# Safety Assessment of Polyol Phosphates as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 29, 2018
Panel Date: September 24-25, 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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**Memorandum**

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: August 29, 2018
Subject: Draft Final Report on Polyol Phosphates

At the June 4-5, 2018 Panel meeting, the Panel reviewed the safety of 10 polyol phosphates, and issued a Tentative Report with the following split conclusion:

- Sodium Phytate, Phytic Acid, Phytin, and Trisodium Inositol Triphosphate are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

- The data are insufficient to determine the safety of the following 6 ingredients: Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate.

The Panel determined that the following data are needed to assess the safety of these 6 ingredients: (1) Method of manufacture, (2) Impurities data, and (3) Absorption, distribution, metabolism, and excretion (ADME) data. To date, the data requested have not been received. The data needs are stated in the discussion section of the draft Final Report.

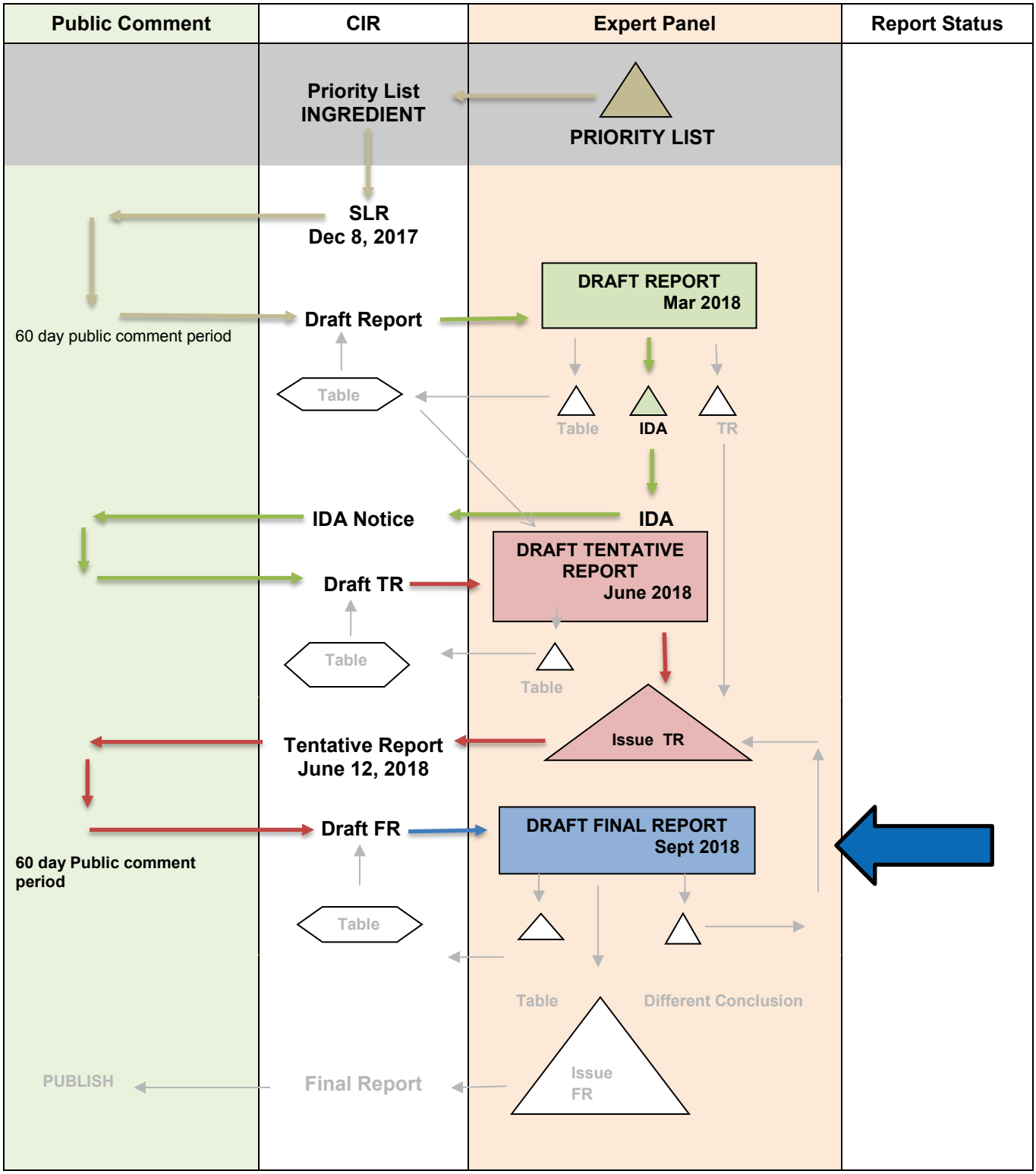
Also included in this package for your review are the draft Final Report (*phytic092018rep)*, the CIR report history (*phytic092018hist*), flow chart (*phytic092018flow*), literature search strategy (*phytic092018strat*), ingredient data profile (*phytic092018prof*), 2018 FDA VCRP data (*phytic092018FDA*), minutes from the June 4-5, 2018 CIR Expert Panel meeting and prior Panel meetings (*phytic092018min*), comments on the tentative report (*phytic092018pcpc1*) that were received from the Personal Care Products Council (Council), and the Council's comments on the draft report (*phytic092018pcpc2*) that were received prior to the June Panel meeting. The Council's comments have been addressed.

After reviewing the data included in the safety assessment, the Panel will need to determine whether or not a Final Report with the conclusions stated above should be issued.

# SAFETY ASSESSMENT FLOW CHART

**INGREDIENT/FAMILY** Polyol Phosphates

**MEETING** Sept 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).

The Panel issued a tentative report with the following 2 conclusions:

- Sodium Phytate, Phytic Acid, Phytin, and Trisodium Inositol Triphosphate are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

- The data are insufficient to determine the safety of the following 6 ingredients: Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate.

The Panel determined that the following data are needed to assess the safety of these 6 ingredients: (1) Method of manufacture, (2) Impurities data, and (3) Absorption, distribution, metabolism, and excretion (ADME) data.

**Draft Final Report, Teams/Panel: September 24-25, 2018**

To date, the data needs on 6 ingredients that were requested at the June Panel meeting have not been met. The Council's comments on the tentative report that was issued have been addressed.

**Data Profile on Polyol Phosphates September 24th-25th, 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; 7/30/18)]

| 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.

**Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team**

## Polyol Phosphate

**DR. BELSITO:** Okay, so the next order of business is the polyol phosphates.
**DR. BERGFELD:** You want to take a break?
**DR. BELSITO:** Pardon?
**DR. BERGFELD:** You want to take a break? Dan had to leave.
**DR. BELSITO:** Dan, you need a break. Okay. What time is it?
**DR. KLAASSEN:** I need some coffee.
**DR. BELSITO:** 10:05.
**DR. KLAASSEN:** At this rate, we'll be done by midnight.
**DR. BELSITO:** Regroup at 10:20, 10:15. How long do we need, 10 minutes? Yeah, 10:15.
**[BREAK]**
**DR. BELSITO:** We're going to start with the polyol phosphates. At the March meeting we issued an insufficient data announcement with a number of requests, primarily, dealing with -- I guess for lack of a better word -- the sugar components of this, which the other team actually wanted to separate out of the report. Which had to do with the method of manufacture and impurities of all of the glucose, fructose, xylose ingredients. Chemical characterization, ADME for those ingredients.

And then for the phytic components, our major issue was we wanted an HRIPT at 2 percent. And we received a whole bunch of data, HRIPTs on sodium phytate, phytic acid. Most of them below what we wanted, but we did get one at 5 percent phytic acid, which covered that. We really didn't get any of the data that we wanted on the sugar molecules in this group.

My sense was that sodium phytate, phytic acid, phytin and trisodium inositol triphosphate were okay. But the saccharide phosphates were insufficient for all of the data we had previously requested, essentially.

**DR. LIEBLER:** I think the full panel discussion kind of skewed the data needs, in my view, a bit. Because I think Ron Hill came in with a number of requests, as the discussion progressed, that I didn't necessarily share but we didn't argue either. What I agreed on is that we are still insufficient for method of manufacture, composition and impurities for everything but the phytic acid and the sodium phytate. We just don't have those.

On the other hand, sort of the chemistry, I didn't understand his point about the redox chemistry, what he needed, so, I didn't share that. But that was one of the bullets in the discussion.

And I also didn't think we were really lacking for ADME data. We do have the data for the phytic acid. We do have the data for that potassium phytate, which I think is an appropriate read across. It certainly tells us these molecules are absorbed and metabolized. And they're metabolized to common biologic intermediates or common nutrients.

I don't think that's a problem. I think the main insufficiency, still, on my end of the workload, is the method of manufacture, composition and impurities.

**DR. BELSITO:** But Dan, the ones you mentioned were the inositol phosphates, which we didn't ask for before. We asked for them for the saccharide phosphates. So, are you now adding new insufficient data? Because you were saying you were okay with sodium phytate and --

**DR. LIEBLER:** Phytic acid.

**DR. BELSITO:** Phytic acid. So, you think phytin and trisodium inositol triphosphate are insufficient for --

**DR. LIEBLER:** Those are probably reasonably represented by the sodium phytate phytic acid data which we do have. The saccharide phosphates, we don't have anything.

**DR. BELSITO:** Okay. So, then you would agree with what I said, based on the fact we now have an HRIPT at 5 percent; that we would go safe as used for the inositol phosphates. And the saccharide phosphates we still need all of the data that we requested --

**DR. LIEBLER:** Right.

**DR. BELSITO:** -- which is basically method of manufacture, impurities and sensitization.

**DR. LIEBLER:** Correct.

**DR. BELSITO:** Because we now have a concentration of use for -- is it trisodium? We have one of them that we didn't have before. I think it's the trisodium fructose diphosphate. Or which one is it that we have -- table 3. Because before there were no concentration of use for these sucrose phosphates.

I just passed it. Yeah, so we have sodium mannose phosphate. Now we have a concentration of use of .1 percent in 30 leave-ons. And previously, we had no reported uses which was one of the arguments the

other team used to say we should just bounce them out of the report.

**DR. LIEBLER:** Right. I normally don't agree with that logic. I've learned not to do that. If it's in the dictionary, we review it.

**DR. BELSITO:** I mean, I guess, my question to you is based upon all of the HRIPT data we have on the inositol phosphates. Do we need data for the sodium mannose phosphate, which is used at .1 as opposed to the phytic acid, which is used at 2 percent?

**DR. LIEBLER:** I think we're fine. I mean, I think for the HRIPT, if you're satisfied with the quality of the studies, I can further add that there's no fundamental difference in reactivity toward proteins and sort of the biochemical propensity to induce sensitization.

**DR. BELSITO:** We have a huge number of HRIPTs now on phytic acid. We were asking for two because that was concentration of use. But we now have five. We have 1 percent. We have multiple reports at less than 1 percent. And the level of use that we're being told for the sodium mannose phosphate is .1.

**DR. LIEBLER:** Right. I think we're okay.

**DR. BELSITO:** So, for HRIPT we're okay. Our insufficiency is still manufacturing and impurities.

**DR. LIEBLER:** And impurities. Right.

**DR. BELSITO:** Okay.

**DR. LIEBLER:** These were all probably derived from similar mechanisms of the phytic acid and phytate. They're probably all derived from plant sources with a little chemistry and biochemistry added. And a little purification. But we have nothing.

So, we normally don't like to have nothing on a set of ingredients. If we had it on most of these, but not necessarily all of them, I could be persuaded that we have enough information to proceed. But right now, we've got nothing.

**DR. BERGFELD:** You're going to ask for the repeat insult patch test; but are you going to, in your discussion, discuss why you're going to accept the sodium mannose sulfate as a representative of that group? And then talk about why the inositol phosphates would cover some of those needs?

**DR. LIEBLER:** Oh, I think we can do that.

**DR. BERGFELD:** Okay.

**DR. BELSITO:** I'm not talking about the sensitization data; I'm talking about just method of manufacture, composition, impurities. Which is what I mean when I say we don't have anything.

**DR. BERGFELD:** On your draft discussion, as it stand now, the skin sensitization is only asking for phytic acid. Is that going to stand for the saccharide group? Or are you going to ask for something in that group?

**DR. BELSITO:** We've got the sensitization. We got an HRIPT at 5 percent.

**DR. BERGFELD:** Okay. Oh, 5 percent on that.

**DR. BELSITO:** What I'm saying is the inositol phosphates were taken care of. The saccharide phosphates, we're asking for manufacturing, impurities and that's it, correct?

**DR. LIEBLER:** Correct.

**DR. BERGFELD:** I thought it was only the phytic acid you had at 5 percent.

**DR. LIEBLER:** I think the inositol phosphate data would suffice to read across for sensitization for the saccharide phosphates. Because the chemical similarity, the lack of any kind of liability with respect to protein modification, which would be considered a key initiating event in sensitization reaction, that's just not happening with these molecules, any of them.

**DR. BERGFELD:** A discussant then?

**DR. LIEBLER:** Yup.

**DR. BELSITO:** Paul, Curt?

**DR. SNYDER:** I'm fine.

**DR. BELSITO:** Okay. So, we're going sufficient for the inositol phosphates. Insufficient for the saccharide phosphates and manufacturing and impurities.

**DR. EISENMANN:** You mean safe as used or?

**DR. BELSITO:** Pardon me, Carol.

**DR. EISENMANN:** Safe as --

**DR. BELSITO:** Safe as used.

**DR. EISENMANN:** Okay.

**DR. BELSITO:** We just need to update our draft discussion indicating that we received --

**MR. JOHNSON:** Update the discussion indication the data that have been received?

**DR. BELSITO:** Yes.
**MR. JOHNSON:** Okay.
**DR. BELSITO:** Because right now the discussion says we're still insufficient for phytic acid because we don't have HRIPT at 2 percent. Okay, so that was Wave 2.

**Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Marks' Team**

**Polyol Phosphates**

**DR. MARKS:** Okay, so we're on to the polyol phosphates. Is that how you say that?

**DR. HILL:** Yes, that will work.

**DR. MARKS:** Polyol phosphates. And in March of this year an insufficient data announcement was made. And so, we are in the position to add a tentative report. You can see from Wilbur's memo what the insufficient data was. And actually --

**DR. SLAGA:** Where is Wilbur?

**DR. MARKS:** -- our team --

**DR. SLAGA:** Where is Wilbur?

**DR. MARKS:** I don't know.

**DR. HELDRETH:** He's finishing up his last one in the Belsito team right now. He'll be over here soon.

**DR. MARKS:** Yeah, and Wilbur wasn't there. Well, what would you suggest, Bart? Should we skip to the next one and wait until Wilbur finishes?

**DR. HELDRETH:** All the rest of these are Wilbur's.

**DR. HILL:** All the rest of these are Wilbur's.

**DR. HELDRETH:** I'll take notes for him.

**DR. MARKS:** Let's move forward, yeah. At the last meeting we actually, our team, suggested that most of these insufficient needs were with a sugar phosphate. That we suggested having a safe for the non-sugar phosphates. That may have been your suggestion, Ron Shank.

**DR. SHANK:** It was.

**DR. MARKS:** And then do an insufficient for the sugar phosphates. We can go back to that, since we're at this point of issuing a tentative report. We did get data, HRIPT, for phytic acid at 5 percent. And the sensitization was okay for that. And that's above what the use concentration is.

So where do you want to go? Ron, Ron and Tom, do you want to go to what our thoughts were the last time? Or do we want to just say insufficient? We got a lot of sensitization data, but really relevant to us and all the other needs. It's mainly the sugar phosphates where the needs are.

**DR. SHANK:** Yes.

**DR. SLAGA:** Yeah. We still need the a, b and c for the sugars, right? Even if we go that way?

**DR. HILL:** Yes. And then xylitol was included in that list, which was really my doing because there were some question marks. But that would be a non-sugar.

**DR. MARKS:** Yes.

**DR. HILL:** And I think it could probably be covered by the phytic acid quite frankly.

**DR. MARKS:** Okay.

**DR. HILL:** Just I'm making an educated leap.

**DR. SLAGA:** That's what I have.

**DR. HILL:** I don't think I had anything else new this time around.

**DR. MARKS:** So, safe for the non-sugar phosphates and insufficient for the sugar phosphates?

**DR. SLAGA:** Yes.

**DR. HILL:** I can just see if there's anything in the discussion I had flagged. Oh, this is just a draft discussion at this point.

**DR. MARKS:** Yes. That's correct. Because we will be issuing a tentative report. Safe for the non-sugar phosphates. And insufficient for the sugar phosphates. And the needs are listed below, which include method of manufacture and impurities, that's in there. Again, we don't feel we need the method of manufacture or impurities for the xylitol phosphates. We're okay with that at this point.

**DR. HILL:** I'm okay with that, yeah.

**DR. MARKS:** Chemical characterization, we're okay. Absorption distribution, metabolism and excretion for the sugar phosphates. And we got the skin sensitization for the phytic acid. I think the insufficient would be what's listed below in the bullets. Basically, method of manufacture, impurities, absorption distribution, metabolism and excretion, ADME. Does that sound good?

**DR. SLAGA:** Mm-hmm.

**DR. HILL:** Mm-hmm.

**DR. MARKS:** Okay. Let me put this -- method of manufacture, impurities and ADME. Okay.

So, I'll be moving tomorrow's, meaning I will propose the motion of just what I said. And there will be a tentative report with that conclusion.

I'll move tomorrow a tentative report be issued with safe for the non-sugar phosphates. And do you want me to say those? That would be sodium phytate, phytic acid, phytin trisodium, inositol triphosphate and xylitol phosphate. Those are the five non-sugars.

**DR. SHANK:** Xylitol phosphate is a sugar, isn't it?

**DR. HILL:** No. It's fully saturate, but it's ring-open. That's why I had flagged it the last time, in that insufficient. So, it's ring-open. Whereas the phytin, the inositol triphosphate, those are ring-close.

**DR. SHANK:** Okay.

**DR. HILL:** And they're not sugars. They're cyclohexane masquerading as sugar basically.

**DR. MARKS:** So those five okay? That's why I read them. I want to be sure we're on the same page. They're the ones that I had circled from our last meeting. And you questioned the xylitol phosphate.

**DR. HILL:** I did.

**DR. MARKS:** And Ron, you had questioned that, is that a sugar or not. But it's really not a sugar.

**DR. HILL:** It's not a sugar. It's a fully saturated sugar, I guess, would be one way to look at it.

**DR. ANSELL:** Or sugar alcohol.

**DR. SHANK:** So, it shouldn't be listed as a saccharide.

**DR. HILL:** Sugar alcohol is the best way to say it actually.

**DR. MARKS:** I'm sorry, Ron Shank, what -- any other comments? Are those five okay? Not characterizing them as non-sugar phosphates.

**DR. HILL:** I thought I heard you read inositol something, and I was trying to figure out where that came from.

**DR. MARKS:** No. Sodium phytate, phytic acid, phytin trisodium, inositol --

**DR. HILL:** Oh, inositol triphosphate, that's right. Inositol triphosphate. That's correct.

**DR. MARKS:** Oh, inositol. Is that how you say it.

**DR. HILL:** That's right.

**DR. MARKS:** Triphosphate, and then the xylitol phosphate. So those would be the five that would be safe. And I'll read those tomorrow. And then the remainder, which are sugar phosphates, like the glucose, fructose, mannose, would be insufficient. Sound good?

**DR. SHANK:** Mm-hmm.

**DR. HILL:** All the data we have is really for phytic acid or phytate or phytin. So, them is fighting words to me.

**DR. MARKS:** Okay. Put that, and I want to put this off to the side because I want to make sure tomorrow, rather than type it all in here and keep you guys waiting.

**DR. MARKS:** That was such an in-depth discussion it's taking me a minute to move on to the next ingredients.

At the March meeting of this year an insufficient data announcement was given for the Polyol Phosphates. We had the needs listed there and our team felt, with what we had from previously and what we've gotten since, that we could move forward with a tentative report, which is split conclusions.

Safe for the five non-sugar phosphates, that's the sodium phytate, phytic acid, phytin, trisodium inositol triphosphate, and the xylityl phosphate, and insufficient for the sugar phosphates, the remaining five ingredients. Where we needed similar data, as is listed here, the method and manufacture impurities and the absorption, et cetera. So that's a motion.

**DR. BERGFELD**: Is there a second?

**DR. BELSITO:** Could you repeat that because I think you included some of the saccharide phosphates in what you said were safe. It's three inositol phosphates, sodium phytate, phytate, and trisodium inositol triphosphate that are safe as used, correct?

**DR. MARKS:** Yes.

**DR. BELSITO:** Okay. And then the saccharide phosphates, all six of them, are insufficient for the prior data needs.

**DR. MARKS:** We had the discussion -- did you include the xylityl phosphate? We included that as a non-sugar. We did have a discussion whether that was a sugar or non-sugar. So, is that the one, Don, where our numbers don't match? You have four, I have five as safe.

**DR. BELSITO:** Yes.

**DR. MARKS:** That's the one I figured. And we had that discussion on our team and we decided to include it as a non-sugar. So, making it go into chemistry as to whether it's a sugar or non-sugar, but that sounds like the only ingredient of discussion.

**DR. BELSITO:** We don't have method and manufacture or impurities for that either.

**DR. HILL**: We do not. And I don't feel strongly about keeping it in; so, if we come to agreement without it, I think we leave it out.

**DR. BELSITO:** Dan, you want to comment?

**DR. LIEBLER:** I didn't see any reason not to include it. I'm still in favor of including all of the ingredients, and I think we're short on method and manufacture and impurities on the saccharide phosphates. So, once we have those, then I think we will be able to most likely come to a safe as used conclusion on these. But right now, we're still insufficient on the saccharide phosphates.

**DR. BELSITO:** But what the Marks team was saying, Dan, is they wanted to move xylityl phosphate over to an inositol phosphate rather than a saccharide phosphate.

**DR. LIEBLER:** Well it's certainly not that. It's in the report. And it's not really a saccharide phosphate; it's a -- you know, these two categories don't really help us that much, I suppose, in retrospect. And I know the idea of putting them into these two groups was mentioned last time. I don't think they really solving the problem for us.

So, we could take that away and just have them as a list. Because we don't really treat them distinctly, in the rest of the report, as distinct entities with different properties, biological effects, et cetera, so -- and uses, right? Uses are similar?

**DR. BERGFELD**: Dr. Marks, you want to comment?

**DR. MARKS:** Yes. So, do I understand correctly, Don and Dan, it'd be the four ingredients; not that we would move forward with safe, the sodium phytate, the phytic acid, the phytin, and the trisodium inositol triphosphate? And would move the xylityl phosphate over to the insufficient group; that'd be four and six, four safe, six insufficient for the reasons you mentioned?

**DR. BELSITO:** No, three safe.

**DR. MARKS:** Three?

**DR. BELSITO:** Just the three under inositol.

**DR. HELDRETH**: There's actually an error in the report. In the conclusion, phytic acid wasn't listed underneath the inositol phosphates. If you move up to the introduction, you'll see there's actually four under that grouping. It's a mistake on our part in the current conclusion.

**DR. MARKS:** I don't think our team has a problem making it four.

**DR. BELSITO:** Okay, so what you're saying, in the inositol phosphates, the fourth is phytic acid. So, we're saying sodium phytate, phytin, phytic acid, and trisodium inositol triphosphate, those four are safe as

used. All of the other listed under the saccharide phosphates are insufficient for manufacturing impurities.

**DR. MARKS:** And how about absorption; do you want that, the ADME, or you feel you're comfortable with that at this point?

**DR. LIEBLER:** We're fine.

**DR. MARKS:** Okay.

**DR. LIEBLER**: We're fine on that.

**DR. HILL**: I don't feel fine on that. That's one of the reasons why I didn't -- sorry. I feel like we don't understand the biological chemistry of those sugar phosphates. So, that's why I had the ADME in there, which is not to focus on the A for absorption; although interestingly, phytic acid is absorbed, so there's clearly a route.

**DR. BERGFELD**: So, you're requesting that that stay in there -- the absorption?

**DR. HILL**: I would like it to stay in.

**DR. MARKS:** We can certainly leave it in at this point.

**DR. BELSITO:** Yeah. So, method and manufacturing and absorption, distribution, metabolism, and excretion.

**DR. BERGFELD**: So, there's been a second, is there any further comments?

**DR. MARKS:** No. I have to withdraw my motion.

**DR. BERGFELD**: Okay.

**DR. MARKS:** I'll withdraw my motion and --

**DR. BERGFELD**: And restate it.

**DR. MARKS:** -- restate it, it's safe for the four non-sugar phosphates, which we identified, and insufficient for the six other phosphates, for the data needs we need.

**DR. BERGFELD**: And the data needs have been just explained?

**DR. MARKS:** Yes.

**DR. BERGFELD**: All right. May I call to question, all those in favor of this conclusion? Unanimous. Thank you. Moving on to the Polyfluorinated Polymers, Dr. Belsito.

# Safety Assessment of Polyol Phosphates as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 29, 2018
Panel Date: September 24-25, 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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**ABSTRACT**: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of polyol phosphates, and some of the possible functions in cosmetics that are reported for this ingredient group are: chelating agents, oral care agents, and skin conditioning agents. The Panel reviewed relevant data relating to the safety of these ingredients under the intended conditions of use in cosmetic formulations and concluded that Sodium Phytate, Phytic Acid, Phytin, and Trisodium Inositol Triphosphate are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel also concluded that the data are insufficient to determine the safety of the following 6 ingredients as used in cosmetics: Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate.

## INTRODUCTION

The safety of the following 10 polyol phosphate ingredients in cosmetics is reviewed in this CIR safety assessment.

Sodium Phytate
Phytic Acid
Phytin
Trisodium Inositol Triphosphate
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 is reported to function 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 anti-acne agent, antidandruff agent, deodorant agent, and exfoliant. Functioning as an anti-acne or antidandruff agent is not considered a cosmetic function in the United States (US) and, therefore, the Panel did 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 used for the purposes of read across (see Table 2): human dermal penetration data on Potassium Phytate (read-across for Sodium Phytate, Phytic Acid, and Phytin); tumor promotion data on phytic acid hexamagnesium salt *n*-hydrate (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).

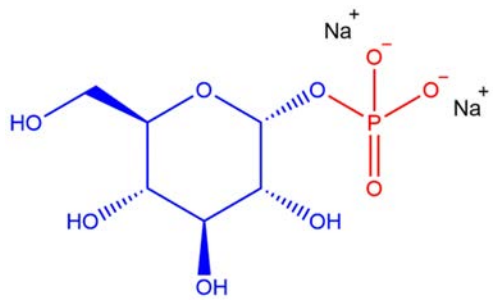



Figure 1. Disodium Glucose Phosphate, example of a saccharide phosphate

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]

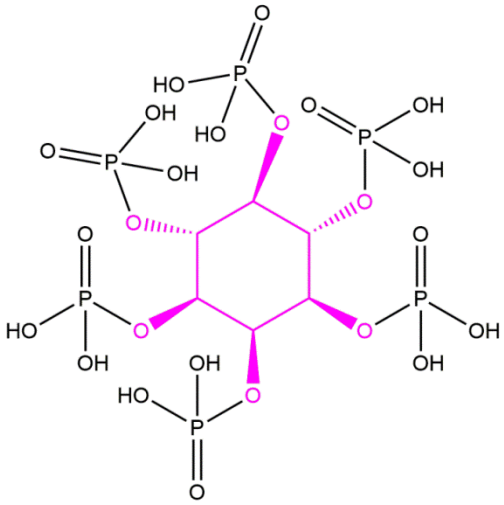


Figure 2. Phytic Acid, example of an inositol phosphate

The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.

## 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

The methods for the production of Phytic Acid, summarized below, involve acid hydrolysis (e.g., sulfuric acid or hydrochloric acid) of one or more of the following plant materials: maize seed (kernels), defatted food-grade rice bran, rice bran, or rice husks (hulls).

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 crude phytin paste 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 (USP) Convention's 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 US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in 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 reportedly 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 used at concentrations up to 2% in leave-on products (body and hand products [not spray]), which is the greatest reported use concentration for these ingredients.[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 used in cosmetic products in the US: 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]

### Non-Cosmetic

**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 US 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

**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.[22]

### Absorption, Distribution, Metabolism, and Excretion

**Animal**

**Dermal**

**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.[23] 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. Phytic Acid was absorbed through the skin layers (having crossed the epidermis and dermis), entered the bloodstream, and urinary excretion was increased.

**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.[26] The highest Phytic Acid concentrations were detected in the brain ($5.89 \times 10^{-2}$ mg/g DM), and concentrations detected in other organs were 10-fold less. 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.[27] 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.

**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; 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 amount of Phytic Acid that is usually 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 two 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.[38] 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.

### 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 a 12-week dose range-finding study (for 108-week oral carcinogenicity study), groups of 20 F344 rats (10 males and 10 females) received Phytic Acid at concentrations up to 10% in drinking water.[43] 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.

In another study, 10 female C7BL/6J mice received Phytic Acid (2% in distilled drinking water) for a 70-day period. Dosing with Phytic Acid was well tolerated.[44]

### Chronic Toxicity Study

In a chronic study, 8 female Tg2576 mice (Alzheimer's mouse model) and 10 female C7BL/6J mice received Phytic Acid at a concentration of 2% in distilled water for 6 months.[44] Seven control female Tg2576 mice and 12 control female 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.

## DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

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

**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; number of implantations; or incidence of early

resorptions.[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 typhimurium* 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, in chromosomal aberrations assays using Chinese hamster ovary (CHO) cells, 2 mg/ml Phytic Acid was non-genotoxic,[47] but at an unknown high concentration, it was genotoxic in CHO cells.[9]

**Sodium Mannose Phosphate**

The genotoxicity of Sodium Mannose Phosphate was evaluated in the Ames test using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A.[49] Sodium Mannose Phosphate was tested at doses up to 5000 µg/plate, with and without metabolic activation. The test material was not genotoxic in any of the bacterial strains tested, with or without metabolic activation.

### In Vivo

**Phytic Acid**

In the micronucleus test involving bone marrow cells (polychromatic erythrocytes) 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.[43] Renal papillomas (related to calcification and necrosis of renal papillae) were observed in 3 male and 4 female rats treated with 2.5% Phytic Acidand 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, Sodium Phytate, and 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 pre-neoplastic 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.[50] Both Sodium Phytate and potassium phytate caused an increase in urinary pH.

## ANTI-CARCINOGENICITY STUDIES

The anti-carcinogenicity 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.[51] 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.[52]

### 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.[53]

### 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.[54] 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.[55] Phytic Acid (2% in drinking water) was administered to 15 female Crl:SKH1-*hr* hairless mice prior to mid-wavelength ultraviolet light (UVB) exposure, and another group of 15 received UVB exposure only. Tumor formation was monitored until week 31, and Phytic Acid + UVB exposure caused a statistically significant decrease in the skin tumor incidence, an anti-photocarcinogenic effect.[56]

## 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.[57] 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.[58] 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.[59] 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.[60] 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 12.

### 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%, which is 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.[61] Phytic Acid (50%) elicited an $ET_{50}$ that was significantly less than 1 h. The authors concluded that 50% Phytic Acid has an expected in vivo dermal irritancy potential in the severely irritating to possibly corrosive range.

**Sodium Mannose Phosphate**

The skin irritation potential of 3% Sodium Mannose Phosphate was evaluated using the Epiderm™ skin model (reconstructed human epidermis).[62] Epiderm™ tissues were treated in triplicate with the test material for 60 ± 1 min and then transferred to well plates. Test results indicated that the test substance was not predicted to be a skin irritant.

**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.[63] 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.”

**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.[64] Test results were negative.

## Sensitization

**In Vitro**

**Sodium Phytate**

The skin sensitization potential of a dried Sodium Phytate trade name material (defined in skin irritation study on Sodium Phytate) 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.

**Sodium Mannose Phosphate**

The sensitization potential of Sodium Mannose Phosphate was evaluated using the KeratinoSens™ assay.[65] Sodium Mannose Phosphate (in dimethyl sulfoxide (DMSO)) was tested at 12 concentrations ranging from 0.49 to 1000 ppm, and was classified as a non-sensitizer.

**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 human repeated insult patch test (HRIPT) involving 111 subjects.[66] 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),[66] a leave-on product containing 0.1% Sodium Phytate (undiluted, 112 subjects), [66] a rouge containing 0.19% Sodium Phytate (undiluted, 106 subjects), [67] and a topical coded product containing 1% Sodium Phytate (maximization test, 25 subjects) [68]

**Phytic Acid**

A moisturizer containing 5% Phytic Acid was classified as a non-sensitizer in an HRIPT involving 110 subjects.[69] The skin irritation and sensitization potential of a cosmetic product containing 1% Phytic Acid was evaluated in an HRIPT involving 104 male and female subjects.[70] Application of the product was not associated with clinically significant skin irritation or allergic contact dermatitis. The same results were reported for another cosmetic product containing 1% Phytic Acid in an HRIPT (same procedure) involving 98 male and female subjects.[71] In a maximization test involving 25 subjects, a face gel containing 0.25 % Phytic Acid produced negative results. [72]

## Photosensitization/Phototoxicity

A photosensitization test (HRIPT) on a clear liquid containing 1% Sodium Phytate was performed using 25 subjects (21 females and 4 males).[73] 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 13.

**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.[74] 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[63] and for a coded product containing 50% Sodium Phytate.[75] In a bovine corneal opacity and permeability (BCOP) 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 Phytate trade 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).[76]

**Sodium Mannose Phosphate**

The ocular irritation potential of 3% Sodium Mannose Phosphate was evaluated in the BCOP assay using excised corneas.[77] An aliquot (750 µl) of the test material was introduced into the anterior chamber of 5 corneas. The in vitro ocular irritation score was 0.

## 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 *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 is reported to function 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 did 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 USP Convention's 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 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.

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 drinking 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 (Alzheimer's mouse model) 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 21 to 24 pregnant female 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 and Sodium Mannose Phosphate were non-genotoxic in the Ames test. Also, Phytic Acid was non-genotoxic in the 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 trade name material consisting of 50% water and 1% ethanol (test concentration not stated) was evaluated in the Ames test using the following *S. typhimurium* 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 anti-photocarcinogenic (2% in drinking water [mice]) as well as anti-carcinogenic (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 anti-carcinogenic (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 trade name material consisting of 50% water and 1% ethanol (test concentration not stated) 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. Sodium Mannose Phosphate (3%) also was not predicted to be a skin irritant using the same model.

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. The sensitization potential of Sodium Mannose Phosphate (in DMSO) was evaluated at 12 concentrations (ranging from 0.49 to 1000 ppm) using the KeratinoSensTM assay. The test substance was classified as a non-sensitizer.

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. The application of cosmetic products containing 1% Phytic Acid was not associated with clinically significant skin irritation or allergic contact dermatitis in HRIPTs involving 98 and 104 subjects. 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. An HRIPT on a rouge containing 0.19% Sodium Phytate (undiluted) was performed using 106 male and female subjects. Repeated applications of the product did not cause significant skin irritation, and there was no evidence of an allergic reaction.

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. Sodium Mannose Phosphate (3%) was a non-irritant in the in vitro BCOP assay using excised corneas. The ocular irritation potential of a Sodium Phytate (concentration not stated) trade name material was also evaluated in the following in vitro assays: BCOP test, RhCE test, and HET-CAM assay. Test results indicated that the trade name material was non-irritating/non-corrosive to slightly irritating.

A clinical study evaluated the effect of phytates in the diet. No overt signs of toxicity were reported when 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.

## DISCUSSION

The Panel determined that the data were sufficient to conclude on the safety of four polyol phosphates, but additional data are needed for completion of the safety assessment of the remaining six polyol phosphates. Of these six ingredients for which the data are insufficient to determine safety, only Sodium Mannose Phosphate is reported to be in use. 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
- 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

The Panel previously requested 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. A negative human maximization test on a product containing 1% Sodium Phytate, negative HRIPT data on products containing Sodium Phytate (up to 0.1%) and on a moisturizer containing 5% Phytic Acid (highest ingredient concentration tested), and negative human photosensitization data on a clear liquid containing 1% Sodium Phytate were among the data that were received in response to this request. The Panel agreed that the results of these studies indicate that these ingredients do not have skin sensitization potential at cosmetic use concentrations.

The Panel discussed the issue of incidental inhalation exposure from perfumes. Sodium Phytate is reportedly 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 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.

## CONCLUSION

The Panel concluded that the following ingredientsare safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Sodium Phytate
Phytic Acid
Phytin*
Trisodium Inositol Triphosphate*

**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.*

The Panel also 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.

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

***Not reported to be in use.*

# TABLES

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

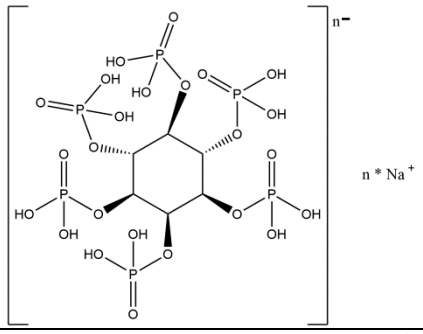
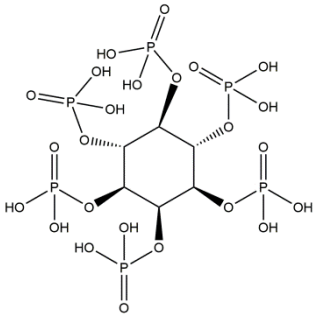
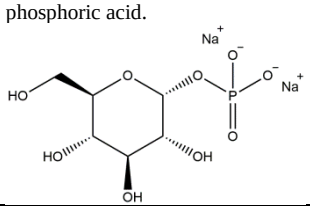
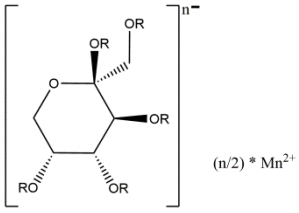
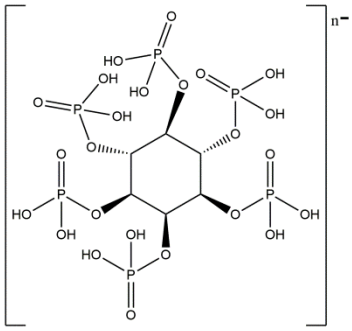
| Ingredient CAS No. | Definition & Monomer Structures | Function(s) |
|---|---|---|
| Sodium Phytate<br>14306-25-3<br>34367-89-0 | Sodium Phytate is the complex sodium salt of Phytic Acid.<br>  <br> | Chelating Agents; Oral Care Agents |
| Phytic Acid<br>83-86-3 | Phytic Acid is the hexaphosphoric acid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

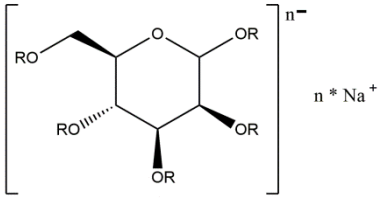
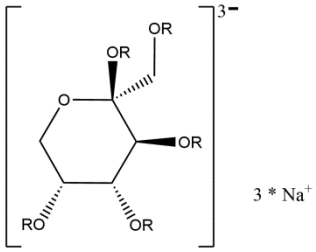
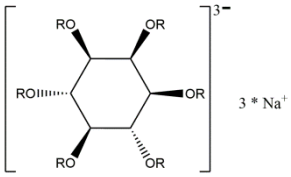
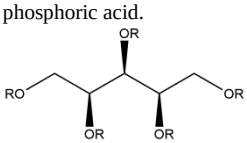
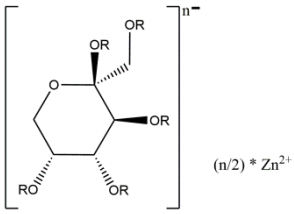
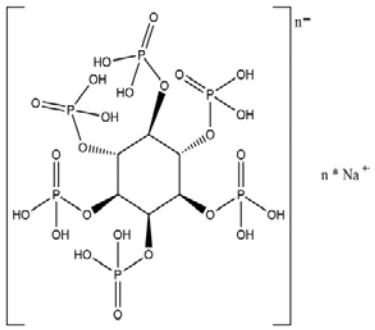
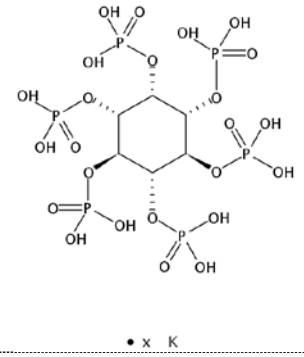
| Ingredient CAS No. | Definition & Monomer Structures | Function(s) |
|---|---|---|
| Sodium Mannose Phosphate<br>70442-25-0 | Sodium Mannose Phosphate is the sodium salt of a complex mixture of esters of phosphoric acid and Mannose.<br>  <br>[wherein R is phosphate in at least one instance and hydrogen in all other instances] | Skin-Conditioning Agents – Humectant; Skin-Conditioning Agents – Miscellaneous |
| Trisodium Fructose Diphosphate<br>81028-91-3 | Trisodium Fructose Diphosphate is a trisodium salt of a complex mixture of esters of fructose and phosphoric acid.<br>  <br>[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.<br>  <br>[wherein R is hydrogen in 3 instances and phosphate in 3 instances] | Skin-Conditioning Agents - Miscellaneous |
| Xylityl Phosphate<br>1224593-11-6 | Xylityl Phosphate is the complex mixture of esters formed between xylitol and phosphoric acid.<br>  <br>[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.<br>  <br>[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)[78] |
| log $K_{ow}$ (estimated) | -6.54. [5] | -26.31[79] |

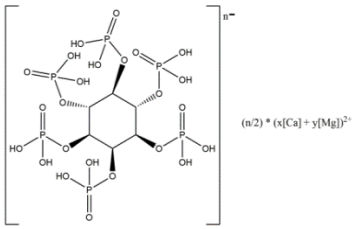
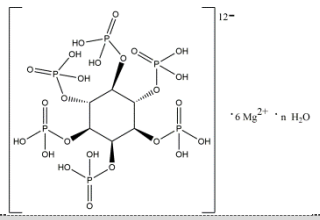
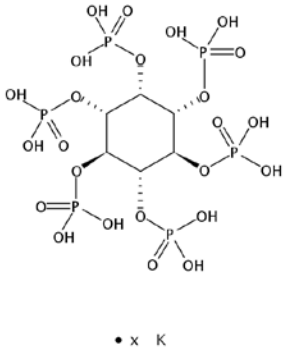
| | | |
|---|---|---|
| **Name** | ***Phytin*** | Phytic acid hexamagnesium salt n-hydrate |
| **CAS No(s).** | 3615-82-5 | |
| **Structure** |  |  |
| **Name** | | ***potassium phytate*** |
| **CAS No(s).** | | 33705-24-7 |
| **Structure** | |  |
| **read-across endpoints** | • tumor promotion | |
| **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: | Similarly, another salt of Phytic Acid, Potassium Phytate, may useful in evaluating tumor promotion potential. | |
| Formula weight (Da) | 841 (est. for tri-calcium tri-magnesium)<br>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[a] | 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.[23] |
| **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.[22] |

**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 |
|---|---|---|
| **<u>Oral Studies</u>** | | |
| 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] |
| **<u>Intravenous Studies</u>** | | |
| 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]<br><br>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 Oral Toxicity Studies

| Ingredient | Animals | Protocol | Results |
|---|---|---|---|
| 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.[43] |
| Phytic Acid (2% in distilled drinking water) | Groups of 10 female C7BL/6J mice | Exposure for 70-day period | Dosing with Phytic Acid was well tolerated. The same was true for the 10 control mice that received distilled drinking water only.[44] |
| 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 Oral 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 |
|---|---|---|
| 50% Phytic Acid solution (as supplied) (administered as 1.6%, 3.1%, or 6.31% aqueous solution) | Groups of 21 to 24 JcI:ICR mice received oral doses (gavage) of the1.6%, 3.1%, or 6.31% concentration of the supplied solution (equivalent to 80, 155, or 315 mg/kg body weight/day) on gestation days 7 to 15. The dose volume administered was 10 ml/kg/day. The control group received water that did not contain Phytic Acid. 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., $3.8 \pm 4.2$). 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 alteration 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.[43] |
| **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.[50] |

**Table 11.** Anti-Carcinogenicity 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.[51] |
| 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.[52] |

**Table 11.** Anti-Carcinogenicity 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.[53] |
| 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.[54] |
| 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.[55] |
| 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.[56] |

**Table 12.** Skin Irritation and Sensitization Studies of 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.[61] |
| 3% Sodium Mannose Phosphate | Epiderm™ skin model (reconstructed human epidermis) | Epiderm™ tissues treated in triplicate with the test material for 60 ± 1 min and then transferred to well plates. A 1 mg/ml solution of 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) solution was added to each well to assess ability of test material to directly reduce MTT during a 3 ± 0.1 h incubation period (i.e., MTT cytotoxicity assay). Negative control was calcium and magnesium free Dulbecco's phosphate buffered saline (CMF-DPBS) and positive control was 5% sodium dodecyl sulfate. Relative cell viability calculated as % of mean of negative control tissues. Skin irritation is predicted if the remaining relative cell viability is below 50%. | Test material was not observed to directly reduce MTT in the absence of viable cells. Mean viability in the presence of the test material was 101.1%. Mean viability in the presence of positive control was 3.34%. Tet substance was not predicted to be a skin irritant.[62] |

**Table 12.** Skin Irritation and Sensitization Studies of Polyol Phosphates

| Test Substance | Subjects/Tissues Tested | Test Protocol | Results |
|---|---|---|---|
| **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.[64] |
| 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.[63] |
| **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] |
| Sodium Mannose Phosphate (up to 1000 pm) | KeratinoSens™ assay, cell-based assay with a reporter cell line for the detection of potential skin sensitizers by their ability to induce the Nrf2-response. KeratinoSens™ cell line is derived from the human keratinocyte culture HaCaT | Sodium Mannose Phosphate (in dimethyl sulfoxide (DMSO)) tested at 12 concentrations ranging from 0.49 to 1000 ppm. Cinnamic aldehyde was positive control. The following 2 endpoints were measured: 1) luciferase induction after a 48-h treatment with the test material and 2) cytotoxicity, as determined with the MTT assay. For Luciferase induction, the maximal fold-induction over solvent control ($I_{max}$) and the concentration needed to reach a 1.5-, 2-, and 3-fold induction (EC1.5, EC2, and EC3) were calculated. For cytotoxicity, the $IC_{50}$ value was extrapolated. | Sodium Mannose phosphate did not induce the luciferase gene above the threshold of 1.5 at any concentration in 2 of 3 repetitions, whereas a weak induction at the highest concentration was noted in the third repetition. Test substance classified as a non-sensitizer.[65] |

**Table 12.** Skin Irritation and Sensitization Studies of Polyol Phosphates

| Test Substance | Subjects/Tissues Tested | Test Protocol | Results |
|---|---|---|---|
| **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.[68] |
| Rouge containing 0.19% Sodium Phytate (undiluted) | 106 male and female subjects (Fitzpatrick skin types II to IV) | HRIPT. Product (20 µl) applied to upper back (dose per $cm^2$ not stated), under an occlusive patch (standard Finn chamber used), and procedure repeated for a total of 9 induction patch applications over a period of 3 consecutive weeks. Induction applications (application period undefined) followed by 2-week non-treatment period, after which challenge phase initiated. Challenge patches applied (application period undefined) to induction site and a new test site. Occlu-sive patch application of distilled water served as control. | Repeated applications of product did not cause significant skin irritation, and the product had very good skin compatibility. No evidence of an allergic reaction at challenge.[67] |
| 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.[66] |
| 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.[66] |
| 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.[66] |

**Table 12.** Skin Irritation and Sensitization Studies of 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. [69] |
| Cosmetic product containing 1% Phytic Acid | 104 male and female subjects. | HRIPT. Product (~ 0.2 ml on 2 cm x 2 cm semiocclusive patch) applied for 24 h to back (between scapulae), which means that ~0.05 mL/$cm^2$ applied. Procedure repeated on Mondays, Wednesdays, and Fridays for total of 9 induction applications. Patch removals on Tuesdays and Thursdays followed by 24-h non-treatment period. Patch removals on Saturdays followed by 48-h non-treatment period. Removal of last induction patch followed by 2-week non-treatment period. Challenge patch applied to new test site, and reactions scored at 24 h and 72 h after patch application. | Reactions not observed during induction phase. Challenge reaction (+ reaction (barely perceptible erythema) at 72-h reading) observed in 1 subject, and classified as negative for skin sensitization. Product application not associated with clinically significant skin irritation or allergic contact dermatitis.[70] |
| Cosmetic product containing 1% Phytic Acid | 98 male and female subjects | HRIPT (same as above). Product (~ 0.2 ml on a 2 cm x 2 cm semiocclusive patch) applied to the back. | Skin reactions not observed at any time during the study. Application of the product was not associated with clinically significant skin irritation or allergic contact dermatitis.[71] |
| 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.[72] |
| 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.[66] |

**Table 13.** 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).[74] |
| 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.[75] |
| Cream containing 0.48956% Sodium Phytate | EpiOcular™ eye irritation test | $ET_{50}$ > 24 h (no ocular irritation potential).[63] |
| Dried Sodium Phytate (concentration not stated) trade name material | Bovine corneal opacity and permeability test (BCOP; 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) | BCOP 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 13.** 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 ($\leq$ 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.[76] |
| 3% Sodium Mannose Phosphate | Bovine opacity and permeability assay using excised corneas. An aliquot (750 µl) of test material introduced into anterior chamber of 5 corneas, and the corneas incubated for 10 min. Positive and negative controls were ethanol and deionized water, respectively. Change in opacity for each cornea calculated. For permeability measurements, corneas incubated for 90 min, and optical density (OD) of medium at 490 nm determined. | Opacity value was -0.1 and the $OD_{490}$ value was 0.004. The in vitro ocular irritation score was 0.[77] |

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

**DATE:** June 26, 2018

**SUBJECT:** Tentative Report: Safety Assessment of Polyol Phosphates as Used in Cosmetics (report posted on June 12, 2018)

The Council respectfully submits the following comments on the tentative report, Safety Assessment of Polyol Phosphates as Used in Cosmetics.

Method of Manufacture - Although from different references, the three methods of manufacture reported for Phytic Acid are essentially the same, acid hydrolysis of plant material. It would be helpful to have an opening sentence/paragraph to indicate the similarities in the reported methods.

Short-term, Phytic Acid - The 70-day study in mice (reference 43) is presented twice (last sentence of first paragraph and last paragraph). The second version is more complete as it states that the mice were dosed in "distilled drinking water", while the first version only says "distilled water".

DART, Oral, Phytic Acid - As the results per litter are what is relevant, it is not necessary to stated "number of live fetuses" and "number of live fetuses per litter".

Tumor Promotion - As the pH of urine can affect bladder cancer, it would be helpful to also state that Sodium Phytate and potassium phytate increased urinary pH.

Cytotoxicity - Is reference 50 the correct reference for the cell growth inhibition study (the title suggests it is about bladder carcinogenesis)?

Summary - Please indicate that female C7BL/6J mice were dosed in drinking water. The BCOP study of Sodium Mannose Phosphate still needs to be added to the Summary.

Discussion - It would be helpful if the names of the safe ingredients were included in the Discussion. In the paragraph concerning the sensitization studies received, it would be helpful to mention the maximization test (n=25) of the product containing 1% Sodium Phytate (reference 67).

Conclusion - The insufficient data ingredients with no reported uses still need to be marked with an asterisk.

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Table 2 - As potassium phytate was also included in the tumor promotion study, "tumor promotion" should be added to the read-across endpoints for potassium phytate. As the Target materials for potassium phytate says "(also Phytic Acid & Phytin)", "for these two salts of Phytic Acid" needs to be revised in the justification row.

Table 7, Table 8 - The dosing solutions used in the mouse developmental toxicity study should be clarified. Are the concentrations presented the concentrations of Phytic Acid, or of the 50% Phytic Acid? It should be made clear that the control mice were treated with water not containing any Phytic acid (rather than 50% solution administered as 0%).

Table 8 -As "enhancement" was not observed in the study of the effects of Phytic Acid on the reproductive toxicity of aflatoxin B1, a more neutral word should be used,, e.g., "Study to evaluate the influence of Phytic Acid on aflatoxin B1-induced reproductive toxicity" (the study title uses the word "alters").

Skin Irritation and Sensitization Table - In the title of this table, "Table 1" needs to be corrected to "Table 12".

Ocular Irritation Table - In the title of this table, "Table 2" needs to be corrected to "Table 13". It would be helpful if the studies on the same ingredient were presented together. The BCOP on Sodium Mannose Phosphate is presented between studies on Sodium Phytate; it should be presented after all of the *in vitro* studies on Sodium Phytate.

Reference 9 - The link to the reference is not working.

Personal Care Products Council
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**Memorandum**

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

**FROM:** Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

**DATE:** May 30, 2018

**SUBJECT:** Draft Tentative Report: Safety Assessment of Polyol Phosphates as Used in Cosmetics (draft prepared for the June 4-5, 2018 CIR Expert Panel meeting)

The Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Polyol Phosphates as Used in Cosmetics.

Key Issues

Draft Conclusion - As new information has been submitted to support the safety of Phytic Acid, Sodium Phytate and Sodium Mannose Phosphate, developing a conclusion should have been left to the CIR Expert Panel as stated in the Abstract, e.g., "and the issuance of a conclusion is expected". Phytic Acid needs to be added to the list of Inositol Phosphates in the Conclusion.

Introduction - At the March meeting, the CIR Expert Panel indicated that they found the read-across table acceptable. Therefore, "potential read-across" needs to be deleted from the last paragraph of the Introduction.

Additional Considerations

Dermal Penetration, Animal - The protocol of the study described in reference 22 is not clear. It says the rats were treated topically once per day for 14 days, then it says "When topical application was discontinued after day 30...." Perhaps there were multiple groups that were treated for varying durations.

Chronic - It should be made clear that all mice in this study were female and that the Tg2576 mouse strain is an Alzheimer's mouse model.

Genotoxicity, In Vitro, Phytic Acid - Please state the cell system used in the chromosomal aberrations assay (reference 9).

Dermal Irritation, Table 1 - The table containing the dermal irritation and sensitization information should be titled Table 12 (not Table 1).

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Sensitization - It is not clear where the dried Sodium Phytate is "defined in the preceding section". Perhaps it is defined in Table 12.

Ocular Irritation, Table 2 - The table containing the ocular irritation information should be titled Table 13 not Table 2.

Supplemental, Irritation, Sodium Mannose Phosphate - The summary says that CMF-DPBS is not defined in the report of the Epiderm skin study. This is not correct. On p. 9 of the report CMF-DPBS is defined as "Calcium and Magnesium Free Dulbecco's Phosphate Buffered Saline". The concentration of sodium dodecyl sulfate (5%) used as the positive control should be stated.

Supplemental, Sensitization, Human, Sodium Phytate - The description of the HRIPT of the rouge containing 0.19% Sodium Phytate should also state that they used standard Finn chambers.