39 subjects). These were described as "blemishes" or small pimple-like eruptions. They numbered between 1 and 3 in the patch area. When these blemishes opened, they were described as "sores", which later scabbed. Since reactions of this nature are not described in the HRIPT scoring scale, a separate table was prepared describing the occurrence and frequency of these responses (see Appendix IV).

These reactions generally first occurred midway in the induction period after several uneventful applications. They did not increase in number with repeated patch applications. They tended not to recur immediately upon movement of the patch to a new induction site. The eruptions were very small in size and mild in severity.

Residual scabbing at the original patch sites was noted in five subjects just before challenge, and patches were placed on normal skin. One subject had three blemishes on her original arm at the 48 hour challenge scoring, but this site was clear at 96 hours.

Information Concerning Unusual Responses at Patch Sites: (Continued)

The appearance of these unusual reactions, the pattern of their occurrence and resolution, and their frequency in the study population suggested that they were irritant in nature and not indicative of sensitization.

RECORD OF MONITORING VISITS/VISITORS TO STUDY SITE:

The study was monitored by [redacted] on 8/15/94 and by [redacted] on 09/16/94.

TEST ARTICLE INFORMATION:

Investigator Code:	A A moisturizer with 5% phytic acid
Sponsor Identification Numbers:	[redacted]
Color:	Opaque white
Physical Form:	Cream
Date Received:	7/19/94
Amount Received:	6 tubes 1 = 134.56 g, 2 = 133.46 g, 3 = 137.29 g 4 = 135.09 g, 5 = 133.48 g, 6 = 134.78 g
Weight of Tubes After Use:	1 = 29.72 g, 2 = 37.09 g, 3 = 39.25 g 4 = 33.32 g, 5 = 27.38 g, 6 = 71.80 g
Concentration Tested:	Neat
Vehicle:	NA
Test Article Preparation:	
Method:	NA
Frequency:	NA

TEST ARTICLE INFORMATION: (continued)

Storage:

Stock:	Room temperature
Dosing:	NA

Patch Type:	Occlusive: 2 cm x 2 cm Webril pad backed by 4 cm x 4 cm Blenderm tape (Professional Medical Products, Inc. Lot # RH9220)
Amount Placed on Patch Pad:	0.2 g
Method of Application:	Dispensed onto the webril pad using an Eppendorf repeater pipette. Ten patches were weighed daily to confirm that approximately 0.2 g of the test article was dispensed. The test article was applied to the patch no longer than 30 minutes prior to application.

ADVERSE EVENTS REPORTS:

None

RESULTS:

Table 1A	Reactions for each individual subject on all scoring days
Table 2A	Summary totals for the complete panel of subjects during induction and challenge

Project No.: [redacted] FINAL REPORT
[redacted]

QUALITY ASSURANCE STATEMENT

This study was inspected in accordance with the Standard Operating Procedures of the Hill Top Companies. To assure compliance with the study protocol, the Quality Assurance Unit performed an inspection during the conduct of this study and completed an audit of the study records and final report.

Report Reviewed by:

Karen Graham
Auditor, Quality Assurance

4/21/95
Date

REV 1/93

Project No.: [redacted] FINAL REPORT

TABLE 1A

(Total number of pages = 5)

Reactions for Individual Subjects

[redacted]

Date Printed: 09-19-1994
Page: 1

Table 1A. Individual reaction scores following the application of test material.
Sample: A [redacted]

Subject Number	Application Number 1	2		3			4			5			6			7			8			9			NU			Challenge			
	O	O	M	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	A	O'	A'
1	0	0		0			0			0			0			0			0			0						0	0	0	0
2	-	0		0			0			0			0			0			0			0						0	0	0	0
3	0	0		Dropped																		0			0			0	0	0	0
4	0	0		0			0			0			0																		
5	0	?P		0			?P			1			1			0			0			1						0	0	0	0
6	0	1		0			1			1			0			1			1	0		1	0					1	0	0	0
7	0	Dropped																				1						0	0	0	0
8	0	0		0			0			1			0			1			1			1						0	0	0	0
9	0	0		0			0			0			0			1			1	0		1	1					0	0	0	0
10	0	0		0			0			0			0			1			0			0						0	0	0	0
11	0	0		0			0			0			0			0			0			0						0	0	0	0
12	0	0		0			0			0			0			0			0			0						0	0	0	0
13	0	0		0			0			0			0			0			0			1						0	0	0	0
14	0	0		0			0			0			0			1			1			0						0	0	0	0
15	0	0		0			0			0			0			0			0			0						0	0	0	0
16	0	0		0			0			0			0			0			0						0			0	0	0	0
17	0	0		0			0			0			0			0			0			0						0	0	0	0
18	0	0		0			0			0			-			0			0			0			0			0	0	0	0
19	0	0		-			0			0			0			0			0			0						0	0	0	0
20	0	0		LD			0			0			0			1			1			1			1			0	0	0	0
21	0	0		0			0			0			0			0			0			0						0	0	0	0
22	0	0		0			0			0			0			0			0			0						0	0	0	0
23	0	0		0			0			0			0			0			0			1						0	0	0	0
24	0	0		0			-			Dropped															0			0	0	0	0
25	0	0		-			Dropped																								
26	0	0		0			1			1			1	0		1	0		1	0		1	0					0	0	Dropped	
27	0	0		0			1			1			2			2	0		2	0		1	1					0	0	0	0
28	0	0		0			0			0			1			1			2			1						0	0	0	0
29	0	0		0			0			1			1	0		1	0		1	0		1	1					0	0	0	0
30	0	0		-			Dropped																								

O = original site; M = first moved site; M1 = second moved site
O,A = first scoring of original and adjacent challenge sites (48 hours)
0 = No visible erythema
1 = Mild erythema (faint pink to definite pink)
2 = Moderate erythema (definite redness)
3 = Severe erythema (very intense redness)

E = Edema - definite swelling
P = Papules - many small, red, solid elevations; surface of reaction has granular feeling
V = Vesicles - small, circumscribed elevations having translucent surfaces so that fluid is visible (blister-like). Vesicles are 0.5cm or smaller in diameter
B = Bullae - vesicles with a diameter >0.5cm; vesicles may coalesce to form one or a few large blisters that fill the patch site
S = Spreading - evidence of the reaction beyond the pad area (does not include obvious signs of leakage of test material away from pad)
W = Weeping - evidence of release of fluid from a vesicular or bullous reaction
? = Appended to any of the above letter grades means this grade is questionable or minimal

O',A' = second scoring of challenge sites (96 hours)
- = Absence
L = Patch lost (came off) during first twelve hours
A = Marked reaction to adhesive (patch relocated)
X = Succeeding patch not applied and succeeding grade is for residual reaction. At challenge, an "X" denotes that the patch was not applied.

[redacted]

Date Printed: 09-19-1996
Page: 2

Table 14. Individual reaction scores following the application of test material.
Sample: A [redacted]

Subject Number	Application Number 1	2	3	4	5	6	7	8	9	NI	Challenge
	O	C H	O H HI	O H HI	O H HI	O H HI	O H HI	O H HI	O H HI	O H HI	O A O' A'
31	0	0	0	0	0	0	0	0	0		0 0 0 0
32	0	0	0	0	-	0	NS	0	0	0	0 0 0 0
33	0	0	0	0	1	1 0	1 0	1 0	1 0		0 0 Dropped
34	0	0	0	0	1	1 0	1 0	1 0	1 1		0 1 0 0
35	0	0	0	0	1	1 0	1 0	1 0	1 1		
36	0	-	0	0	Dropped						0 0 0 0
37	0	0	0	LO	0	0	0	0	0	0	0 0 0 0
38	-	0	0	0	0	0	0	0	0		0 0 0 0
39	0	0	0	0	0	0	0	1	-	N9G	0 0 0 0
40	0	0	0	0	0	0	1	1 0	1 0		0 0 0 0
41	0	0	0	0	0	0	1	1 0	1 1	1 1 0	0 0 0 0
42	0	0	-	0	0	1	1 0	1 0	1 0		0 0 0 0
43	0	0	0	0	1	1		0	0		0 0 0 0
44	0	0	0	0	0	0	1 0	1 1	1 1	1 1 0	0 0 0 0
45	0	0	0	0 -	-	1				1 0	0 0 0 0
46	0	0	0	- 0	0	0	0	1	1		0 0 0 0
47	0	0	0	0	0	0	0	0	0		0 0 0 0
48	0	0	0	0	0	0	0	0	0		0 0 0 0
49	0	0	0	0	0	0	0	0	0		0 0 0 0
50	0	0	0	0	1	1	1 0	1 0	1 0		0 0 0 0
51	0	0	0	0	0	0	0	0	0		
52	0	-	0	Dropped							0 0 0 0
53	0	0	0	0	0	0	0	0	0 -	1	0 0 0 0
54	0	0	0	0	1	0 0	0	0	0	0	0 0 0 0
55	0	0	0	0	-	0 -	0	0	0	1	0 0 0 0
56	0	0	0	0	0	0	0	0	0		0 0 0 0
57	0	0	0	0	0	- 0	-	0	0	0	0 0 0 0
58	0	0	0	0	0	0		0	0		0 0 0 0
59	0	0	0	0	0	0	0	0	0		0 0 0 0
60	Dropped										

O = original site; H = first moved site; HI = second moved site
O,A = first scoring of original and adjacent challenge sites (48 hours)
0 = No visible erythema
1 = Mild erythema (faint pink to definite pink)
2 = Moderate erythema (definite redness)
3 = Severe erythema (very intense redness)

E = Edema - definite swelling
P = Papules - many small, red, solid elevations; surface of reaction has granular feeling
V = Vesicles - small, circumscribed elevations having translucent surfaces so that fluid is visible (blister-like). Vesicles are 0.5cm or smaller in diameter
B = Bullae - vesicles with a diameter >0.5cm; vesicles may coalesce to form one or a few large blisters that fill the patch site
S = Spreading - evidence of the reaction beyond the pad area (does not include obvious signs of leakage of test material away from pad)
W = Weeping - evidence of release of fluid from a vesicular or bullous reaction
? = Appended to any of the above letter grades means this grade is questionable or minimal
N9G = No ninth grade

O',A' = second scoring of challenge sites (96 hours)
- = Absence
L = Patch lost (came off) during first twelve hours
A = Marked reaction to adhesive (patch relocated)
X = Succeeding patch not applied and succeeding grade is for residual reaction. At challenge, an "X" denotes that the patch was not applied.

NS = Not scored

[redacted]

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Page: 3

Table 1A. Individual reaction scores following the application of test material.
Sample: A [redacted]

Subject Number	Application Number 1	2		3			4			5			6			7			8			9			MU			Challenge			
	O	O	M	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	A	O'	A'
61	0	0		0			0			-			0			0			0			0			0			0	0	0	0
62	0	0		0			0			0			0			0			0			0						0	0	0	0
63	0	0		0			0			0			0			0			0			1						0	0	0	0
64	0	0		0			-			0			0			0			1			0			1			0	0	0	0
65	0	0		0			0			0			0			0			0			0						0	L	0	0
66	0	0		0			0			0			0			0			1			0						0	0	0	0
67	0	0		0			0			0			0			0			0			0						0	0	0	0
68	0	0		0			0			0			0			0			0			0						0	0	0	0
69	0	0		0			0			0			0			0			0			0						0	0	0	0
70	-	0		0			0			0			0			0			0			0			0			0	0	0	0
71	L0	0		0			0			0			0			0			0			0						0	0	0	0
72	0	0		0			-			Dropped																					
73	0	-		0			0			0			0			0			0			0			0			0	0	0	0
74	0	0		0			0			0			0			0			0			0						0	0	0	0
75	0	1		0			1			1			1			1			1			1						0	0	0	0
76	-	Dropped																													
77	0	0		0			0			0			-			0			0			0			0			0	0	0	0
78	0	1		1			1p			1			-			0			0			0			0			0	0	0	0
79	0	0		0			0			0			0			0			0			0						0	0	0	0
80	0	0		0			0			0			0			0			1			1						0	0	0	0
81	0	0		0			0			0			0			0			0			0						0	0	0	0
82	0	0		0			0			0			0			0			0			0						0	0	0	0
83	0	0		0			0			-			0			0			0			0			0			0	0	0	0
84	0	0		0			0			0			0			0			·			0			0			0	0	0	0
85	0	0		0			0			0			0			0			0			0						0	0	0	0
86	0	0		0			·			0			0			0			0			1			1	0		0	0	0	0
87	0	0		0			0			0			0			0			0			0						0	0	0	0
88	0	0		0			0			0			0			0			0			0						0	0	0	0
89	0	0		0			0			0			0			1			0			0						0	0	0	0
90	0	0		0			0			0			0			0			0			0						0	0	0	0

O = original site; M = first moved site; M1 = second moved site
O,A = first scoring of original and adjacent challenge sites (48 hours)
O',A' = second scoring of challenge sites (96 hours)

0 = No visible erythema
1 = Mild erythema (faint pink to definite pink)
2 = Moderate erythema (definite redness)
3 = Severe erythema (very intense redness)

· = Absence
L = Patch lost (came off) during first twelve hours
A = Marked reaction to adhesive (patch relocated)
X = Succeeding patch not applied and succeeding grade is for residual reaction. At challenge, an "X" denotes that the patch was not applied.

E = Edema - definite swelling
P = Papules - many small, red, solid elevations; surface of reaction has granular feeling
V = Vesicles - small, circumscribed elevations having translucent surfaces so that fluid is visible (blister-like). Vesicles are 0.5cm or smaller in diameter
B = Bullae - vesicles with a diameter >0.5cm; vesicles may coalesce to form one or a few large blisters that fill the patch site
S = Spreading - evidence of the reaction beyond the pad area (does not include obvious signs of leakage of test material away from pad)
W = Weeping - evidence of release of fluid from a vesicular or bullous reaction
? = Appended to any of the above letter grades means this grade is questionable or minimal

[redacted]

Date Printed: 09-19-1994
Page: 4

Table 1A. Individual reaction scores following the application of test material.
Sample: A [redacted]

Subject Number	Application Number 1	2	3	4	5	6	7	8	9	10	Challenge			
	O	O M	O M M1	O M M1	O M M1	O M M1	O M M1	O M M1	O M M1	O M M1	O	A	O'	A'
91	0	0	0	0	0	0	1	1 0	1 0		0	0	0	0
92	0	0	0	0	-	0	0	0	0	0	0	0	0	0
93	-	Dropped												
94	0	0	0	0	0	0	0	0	0		0	0	0	0
95	0	1P	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0		0	0	0	0
97	0	0	0	0	0	0	0	0	0		0	0	0	0
98	0	0	0	0	0	0	0	0	0		0	0	0	0
99	0	0	0	0	-	0	0	0	1		0	0	0	0
100	0	0	0	0	0	0	0	0	1	1	0	0	0	0
101	0	0	0	0	0	0	0	1	1		0	0	0	0
102	0	0	0	0	0	0	0	0	0		0	0	0	0
103	0	0	0	0	0	0	0	0	0		0	0	0	0
104	0	0	0	0	1	2	1 0	1 0	1 0		0	0	0	0
105	0	0	0	0	0	0	0	0	0		0	0	0	0
106	0	0	0	0	0	0	0	0	0		0	0	0	0
107	0	0	0	0	0	0	0	0	0		0	0	0	0
108	0	0	0	0	1	1	1 0	1 0	1 0		0	0	0	0
109	0	0	0	0	0	0	0	0	0		0	0	0	0
110	0	0	0	0	0	0	0	0	-	1	0	0	0	0
111	0	0	0	0	1	1 0	1 0	1 0	1 1		0	0	0	0
112	-	0	0	0	0	0	0	0	Dropped					
113	0	0	0	0	0	0	0	0	0		0	0	0	0
114	0	0	0	0	1	1 0	1 0	0 0	0 0		0	0	0	0
115	0	0	0	0	0	0	0	0	0		0	0	0	0
116	-	Dropped												
117	0	0	0	0	0	0	0	0	0		0	0	0	0
118	0	0	0	0	0	0	0	1	L1		0	0	0	0
119	Dropped													
120	Dropped													

O = original site; M = first moved site; M1 = second moved site
O,A = first scoring of original and adjacent challenge sites (48 hours)
0 = No visible erythema
1 = Mild erythema (faint pink to definite pink)
2 = Moderate erythema (definite redness)
3 = Severe erythema (very intense redness)

E = Edema - definite swelling
P = Papules - many small, red, solid elevations; surface of reaction has granular feeling
V = Vesicles - small, circumscribed elevations having translucent surfaces so that fluid is visible (blister-like). Vesicles are 0.5cm or smaller in diameter
B = Bullae - vesicles with a diameter >0.5cm; vesicles may coalesce to form one or a few large blisters that fill the patch site
S = Spreading - evidence of the reaction beyond the pad area (does not include obvious signs of leakage of test material away from pad)
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? = Appended to any of the above letter grades means this grade is questionable or minimal

O',A' = second scoring of challenge sites (96 hours)
- = Absence
L = Patch lost (came off) during first twelve hours
A = Marked reaction to adhesive (patch relocated)
X = Succeeding patch not applied and succeeding grade is for residual reaction. At challenge, an "X" denotes that the patch was not applied.

[redacted]

Date Printed: 09-19-1994
Page: 5

Table 1A. Individual reaction scores following the application of test material.
Sample: A [redacted]

Subject Number	Application Number 1	2		3			4			5			6			7			8			9			RU			Challenge			
	O	O	M	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	M	M1	O	A	O'	A'
121	0	0		0			0			0			0			0			0			0						0	0	0	0
122	0	0		0			0			0			0			0			0			0						0	0	0	0
123	0	0		0			0			0			0			0			0			0						0	0	0	0
124	0	0		0			0			-			1			1			1	0		1	0					0	0	0	0
125	0	Dropped											1			1			1			1	0		N9G			0	0	0	0
126	Dropped																												L		
127	0	0		0			0			0			1			1	0		1	0		1	0					0	0	0	0
128	0	Dropped																													
129	0	0		0			0			0			1			1	0		1	0		1	0					0	0	0	0
130	0	0		0			0			1			1	0		1	0		1	0		1	0					0	0	0	0

O = original site; M = first moved site; M1 = second moved site
O,A = first scoring of original and adjacent challenge sites (48 hours)
0 = No visible erythema
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L = Patch lost (came off) during first twelve hours
A = Marked reaction to adhesive (patch relocated)
X = Succeeding patch not applied and succeeding grade is for residual reaction. At challenge, an "X" denotes that the patch was not applied.

TABLE 2A

(Total number of pages = 1)

Summary Totals for the Complete Panel

[redacted]

Date Printed: 09-19-1996
Page: 1

Table 2A. Group total reaction scores following the application of test material.
Sample: A [redacted]

	Application Number																								Challenge			
	1	2		3			4			5			6			7			8			9			MU					
Scores	O	D	N	O	N	N1	O	N	N1	O	N	N1	O	N	N1	O	N	N1	D	N	N1	D	N	N1	D	N	N1	O	A	O'	A'
0	118	112	0	113	0	0	104	0	0	86	0	0	88	8	0	80	16	0	77	21	0	66	17	0	17	2	2	110	111	110	110
1	0	5	0	1	0	0	6	0	0	19	0	0	11	0	0	14	1	0	13	1	0	15	7	0	6	0	0	1	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sub Total	118	117	0	114	0	0	110	0	0	105	0	0	101	8	0	94	17	0	90	22	0	81	24	0	23	2	2	111	111	110	110
Drop	4	10	0	11	0	0	14	0	0	17	0	0	17	0	0	17	0	0	17	0	0	18	0	0	0	0	0	19	19	20	20
NPG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
-	7	3	0	4	0	0	5	0	0	5	0	0	4	0	0	1	0	0	1	0	0	6	0	0	0	0	0	0	0	0	0
X	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
NS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sub Total	12	13	0	16	0	0	20	0	0	25	0	0	21	0	0	19	0	0	18	0	0	25	0	0	2	0	0	19	19	20	20
Grand Total	130	130		130			130			130			130			130			130			130			29			130	130	130	130
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P	0	2	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Letter Totals	0	2	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

O = original site; N = first moved site; N1 = second moved site
O,A = first scoring of original and adjacent challenge sites (48 hours)
0 = No visible erythema
1 = Mild erythema (faint pink to definite pink)
2 = Moderate erythema (definite redness)
3 = Severe erythema (very intense redness)

E = Edema - definite swelling
P = Papules - many small, red, solid elevations; surface of reaction has granular feeling
V = Vesicles - small, circumscribed elevations having translucent surfaces so that fluid is visible (blister-like). Vesicles are 0.5cm or smaller in diameter
B = Bullae - vesicles with a diameter >0.5cm; vesicles may coalesce to form one or a few large blisters that fill the patch site
S = Spreading - evidence of the reaction beyond the pad area (does not include obvious signs of leakage of test material away from pad)
W = Weeping - evidence of release of fluid from a vesicular or bullous reaction
NPG = No ninth grade

O',A' = second scoring of challenge sites (96 hours)
- = Absence
L = Patch lost (came off) during first twelve hours
A = Marked reaction to adhesive (patch relocated)
X = Succeeding patch not applied and succeeding grade is for residual reaction. At challenge, an "X" denotes that the patch was not applied.

NS = Not scored

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 24, 2018

SUBJECT: Studies on Phytic Acid or Sodium Phytate

KGL Inc. 2011. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (face gel containing 0.25% Phytic Acid).

Anonymous. 2010. Clinical evaluation report: Human patch test (product containing 0.25% Phytic Acid).

KGL, Inc. 2009. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (clear liquid containing 1% Sodium Phytate).

KGL, Inc. 2009. An assessment of the photosensitization potential of two topical coded test products using a human photocontact allergenicity assay (clear liquid contains 1% Sodium Phytate).

MB Research Laboratories. 2009. MatTek EpiOcular™ MTT viability assay (coded product RI109837 contains 50% Sodium Phytate in 49% water 1% alcohol).

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

FINAL REPORT dated January 4, 2011
KGL Protocol: #7170
Sample: Face Gel [redacted]

www.kgl-inc.com or www.ivylabs.com

Ivy Laboratories (KGL, INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)

Telephone: [215] 387-8400
FAX: [215] 387-1046

E-mail address: ivystudies@verizon.net

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

Face gel containing 0.25% phytic Acid

Sponsor: [redacted]

Principal Investigator: Kays Kaidbey, M.D. (Board Certified Dermatologist)

Testing Facility: KGL Inc.
505 Parkway
Broomall, PA 19008-4204 (USA)
(Phone: 215-387-8400)
(FAX: 215-387-1046)

Final Report Date: January 4, 2011

Kays Kaidbey, M.D.
Principal Investigator

January 4, 2011
Date

"The names of Ivy Laboratories (KGL INC.), any officer, employee, or collaborating scientist are not to be used for any advertising, promotional or sale purposes without the written consent of Ivy Laboratories (KGL INC)."

FINAL REPORT

STUDY TITLE:

An assessment of the contact-sensitizing potential of a coded topically-applied test agent using a Human Maximization Assay.

KGL PROTOCOL:

KGL Protocol #7170

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) (21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with KGL's Standard Operating Procedures (SOP's).

STUDY OBJECTIVE:

The objective of this study was to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

DESIGN RATIONALE:

A repeat insult patch test wherein the test product was applied under an occlusive dressing to an SLS (sodium lauryl sulfate) pre-treated site on the upper outer arm or back repeatedly to the same designated area for five 48-hour induction periods followed 7-10 days later by a single challenge to a naïve skin site on the opposite outer arm or the opposite side of the back.

STUDY SPONSOR:

[redacted]

SPONSOR STUDY:

[redacted] Submission Form dated November 10, 2010

TESTING FACILITY:

KGL Inc.
505 Parkway
Broomall, PA 19008-4204 (USA)
Telephone: Philadelphia - (215-387-8400) – Broomall (610-544-1715)
E-mail: ivystudies@verizon.net

PRINCIPAL INVESTIGATOR:

Kays Kaidbey, M.D. (Board Certified Dermatologist)
Medical Director, KGL, INC.
Telephone: (215) 387-8400
FAX: (215) 387-1046
E-mail address: ivystudies@verizon.net

KGL ADMINISTRATIVE STRUCTURE:

Diane Kozubal (Panel Recruitment/Initial Screening)
Jane Chitwood (Technician /Patch Applications/Removals/Recognize/Report AE's)
John B. Chicchi (Evaluator)
Mary J. Massing (Quality Assurance)

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to read and sign the consent form prior to enrollment. Copies of all consent forms are on file at KGL, Inc.

CONDUCTION DATES:

This study was conducted between November 15, 2010 through December 17, 2010.

TEST MATERIAL: containing 0.25% Phytic Acid

The test product , supplied by the sponsor, was Face Gel [redacted]. One jar was supplied. The Face Gel was tested as supplied viz. neat.

TEST PRODUCT ACCOUNTABILITY:

The test sample was received in good condition by our Quality Assurance Department. The test material was checked for (1) amount (2) product number or code (3) material container etc. The material was individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). The test sample was stored under ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test material(s) will be disposed of in accordance with applicable governmental regulations following completion of the study and submission of the final written report to the Sponsor.

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. Panelists had no blemishes, excess hair or other marks on their upper outer arms or back that would obscure grading of the test site. Both male and female panelists were eligible. None of the subjects had a medical or dermatological illness and none were sensitive to sunscreens or to topical preparations and/or cosmetics. A completed subject was a subject who satisfied the admission criteria and who completed the scheduled study procedures.

Inclusion Criteria:

1. Healthy adult male and female volunteers between the ages of 18 and 65 years.
2. All subjects who were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. Subjects with any significant internal diseases e.g., cardiac, pulmonary, renal, hepatic, etc.
2. History of allergy or hypersensitivity to cosmetics, toiletries or other dermatological products
3. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria
4. Pregnancy or mothers who are breastfeeding or planning a pregnancy
5. Scars, moles or other blemishes over the upper arm(s) or back which can interfere with the study
6. Subjects receiving systemic or topical drugs or medications which can interfere with delayed immunologic responses e.g., corticosteroids, non-steroidal anti-inflammatories, retinoids, immunosuppressants
7. Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS:

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

STUDY PROCEDURES:

Method and Procedures[1,2]

Patches were applied to the upper outer arm or back of each subject. The entire test was composed of three distinct phases: (1) an Induction phase and (2) a Rest Phase and (3) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (induction patch). Since the test material [redacted] (Face Gel) contained volatile ingredients, it was allowed to air-dry for ~30 minutes prior to application to the test site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Rest Period**:

No exposure to the test material was made during this rest period, which lasted for 7-10 days after the last induction patch.

(3) **Challenge Phase**:

After a 7-10 day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite upper outer arm or opposite side of the back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and 0.05ml of the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded, and again 24 hours later for any reactions.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions were encountered or reported by any of the panelists.

RESULTS:

A total of twenty-five (25) healthy, adult, male and female volunteers who satisfied the inclusion criteria were enrolled into this study. There were 24 females and 1 male. Their ages ranged from 23 to 64 years. All 25 volunteers completed this investigation, as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Face Gel [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	R-S	64	F	C
02	RMV	49	F	C
03	WHK	50	M	C
04	DLS	26	F	C
05	J-B	37	F	C
06	KKM	49	F	C
07	HGS	37	F	C
08	N-R	41	F	C
09	L-M	53	F	C
10	TLH	53	F	C
11	DJM	57	F	C
12	CCG	44	F	C
13	RCG	39	F	C
14	BAC	61	F	C
15	DKC	39	F	C
16	AAT	24	F	C
17	DMM	43	F	C
18	K-D	48	F	C
19	H-D	39	F	C
20	TAM	25	F	C
21	J-D	39	F	C
22	DSG	45	F	C
23	PDR	55	F	C
24	TMP	23	F	B
25	C-D	37	F	C

C = Caucasian
B = Black

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Face Gel [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0

Challenge Readings:

48-Hour Reading – December 16, 2010
72-Hour Reading – December 17, 2010

[redacted]

RESEARCH AND DEVELOPMENT
CLINICAL EVALUATION DEPARTMENT

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1 **TO:** [redacted]

PRODUCT PROFILE NO: 1017777 DATE: November 3, 2010 LAB REF.: APTC-2245-10

1. TEST MATERIAL: [redacted] Mineral Treatment [redacted] containing 6.25% Phytic Acid

2. CONTROL MATERIAL: [redacted] Overnight Nutrient Peel [redacted]

3. TEST PROCEDURE:

Single-Insult (24hr.)__X__ Occlusive (Blenderm) Patch__X__ Semi-Occlusive Patch_____.

4. CONCENTRATION:

Full-Strength__X____ Aqueous _____ Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

_____Volatiles were allowed to evaporate prior to occlusion on the patch.
_____Patch was hydrated just prior to application to skin.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	+	1	1+	2	2+	3	3+	4	PII
[redacted] Mineral Treatment	21	21	0	0	0	0	0	0	0	0	0.00
[redacted] Overnight Nutrient Peel	21	21	0	0	0	0	0	0	0	0	0.00

___ Skin staining noted. Erythematous response was read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). __X__.

B. _____.

Study Conducted By: [redacted]. Approved By: [redacted]

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

CC:

FINAL REPORT dated December 9, 2009
KGL Protocol: #6916
Sample: Clear Liquid [redacted]

www.kgl-inc.com or www.ivylabs.com

Ivy Laboratories (KGL, INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)

Telephone: [215] 387-8400
FAX: [215] 387-1046

E-mail address: ivystudies@verizon.net

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

Sponsor: [redacted] Clear liquid containing 1% Sodium Phytate

Commitment Letter dated: October 28, 2009

Principal Investigator: Kays Kaidbey, M.D. (Board Certified Dermatologist)

Testing Facility: Ivy Laboratories (KGL, INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)
(Phone: 215-387-8400)
(FAX: 215-387-1046)

Final Report Date: **December 9, 2009**

Kays Kaidbey, M.D.
Principal Investigator

December 9, 2009
Date

FINAL REPORT

STUDY TITLE:

An assessment of the contact-sensitizing potential of a coded topically-applied test agent using a Human Maximization Assay.

KGL PROTOCOL:

KGL Protocol **#6916**

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) (21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with KGL's Standard Operating Procedures (SOP's).

STUDY OBJECTIVE:

The objective of this study was to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

DESIGN RATIONALE:

A repeat insult patch test wherein the test product was applied under an occlusive dressing to an SLS (sodium lauryl sulfate) pre-treated site on the upper outer arm repeatedly to the same designated area for five 48-hour induction periods followed 7-10 days later by a single challenge to a naïve skin site on the opposite outer arm.

STUDY SPONSOR:

[redacted]

SPONSOR STUDY:

Commitment Letter dated October 28, 2009

TESTING FACILITY:

Ivy Laboratories (KGL INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)
Telephone: Philadelphia - (215-387-8400) – Broomall (610-544-1715)
E-mail: ivystudies@verizon.net

PRINCIPAL INVESTIGATOR:

Kays Kaidbey, M.D. (Board Certified Dermatologist)
Medical Director, KGL, INC.
Telephone: (215) 387-8400
FAX: (215) 387-1046
E-mail address: ivystudies@verizon.net

KGL ADMINISTRATIVE STRUCTURE:

Marie Windle (Panel Recruitment/Initial Screening)
Angelit Barnes (Technician /Patch Applications/Removals/Recognize/Report AE's)
John B. Chicchi (Evaluator)
Mary J. Massing (Quality Assurance)

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to read and sign the consent form prior to enrollment. Copies of all consent forms are on file at KGL, Inc.

CONDUCTION DATES:

This study was conducted between November 2, 2009 through December 4, 2009.

TEST MATERIAL: containing 1% Sodium Phytate

The test product , supplied by the sponsor, was labeled Clear Liquid [redacted] and tested as supplied viz. neat.

TEST PRODUCT ACCOUNTABILITY:

The test sample was received in good condition by our Quality Assurance Department. The test material was checked for (1) amount (2) product number or code (3) material container etc. The material was individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). The test sample was stored under ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test material(s) will be disposed of in accordance with applicable governmental regulations following submission of the final written report or returned to the Sponsor via a traceable method, if requested.

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. Panelists had no blemishes, excess hair or other marks on their upper outer arms that would obscure grading of the test site. Both male and female panelists were eligible. None of the subjects had a medical or dermatological illness and none were sensitive to sunscreens or to topical preparations and/or cosmetics. A completed subject was a subject who satisfied the admission criteria and who completed the scheduled study procedures.

Inclusion Criteria:

1. Healthy adult male and female volunteers between the ages of 18 and 65 years.
2. All subjects who were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. Subjects with any significant internal diseases e.g., cardiac, pulmonary, renal, hepatic, etc.
2. History of allergy or hypersensitivity to cosmetics, toiletries or other dermatological products
3. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria
4. Pregnancy or mothers who are breastfeeding or planning a pregnancy
5. Scars, moles or other blemishes over the upper arm(s) or back which can interfere with the study
6. Subjects receiving systemic or topical drugs or medications which can interfere with delayed immunologic responses e.g., corticosteroids, non-steroidal anti-inflammatories, retinoids, immunosuppressants
7. Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS:

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

STUDY PROCEDURES:

Method and Procedures[1,2]

Patches were applied to the upper outer arm of each subject. The entire test was composed of three distinct phases: (1) an Induction phase and (2) a Rest Phase and (3) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (induction patch). Since the test material [redacted] (Clear Liquid) contained volatile ingredients, it was allowed to air-dry for ~30 minutes prior to application to the test site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Rest Period**:

No exposure to the test material was made during this rest period, which lasted for 10 days after the last induction patch.

(3) **Challenge Phase**:

After a ten day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite upper outer arm in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and 0.05ml of the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded, and again 24 hours later for any reactions.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions were encountered or reported by any of the panelists.

RESULTS:

A total of twenty-six (26) healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 21 females and 5 males. Their ages ranged from 19 to 65 years. One subject #12 (initials EJH, a male) failed to return to the testing facility following the challenge phase and was lost to follow-up. He was subsequently dropped from the study. The remaining 25 subjects completed this investigation, as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table. No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Clear Liquid [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	KAL	35	F	C
02	Y-H	41	F	C
03	R-V	48	F	C
04	CNK	19	F	C
05	CAH	37	F	C
06	NSP	61	M	C
07	PLG	45	F	C
08	BAM	60	F	C
09	ALH	40	F	C
10	L-L	43	F	C
11	PJS	22	M	C
12	EJH	21	M	C
13	MDJ	36	F	C
14	CMA	44	F	C
15	BMM	19	F	C
16	JJP	31	F	C
17	M-D	54	F	C
18	DHR	21	M	C
19	AHS	65	F	C
20	LSG	53	F	C
21	FKH	24	M	B
22	MFP	51	F	C
23	LJW	61	F	C
24	NCB	22	F	C
25	MCF	20	F	C
26	ANB	24	F	C

C = Caucasian
B = Black

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Clear Liquid [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	Dropped from the study	
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26	0	0

Challenge Readings:

48-Hour Reading – December 3, 2009
72-Hour Reading – December 4, 2009

KGL INC

FINAL REPORT

Final Report Date: December 3, 2009

KGL Protocol: #6915

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Telephone: [215] 387-8400
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E-mail address: Ivystudies@verizon.net

Title: An Assessment of the Photosensitization Potential of Two Topical Coded Test Products Using a Human Photocontact Allergenicity Assay

Clear liquid contains 1% Sodium Phytate

Sponsor: [redacted]

Sponsor Study: Authorization Letter dated: October 21, 2009

Principal Investigator: Kays Kaldbey, M.D. (Board Certified Dermatologist)

Testing Facility: Ivy Laboratories (KGL, INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)
(Phone: 215-387-8400)

Kays Kaldbey, M.D.
Principal Investigator

December 3, 2009
Date

"The names of Ivy Laboratories (KGL, INC.), any officer, employee, or collaborating scientist are not to be used for any advertising, promotional or sale purposes without the written consent of Ivy Laboratories."

FINAL REPORT

TITLE:

An Assessment of the Photosensitization Potential of Two Topical Test Products Using a Human Photocontact Allergenicity Assay.

KGL PROTOCOL:

KGL Protocol **#6915**

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) ([21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with KGL's Standard Operating Procedures (SOP's).

OBJECTIVE:

The objective of this study was to determine the photosensitization (photocontact allergenicity) potential of two topical cosmetic products to determine if these materials have a detectable photocontact allergenic potential when topically applied to human skin (see references #1 and #2).

DESIGN RATIONALE:

This was a repeat insult patch test wherein the test materials and ultraviolet radiation (solar simulated radiation) were administered to the same designated test sites over the mid or lower back area repeatedly for a total of six (6) induction exposures over a 3 week period followed by a challenge phase after a rest period of 10 to 14 days. The evaluator was blinded as to the identity of the test products.

CONDUCTION DATES:

This study was conducted from October 26, 2009 through November 28, 2009

PRINCIPAL INVESTIGATOR:

Kays Kaidbey, M.D. (Board Certified Dermatologist)

Medical Director, KGL, INC. -- Telephone: 215-387-8400 – FAX: 215-387-1046

E-mail address: ivystudies@verizon.net

KGL ADMINISTRATIVE STRUCTURE:

Marie Windle (Receptionist/Panel Recruitment/Initial Screening)

Jane Chitwood (Technician/Patch Applications and Removals/UV Irradiation)

John B. Chicchi (Laboratory Supervisor/Expert Grader)

Mary Jean Massing (Sr. Associate Director/Quality Assurance)

TESTING FACILITY:

KGL INC.

505 Parkway

Broomall, PA 19008-4204

Telephone: (215-387-8400) - FAX: (215-387-1046)

SPONSOR:

[redacted]

SPONSOR STUDY:

Authorization Letter dated: October 21, 2009

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study.

Each interviewed panelist who qualified was then asked to sign a consent form prior to enrollment. A copy of the study schedule of events, visits and dates was then given to the volunteer.

TEST MATERIALS:

The test samples used in this study were supplied by the sponsor. The products consisted of containers labeled Liquid Blend [redacted] and Clear Liquid [redacted]. The product [redacted] (Liquid Blend) was shaken well prior to application. The Clear Liquid [redacted] was allowed to evaporate for about 30 minutes prior to occlusive application. Both test products were then tested in accordance with the study protocol.

contains 1% Sodium phytate

TEST DRUG ACCOUNTABILITY:

The test samples were received in good condition by our Quality Assurance Department. The test materials were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet signed by the receiver, the laboratory supervisor and the investigator (physician). The test materials were stored at ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test materials will be disposed of in accordance with established procedures following completion of the study and after the final written report has been issued to the Sponsor.

PANEL COMPOSITION:

Healthy, Caucasian, adult volunteers with no excess hair or other marks on their back that would obscure grading of the test sites were recruited for this study. These were fair skin individuals with skin types I, II, or III defined as follows (Federal Register 43: 38260, 1978):

Type I - Always burns easily; never tans
Type II - Always burns easily; tans minimally
Type III - Burns moderately; tans gradually

None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics.

Inclusion Criteria:

1. Healthy adult male and female volunteers (skin types I to III) between the ages of 18 and 65 years.
2. All subjects were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. History of sun hypersensitivity and photosensitive dermatoses.
2. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria.
3. Subjects with any significant internal diseases, e.g., cardiac, pulmonary, renal, hepatic, etc.
4. History of allergy or hypersensitivity to cosmetics, toiletries, or other dermatological products.
5. History of allergy or hypersensitivity to sunscreens.
6. History of allergy or hypersensitivity to any type of tape.
7. Scars, moles or other blemishes over the lower back, which could have interfered with the study.
8. Subjects receiving systemic or topical drugs including steroidal or non-steroidal anti-inflammatory drugs, or medications which could have interfered with the development of an inflammatory response, e.g., immunosuppressive agents or retinoids.
9. Subjects receiving potentially photosensitizing medications, e.g., thiazides, tetracyclines, phenothiazines, etc.
10. Pregnancy or mothers who were breastfeeding or planning a pregnancy.
11. Other conditions considered by the Investigator as sound reasons for disqualification from enrollment into the study.

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. All scores were recorded on the Case Report Forms. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

TEST SITE:

The test site was the mid or lower back. The test sites were inspected prior to test product application to ensure that the skin was normal in appearance and free of irritation or other blemishes.

METHOD[1,2]:

Test patches were applied to the lower back of each subject. The entire test was composed of three distinct phases: (1) Pre-testing phase (2) Induction phase and (3) Challenge phase.

(1) PRE-TESTING PHASE:

After signing an informed consent form (on Day 1), the Minimal Erythema Dose (MED) of each subject was determined by exposing one side of the midback to a series of exposures (1cm diameter circular areas) in 25% increments from the xenon arc solar simulator, the details of which are listed below. The subject's MED is the shortest exposure time that produces a minimally visible faint erythema 20 to 24 hours later.

(2) **INDUCTION PHASE**:

Approximately 40mgs. of each test material was applied to 2x2cm square skin sites over the lower back and covered with 2x2cm squares of non-woven cotton cloth (Webril, Curity). The patches were then fastened to the skin with occlusive tape (Blenderm, 3M). The patches were left in place for twenty-four (24) hours. At the end of that period, the patches were then removed and the sites wiped off with dry gauze and exposed to three minimal erythema doses (MED's) from the xenon arc solar simulator. The sites were then left open for a forty-eight (48) hour period, after which the subjects returned to the testing facility and the patches were again reapplied to the same designated test sites under an occlusive dressing as previously outlined. Twenty-four (24) hours later, the patches were removed and the sites re-exposed to 3 MED's of solar simulated radiation. This sequence was repeated to the same test sites twice weekly for a total of three weeks (total of 6 exposures).

(3) **CHALLENGE**:

Eleven (11) days following the last induction dose, the subjects returned to the testing facility for a single challenge exposure. The test materials were applied as previously specified (40mgs) in **duplicate** to new designated skin sites each measuring 2x2cm on the opposite side of the lower back, under an occlusive dressing for a period of approximately 24 hours. One set of patches was then removed and any excess test material wiped off with dry gauze. The sites were then irradiated with 1/2 an MED of solar simulated radiation (SSR) plus 4J/cm^2 of UVA which was obtained by filtering the beam from the solar simulator to eliminate short (UVB) wavelengths (see Light Source). The duplicate set of patches remained unirradiated and served as control treated sites.

EVALUATION OF SKIN REACTIONS:

All test sites were examined for reactions at 48 and 72 hours following exposure of the sites to UV radiation. Each subject reported back to the testing facility at the two time points to have the responses appraised by an evaluator other than the person applying the test products, and who was unaware of the nature of the test substances.

Skin reactions were scored according to the following scale:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesicula-bullous reaction)

LIGHT SOURCE[3]:

This was a 150-watt compact xenon arc source equipped with UV-reflecting dichroic mirror and a 1mm thick Schott WG-320 filter to produce simulation of the solar spectrum (290nm-400nm). A 1mm thick UG5 filter was added to remove reflected heat and remaining visible radiation. Total irradiance at skin level was measured with a calibrated Eppley Thermopile. The size of the irradiated field was approximately a 1-cm diameter circle. UVA was obtained from this same source by passing the beam through a 1mm Schott WG345 filter (Schott Glass Technologies). This provided a continuous spectrum between 320 and 420nm with a peak between 360-370nm. Total irradiance at skin level was 120mW/cm^2. The UVA intensity was 45mW/cm^2.

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions of any kind were observed or reported during the study.

RESULTS:

A total of 25 healthy, Caucasian volunteers who qualified were enrolled into this study. There were 21 females and 4 males ranging in age from 18 to 63 years. The demography is shown in Table 1. All 25 volunteers completed this investigation, as specified in the protocol.

No side-effects or unexpected reactions of any kind were observed. Following the challenge phase, no reactions suggestive of photocontact allergy were seen in any of the panelists at either 48 or 72 hours post exposure. The results of the challenge are summarized in the enclosed tables (Tables 2 through 5).

CONCLUSIONS:

Under the presently described test conditions, the test materials labeled Liquid Blend [redacted] and Clear Liquid [redacted] do not possess a detectable photocontact-sensitizing potential in human skin.

REFERENCES

(1) Kaidbey, KH and Kligman AM: Photomaximization test for identifying photoallergic contact sensitizers. Contact Dermatitis, 6: 161-169, 1980.

(2) Kaidbey, KH and Kligman AM: Identification of contact photosensitizers by human assay. In "Current concepts in cutaneous toxicity, edited by V.A. Drill and P. Lazar. Academic Press Inc., pp. 55-68, 1980

(3) Berger DS: Specification and design of solar ultraviolet simulators. J.Invest.Dermtol. 53: 192-199, 1969.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	D-M	39	M	C
02	A-O	25	F	C
03	D-C	63	F	C
04	R-K	33	F	C
05	T-C	23	F	C
06	B-G	22	F	C
07	D-M	37	F	C
08	R-P	36	F	C
09	R-H	21	M	C
10	K-L	32	F	C
11	A-H	37	F	C
12	M-C	43	F	C
13	J-G	22	F	C
14	M-W	53	F	C
15	R-S	21	M	C
16	D-W	21	F	C
17	E-P	32	M	C
18	R-C	26	F	C
19	C-B	18	F	C
20	M-C	35	F	C
21	A-M	23	F	C
22	D-T	25	F	C
23	A-R	61	F	C
24	C-B	55	F	C
25	H-S	45	F	C

C = Caucasian

TABLE 4

RESULTS OF PHOTOMAXIMIZATION TESTING (48 Hour Grading)

Sample: Clear Liquid [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	0	0
003	0	0
004	0	0
005	0	0
006	0	0
007	0	0
008	0	0
009	0	0
010	0	0
011	0	0
012	0	0
013	0	0
014	0	0
015	0	0
016	0	0
017	0	0
018	0	0
019	0	0
020	0	0
021	0	0
022	0	0
023	0	0
024	0	0
025	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 5

RESULTS OF PHOTOMAXIMIZATION TESTING (72 Hour Grading)

Sample: Clear Liquid [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	0	0
003	0	0
004	0	0
005	0	0
006	0	0
007	0	0
008	0	0
009	0	0
010	0	0
011	0	0
012	0	0
013	0	0
014	0	0
015	0	0
016	0	0
017	0	0
018	0	0
019	0	0
020	0	0
021	0	0
022	0	0
023	0	0
024	0	0
025	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

MB Research Laboratories

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P.O. Box 178
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Study Title	:	MatTek EpiOcular™ MTT Viability Assay
Test Article	:	[redacted] RI109837, – Contains 50% Sodium Phytate in 49% water 1% alcohol
Positive Control	:	0.3% Triton® X-100, Lot# 100709TTA
Negative Control	:	Tissue culture water, Lot# 128K2318 (TCH_2O)
Internal Control	:	PC-17:0358L
Author	:	Michelle Piehl, Ph.D, Study Director
Study Completed On	:	October 27, 2009
Performing Laboratory	:	MB Research Laboratories 1765 Wentz Road P.O. Box 178 Spinnerstown, PA 18968
MB Research Project #	:	MB 09-18487.19
MB Research Protocol #	:	720-03
Sponsor	:	[redacted]
Citation	:	Michelle Piehl, Ph.D (2009) Unpublished Report by MB Research Laboratories

Study Title : MatTek EpiOcular™ Assay
Project # : MB 09-18487.19
Protocol : 720-03

GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

This study was conducted in accordance with the Good Laboratory Practice requirements of EPA, 40 CFR 160 and 792, FDA 21 CFR 58, and as specified in Principles on Good Laboratory Practices, published by the Organization for Economic Cooperation & Development (OECD), 1997, with the following exception:

The test article characterization was not supplied by the Sponsor prior to study Initiation.

STUDY DIRECTOR:

10-27-09

Michelle Piehl, Ph.D — Date
MB RESEARCH LABORATORIES

PROJECT NUMBER : MB 09-18487.19
SPONSOR : [redacted]
TITLE : MatTek EpiOcular™ MTT Viability Assay
PROTOCOL # : 720-03

ABSTRACT

OBJECTIVE: To provide an estimate of eye irritation potential using an alternative to the Draize Rabbit Eye Test. The exposure time needed for a test article to reduce viability to 50% can be correlated to an estimated Draize Rabbit Eye Score (Modified Maximum Average Score (MMAS)) or a "Predicted Irritancy Class".

METHOD SYNOPSIS: MatTek EpiOcular™ tissue samples were treated in duplicate with the test articles, and positive control, and internal control for various exposure times listed below. Negative controls, treated with tissue culture water, were tested at 16 minutes only. Following treatment, the viability of the tissues was determined using Methyl thiazole tetrazolium (MTT) uptake and reduction. The absorbance of each sample was measured at 540 nm using a reference wavelength of 690 nm. The viability was then expressed as a percent of negative control values. The mean percent viability for each time point was used to calculate an ET_{50}, which represents the time at which the EpiOcular™ tissue viability was reduced 50% compared to control tissues. The ET_{50} scores were converted to an irritancy classification using the Standard Method.

SUMMARY/CONCLUSION:

Test Article Identity	Exposure Times (min)	ET_{50} (min)	Irritancy Classification
[redacted]	64, 256, 1200	1137.2	Non-Irritating, Minimal
	4, 16, 64	9.4	Moderate
RI109837	64, 256, 1200	518.4	Non-Irritating, Minimal
[redacted]	16, 64, 256	>256.0	Non-Irritating, Minimal
	64, 256, 1200	>1200.0	Non-Irritating, Minimal
	16, 64, 256	56.7	Mild
	64, 256, 1200	>1200.0	Non-Irritating, Minimal
	64, 256, 1200	>1200.0	Non-Irritating, Minimal
	64, 256, 1200	>1200.0	Non-Irritating, Minimal
	64, 256, 1200	262.7	Non-Irritating, Minimal
PC-17:0358L (Internal Control)	64, 256, 1200	271.0	Non-Irritating, Minimal
0.3% Triton® X-100 (Positive Control)	15, 45	19.5	Within Range (12.2 - 37.5)

Study Title : MatTek EpiOcular™ Assay
Project # : MB 09-18487.19
Protocol : 720-03

OBJECTIVE

To provide an estimate of eye irritation potential using an alternative to the Draize Rabbit Eye Test. The exposure time needed for a test article to reduce viability to 50% can be correlated to an estimated Draize Rabbit Eye Score (Modified Maximum Average Score (MMAS)) or a "Predicted Irritancy Class".

TEST ARTICLE

Supplied by : [redacted]
Test Article Characterization : Not supplied by the Sponsor.
Stability : Not supplied by the Sponsor.
Storage : Room temperature and humidity.

Identity	Date Received	Description	Sample Preparation
[redacted]			eceived.
RI109837	09/25/09	Clear liquid	Used as received.
[redacted]			100 µl of the test article were added to 900 µl of tissue culture water (TCH_2O) to yield a 10% solution (Slightly white cloudy liquid).
			s received.
			s received.
			s received.
			s received and chopped with razor blade to all pieces.
			Used as received and chopped with razor blade to very small pieces.
			Used as received.

Study Title : MatTek EpiOcular™ Assay
Project # : MB 09-18487.19
Protocol : 720-03

POSITIVE CONTROL

Identity	:	0.3% Triton® X-100, Lot# 100709TTA
Supplied by	:	MatTek
Date Received	:	10/13/09
Expiration Date	:	01/05/10
Storage	:	Refrigerated at approximately 4°C.
Description	:	Clear liquid
Sample Preparation	:	Used as received

NEGATIVE CONTROL

Identity	:	Tissue culture water, Lot# 128K2318 (TCH_2O)
Supplied by	:	Sigma
Date Received	:	06/03/09
Expiration Date	:	12/2010
Storage	:	Room temperature and humidity.
Description	:	Clear liquid
Sample Preparation	:	Used as received.

INTERNAL CONTROL

Identity	:	PC-17:0358L, Lot# 0358L
Provided by	:	
Date Received	:	08/21/09
Expiration Date	:	01/2011
Storage	:	Room temperature and humidity
Description	:	Off-white cream
Sample Preparation	:	Used as received.

Study Title : MatTek EpiOcular™ Assay
Project # : MB 09-18487.19
Protocol : 720-03

TEST DATES

Study Initiation	(date protocol signed)	:	10/12/09
Experimental Start Date	(1st date data collected - OECD)	:	10/13/09
Experimental Start Date	(1st exposure to test substance)	:	10/14/09
Experimental Term Date	(last date data collected)	:	10/16/09
Final Report Signed	(study completion)	:	10/27/09

EXPERIMENTAL DESIGN

EpiOcular™ Tissue Samples:

EpiOcular™ tissues, Lot 10285 Kits H, I & J, were received from MatTek on 10/13/09 and refrigerated at approximately 4°C. Before use, tissues were incubated (37°C ± 1°C, 5% ± 1% CO_2) with assay medium (MatTek) for a one-hour equilibration. Equilibration medium was replaced with fresh medium before dosing.

Test Article Reduction of MTT:

100 µl or 100 mg of the test articles were mixed with 1 ml of MTT solution (1 mg/ml Methyl thiazole tetrazolium diluted in Dulbecco's Modified Eagle's Medium (DMEM)). A negative control, 100 µl of tissue culture water, was tested concurrently. The solutions were incubated at room temperature in the dark for 60 minutes. After incubation, the solutions were visually inspected for purple coloration, which indicates that the test article reduced MTT. Since tissue viability is based on MTT reduction, direct reduction by a test article can exaggerate viability, making a test article seem less irritating than it really is. None of the test articles were found to have reduced MTT and the assay continued as per the protocol.

Dosing:

At the request of the Sponsor, test article [redacted] was diluted to 10% in TCH_2O for dosing. 100 µl of the test article dilution were applied to the top of each EpiOcular™ tissue. All other test articles were dosed neat. 100 µl of test article [redacted] were packed into a syringe, applied to the head of a plastic pushpin, and then gently inverted onto the tissue. 100 µl or 100 mg of the remaining test articles were applied to the top of each EpiOcular™ tissue. At the request of the sponsor, the initial exposure time for test article [redacted] was 16 minutes. The MTT viability at the 16-minute time point was greater than 90%, so additional tissues were treated for 64 and 256 minutes. For the remaining test articles, three exposure times (64, 256, 1200 minutes) were chosen by the Sponsor. However, due to lack of viability at 64 minutes, test article [redacted] was tested at 4, 16 and 64 minutes instead of 64, 256 and 1200 minutes and test article [redacted] was tested at 64, 256 and 1200 minutes to ensure than an ET_{50} could be calculated.

At the request of the Sponsor, an internal control identified as "PC-17:0358L" was used to treat tissues at 64, 256 and 1200 minutes. A negative control was tested using tissue culture water at 16 minutes. A positive control (0.3% Triton® X-100) was tested at 15 and 45 minutes. Each treatment with test article or control was conducted in duplicate.

EXPERIMENTAL DESIGN (cont'd)

Tissue Viability (MTT Reduction):

At the end of the selected exposure periods, each EpiOcular™ tissue was rinsed with phosphate buffered saline (PBS), soaked for 10 minutes in assay media and transferred to a 24-well plate containing 300 µl of MTT solution. The tissues were then returned to the incubator for a three-hour MTT incubation period.

Following the MTT incubation period, each EpiOcular™ tissue was rinsed with PBS and then treated overnight with 2.0 ml of extractant solution (isopropanol) per well. An aliquot of the extracted MTT formazan was measured at 540 nm using a plate reader, subtracting the absorbance at a reference wavelength of 690 nm.

Analysis of Data:

The mean absorbance value for each time point was calculated from the optical density (OD) of the duplicate samples and expressed as percent viability for each sample using the following formula:

$$\% \text{ viability} = 100 \text{ X (OD sample/OD negative control)}$$

The ET_{50}, the time at which the EpiOcular™ tissue viability was reduced 50% compared to control tissues, was then determined using a macro in Microsoft Excel 5.0, provided by MatTek, using the equation:

$$V = a + b \log t$$

Where V = percentage viability, t = time in minutes, and a and b are constants that can be determined by using the viability data for two different exposure times of the test article to the tissue. These exposure times must yield viabilities that flank 50%.

EXPERIMENTAL DESIGN (cont'd)

Correlation of *In vitro* and *In vivo* Results:

As per MatTek, as a general guideline, the following groups can be used to assign expected *in vivo* Irritancy responses[1] based on the ET_{50} results obtained using the EpiOcular™ MTT Viability Assay:

Draize Score	Irritancy Classification	Example	EpiOcular™ ET_{50} (min)	
			Standard Method*	Specific Gravity Method**
0 -15	Non-Irritating, Minimal	PEG-75 Lanolin, Tween® 20	> 60	> 256-26.5
15.1 - 25	Mild	3% SodiumDodecyl Sulfate	30-60	< 26.5-11.7
25.1 - 50	Moderate	5% Triton® X-100	3-29.99	< 11.7-3.45
50.1 - 110	Severe, Extreme	5% Benzalkonium Chloride	< 3	< 3.45

* = ET_{50} ranges as defined by the MatTek protocol "Neat Method for Ocular Irritation"
** = ET_{50} ranges as defined by the MatTek protocol "Dilution Method for Ocular Irritation"

These groups are based on correlation with an analysis of historical animal test data[2] using the following equation derived by MatTek:

$$\text{Draize} = -4.74 + \frac{(101.7)}{\sqrt{ET_{50}}}$$

Retention of Data:

Upon signing the final report, all raw data, supporting documentation and reports are submitted to the Archivist by the Study Director. The raw data is filed at MB Research by project number. The final report is filed at MB Research by Sponsor name and MB project number.

Any remaining test article will be discarded following submission of the report.

[1] J. H. Kay and J. C. Calandra. Interpretation of eye irritation tests. *J Soc Cosmet Chem* (13):281-289, 1962.
[2] M. L. Stern, M. Klausner, R. Alvarado, K. Renskers, and M. S. Dickens. Evaluation of the EpiOcular™ Tissue Model as an Alternative to the Draize Eye Irritation Test. *Toxicol In Vitro* 12 (4 (August)):455-461, 1998.

EXPERIMENTAL DESIGN (cont'd)

Amendment to the Protocol:

Due to low viability at 64 minutes, test article [redacted] was tested at 4, 16 & 64 minutes instead of 64, 256 & 1200 minutes to ensure that an ET_{50} could be calculated.

Due to low viability at 64 minutes, test article [redacted] was tested at 16, 64 & 256 minutes instead of 64, 256 & 1200 minutes to ensure that an ET_{50} could be calculated.

Deviation to the Good Laboratory Practices

Prior to study initiation, the study director was not supplied with test article characterization information. The effect of the lack of test article characterization cannot be fully assessed.

RESULTS AND DISCUSSION

The test articles provided by [redacted] were tested using the MatTek EpiOcular™ MTT Viability Assay (see Appendix A for data). At the request of the Sponsor, test article [redacted] was diluted to 10% in TCH_2O for dosing. All other test articles were dosed neat. The ET_{50} scores were converted to an irritancy classification using the Standard Method. The ET_{50} of the positive control, 0.3% Triton® X-100, was 19.6, which fell within MatTek's acceptance range of 12.2 - 37.5 minutes.

The summarized data and irritation classifications are as follows:

Test Article Identity	ET_{50} (min)	Irritancy Classification Standard Method
[redacted]		
RI109837	518.4	Non-Irritating, Minimal
[redacted]		:al
		ıal
		ıal
		ıal
		Minimal
		Minimal
PC-17:0358L (Internal Control)	271.0	Non-Irritating, Minimal
0.3% Triton® X-100 (Positive Control)	19.5	Within Range (12.2 - 37.5)

FINAL REPORT

Approved by: 10-27-09

Michelle Ptehl, Ph.D — Date
Study Director

APPENDIX A (cont'd)

EXPERIMENTAL DATA (cont'd)

Test Article: RI109837
dose: 100 µl
conc: Neat

TIME (mins)	OD 1	OD 2	MEAN (OD)	SD	VIABILITY %	ERROR %
64.0	1.624	1.732	1.678	0.076	107.3	4.9
256.0	1.271	1.490	1.381	0.155	88.2	9.9
1200.0	0.064	0.077	0.071	0.009	4.5	0.6
neg control	1.529	1.600	1.565	0.050	100.0	3.2

ET_{50} (mins) 518.4
Irritancy Classification: Non-Irritating, Minimal

Test Article: [redacted]
dose: 100 µl
conc: 10%

TIME (mins)	OD 1	OD 2	MEAN (OD)	SD	VIABILITY %	ERROR %
16.0	1.430	1.614	1.522	0.130	97.3	8.3
64.0	1.602	1.602	1.602	0.000	102.4	0.0
256.0	1.437	1.442	1.440	0.004	92.0	0.2
neg control	1.529	1.600	1.565	0.050	100.0	3.2

ET_{50} (mins) > 256.0
Irritancy Classification: Non-Irritating, Minimal

APPENDIX A (cont'd)

EXPERIMENTAL DATA (cont'd)

Internal Control: PC17:0358L
dose: 100 µl
conc: Neat

TIME (mins)	OD 1	OD 2	MEAN (OD)	SD	VIABILITY %	ERROR %
64.0	1.597	1.479	1.538	0.083	98.3	5.3
256.0	0.861	0.759	0.810	0.072	51.8	4.6
1200.0	0.081	0.031	0.056	0.035	3.6	2.3
neg control	1.529	1.600	1.565	0.050	100.0	3.2

ET_{50} (mins) 271.0
Irritancy Classification: Non-Irritating, Minimal

Positive Control: 0.3% Triton X-100
dose: 100 µl
conc: Neat

TIME (mins)	OD 1	OD 2	MEAN (OD)	SD	VIABILITY %	ERROR %
15.0	0.815	1.066	0.941	0.177	60.1	11.3
45.0	0.302	0.255	0.279	0.033	17.8	2.1
neg control	1.529	1.600	1.565	0.050	100.0	3.2

ET_{50} (mins) 19.5
Irritancy Classification: Within Range (12.2-37.5)

Study Title : MatTek EpiOcular™ Assay
Project # : MB 09-18487.19
Protocol : 720-03

QUALITY ASSURANCE EVALUATION

The Quality Assurance Unit has inspected a critical phase of this study, audited the raw data and the report and determined that the methods and results contained herein accurately reflect the raw data. A summary of the compliance inspections is presented below.

Date of Inspection	Phase	Performed By	Date Inspection Results Reviewed	
			Mgmt.	Sty. Dir.
10/14/09	Dose Administration	Krista A. Stayer	10/20/09	10/14/09
10/20/09	Raw data audit	Krista A. Stayer	10/20/09	10/20/09
10/26/09	Final report audit	Erin Range	10/26/09	10/27/09

Erin Range 10/26/09
Erin Range, B.S., LATG Date
Quality Assurance Unit