Safety Assessment of Polyol Phosphates as Used in Cosmetics

Status: Scientific Literature Review for Public Comment
Release Date: December 8, 2017
Panel Date: March 5-6, 2018

All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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INTRODUCTION

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

Sodium Phytate
Phytic Acid
Disodium Glucose Phosphate
Manganese Fructose Diphosphate
Phytin
Sodium Mannose Phosphate
Trisodium Fructose Diphosphate
Trisodium Inositol Triphosphate
Xylityl Phosphate
Zinc Fructose Diphosphate

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

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated.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

The following data on chemicals that are not cosmetic ingredients are included in this safety assessment, and the Panel will address their potential use for read across (see Table 2): human dermal penetration data on Potassium Phytate (potential read-across for Sodium Phytate), data on mannose-6-phosphate (potential identity overlap/read-across for Sodium Mannose Phosphate) in the Developmental and Reproductive Toxicity and Other Clinical Reports sections of the report, and tumor promotion data on phytic acid hexamagnesium salt *n*-hydrate (potential read-across for Phytin, the calcium and magnesium salt of Phytic Acid).

Impurities/physical properties data on an aqueous solution of Phytic Acid (Phytic Acid solution), as defined by the *Food Chemicals Codex*, and chemistry/safety test data from a company's generally recognized as safe (GRAS) exemption claim for Phytic Acid (50% solution) as a food additive are also included.[2,3]

CHEMISTRY

Definition and General Characterization

The ingredients in this report are each the phosphate(s) of a carbohydrate (e.g., a monosaccharide or "sugar alcohol") or a salt thereof. One example of these polyol phosphate salts is Disodium Glucose Phosphate (Figure 1). Some of these ingredients may exist in open chain, furanose and/or pyranose forms, like many sugars do. Some of these ingredients are naturally occurring. Indeed, Phytic Acid is present in practically all mammalian cells.[4] The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.

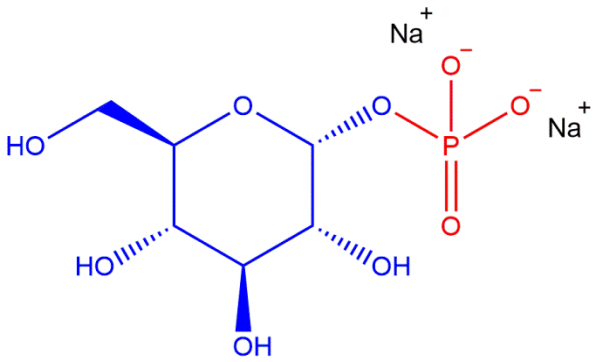


Figure 1. Disodium Glucose Phosphate

Chemical and Physical Properties

Properties of polyol phosphates are presented in Table 3.[5,6,7,8,9] Sodium Phytate is soluble in water and Phytic Acid is soluble in water containing alcohol-ether mixtures.[5] Phytin is poorly soluble in water.

Method of Manufacture

Phytic Acid solution

An aqueous solution of Phytic Acid is obtained by acid hydrolysis of maize seed (kernels), rice bran, or rice husks (hulls).[2] 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.

Phytic Acid

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.[3] 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]

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.[3]

Impurities

Phytic Acid

According to the United States Pharmacopeial Convention's (USP) Food Ingredients Expert Committee, the acceptance criteria for Phytic Acid (aqueous solution) include: arsenic (not more than 3 mg/kg), calcium (not more than 0.02%), chloride (not more than 0.02%), inorganic phosphorus (not more than 0.2%), lead (not more than 1 mg/kg)and sulfate (not more than 0.02%).[2]

Phytic Acid

The following limitations are found in one company's food-grade chemical specification for Phytic Acid (50% solution): 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%).[3]

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.

USE

Cosmetic

The safety of the polyol phosphates is evaluated based on data received from the United States (U.S.) FDA and the cosmetics industry on the expected use of this ingredient 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.[11] 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.[12]

According to 2017 VCRP data, the greatest use frequency is reported for Sodium Phytate, which is reported to be used in 363 cosmetic products (225 of which are leave-on products).[11] 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.[12] Further use frequency and concentration of use data are presented in Table 4.

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

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

Sodium Phytate is reported in the VCRP as being used in a perfume formulation, which may result in incidental inhalation exposure. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm, compared with pump sprays.[13,14,15,16] 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.[13,14]

The polyol phosphates reviewed in this safety assessment are not included on the European Union's list of substances that are prohibited in cosmetic products.[17]

Noncosmetic

Sodium Phytate

Sodium Phytate is used as a complexing agent for the removal of traces of heavy metal ions.[5] It is also used as the starting material in the manufacture of inositol.

Phytic Acid

After reviewing a GRAS exemption claim, the U.S. Food and Drug Administration (FDA) issued the following statement: "Based on the information provided by Tsuno, as well as other information available to FDA, the agency has no questions at this time regarding Tsuno's 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."[18]

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.[19] 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.[6]

TOXICOKINETIC STUDIES

The toxicokinetic studies summarized below are presented in Table 5.

Dermal Penetration

Animal

Sodium Phytate and Phytin

Groups of 6 female Wistar rats were treated topically with a cream supplemented with Sodium Phytate (0.4%, 1.2%, or 2%) or 2.0% Phytin. Sodium Phytate was absorbed at significantly higher amounts than Phytin. When the topical cream contained 2% Sodium Phytate, the value for urinary Phytic Acid was 66.35 ± 5.49 mg/l. When the topical cream contained 2% Phytin, the value for urinary Phytic Acid was 16.02 ± 2.61 mg/l.[20]

Human

Potassium Phytate (read-across for Sodium Phytate)

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.[21]

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Phytic Acid

When [^{14}C]-Phytic Acid was administered orally to groups of 5 male Sprague-Dawley rats, ~6% of the administered dose was recovered in the feces at 48 h post-dosing.[22] Following the oral administration of [^{3}H]-Phytic Acid 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.[23]

Groups of 12 female Wistar rats were fed Phytic Acid in the diet at doses of 11.6 g/kg dry matter (DM) and 9 g/kg DM for 12 weeks; the highest Phytic Acid concentrations were detected in the brain, and concentrations detected in other organs were 10-fold less.[24] In another study, C.B-17 SCID female mice (specific pathogen-free, bearing MDA-MB-231 breast cancer xenografts; number not stated) were dosed orally with 0.01 ml/g [^{14}C]-Phytic Acid and unlabeled Phytic Acid so that each mouse received 20 mg/kg Phytic Acid and 0.150 mCi/kg in phosphate-buffered saline. The % of the administered dose that was excreted in the urine as inositol was 0.3% , and ~10% of the administered dose was present in the feces, primarily as inositol.[25]

Human

Phytic Acid

In human subjects (number not stated), 1% to 3% of the total amount of Phytic Acid administered was excreted in the urine as Phytic Acid.[26] The results of another study indicated that 1% to 10% of the total amount of Phytic Acid ingested was excreted in the urine.[27]

Sodium Phytate, Phytic Acid, and Phytin

In a study in which 7 volunteers received Phytic Acid, Sodium Phytate, or Phytin in the diet, urinary levels of Phytic Acid increased continuously until normal values were reached and the amount of Phytic Acid excreted was not affected by the type of Phytic Acid salt that was administered.[28]

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.[3,29] 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).[3,30]

Intravenous

Sodium Phytate

The intravenous (i.v.) administration of Sodium Phytate to groups of 10 NMRI mice at doses up to 0.56 mg/g (range of doses administered within 7 minutes) yielded an LD_{50} of ~0.5 mg/g, and there were no detectable effects from infusion when the rate was not more than 0.02 mg/g/minute. When Sodium Phytate was administered i.v. to rats at lower doses of 0.035 and 0.07 mg/g, there were no detectable signs when doses were administered at a rate requiring 40 minutes for administration of the total dose. Different infusion rates were used in this study, and whether or not mortalities were observed was dependent on the infusion rate.[31]

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. Statistically significant depression of food intake and growth was observed at dietary concentrations of 5% and 10% Sodium Phytate, but not at lower concentrations.[32] 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 for 8 weeks.[33]

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 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.[34] 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.[35] In another study, dosing with Phytic Acid (2% in distilled water) was well tolerated in 10 female wild-type mice (C7BL/6J strain) treated for 70 days.[36]

Subchronic Toxicity Studies

The subchronic toxicity studies summarized below are presented in Table 8.

Oral

Phytic Acid

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.[37] Additional study results are included in the section on Carcinogenicity. In another study, 8 female Tg2576 mice and 10 C7BL/6J mice received Phytic Acid at a concentration of 2% in distilled water for 6 months. There were no consistent differences in results for control versus test animals.[36]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

The developmental and reproductive toxicity studies summarized below are presented in Table 9.

Oral

Animal

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 JcI:ICR mice. No significant effects on the incidence of external or skeletal malformations were observed at any dose of Phytic Acid. There were also no significant effects on the following: number of live fetuses, number of corpora lutea per litter, number of implantations per litter, incidence of early resorptions, or number of live fetuses per litter.[34] 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.[38]

In Vitro

Mannose-6-Phosphate (potential read-across for Sodium Mannose Phosphate)

A study was performed to establish a mannose-responsive mouse model for a congenital disorder of glycosylation (CDG-Ib) in humans that is normalized by oral mannose supplements.[39] The *Mpi* gene encodes phosphomannose isomerase (MPI), the enzyme that catalyzes the reversible interconversion of fructose-6-phosphate and mannose 6-phosphate. This is the first step in the biosynthesis of active mannose donors that are required for the biosynthesis of various glycoconjugates. Guanosine diphosphate mannose (GDP-mannose)) is the central activated mannose donor in glycosylation reactions. In humans, *Mpi* mutations impair protein glycosylation, causing CDG-Ib. In this study, the *Mpi* gene in C57BL/6 mice (number not stated) was ablated and the dams were provided with water containing mannose (3% or 10%) to rescue the anticipated defective glycosylation. The embryos were identified as $Mpi^{-/-}$ (both alleles of the *Mpi* gene knocked out). The death of embryos occurred around embryonic day 11.5 (E11.5). Providing the dams with water containing 10% mannose before mating and during development resulted in a significant increase (p value not stated) in the number of resorptions and eliminated $Mpi^{-/-}$ embryos from the E11.5 population. The death of embryos was independent of a glycosylation insufficiency. Initiating 3% mannose (n = 54) or 10% mannose supplements at E9.5 to rescue the anticipated defective glycosylation did not reduce the number of resorptions. The authors noted that these results suggest that early mannose supplementation accelerates embryonic lethality in $Mpi^{-/-}$ mice. Growth retardation and placental hyperplasia were also observed in $Mpi^{-/-}$ embryos. Greater than 90% of the $Mpi^{-/-}$ embryos failed to form yolk sac vasculature and 35% had failed chorioallantoic fusion. The results of another in vitro experiment suggested that the mannose-induced embryotoxicity was due to mannose-6-phosphate accumulation and ATP depletion. Data on the embryotoxicity of mannose from another study indicate that embryos cultured in 6 mg/ml mannose for 24 h displayed statistically significant inhibition of yolk-sac

expansion, and were smaller and less advanced than control embryos. Irregularities in the neural groove were observed in embryos cultured in 3 mg/ml or 6 mg/ml mannose for 10 h.[40]

GENOTOXICITY STUDIES

The genotoxicity studies summarized below are presented in Table 10.

In Vitro

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.[41] In the L5178Y TK+/- mouse lymphoma assay, Phytic Acid was non-genotoxic at concentrations up to 5000 µg/ml with or without metabolic activation.[42] Also, Phytic Acid (2 mg/ml) was non-genotoxic to Chinese hamster ovary cells in the chromosomal aberrations assay.[41] However, Phytic Acid (an unknown high concentration) was genotoxic in the chromosomal aberrations assay.[3]

In Vivo

Phytic Acid

In the micronucleus test involving bone marrow cells from ddY mice, Phytic Acid was non-genotoxic at an administered intraperitoneal (i.p.) dose of 30 mg/kg or 60 mg/kg.[3]

CARCINOGENICITY STUDIES

The carcinogenicity studies summarized below are presented in Table 11.

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. Renal papillomas (related to calcification and necrosis of renal papillae) were observed in 3 male and 4 female rats treated with 2.5% Phytic Acid, respectively, and in 3 female rats treated with 1.25% Phytic Acid. The organ distribution of other tumor types observed did not differ significantly from those known to occur spontaneously in the F344 strain.[37]

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 0.05% *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine, in a study involving groups of 6 male F344 rats. Sodium Phytate significantly increased the development of preneoplastic and neoplastic lesions of the urinary bladder. Potassium phytate brought about a tendency for increase in papillomas, whereas hexamagnesium phytate hydrate and Phytic Acid were without effect.[43]

ANTICARCINOGENICITY STUDIES

The anticarcinogenicity studies summarized below are presented in Table 12.

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.[44] 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.[45]

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.[46]

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.[47] 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.[48] Phytic Acid (2% in drinking water) was administered to 15 female Crl:SKH1- *hr* hairless mice prior to UVB exposure, and another group of 15 received UVB exposure only. Tumor formation monitored until week 31, and Phytic Acid + UVB exposure caused a statistically significant decrease in the skin tumor incidence, an antiphotocarcinogenic effect.[49]

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.[50] The animals received doses (in water) 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.[51] The following cell lines were used: HL60 human promyelocytic leukemia cell line, chronic myelogenous leukemia cell lines K562, AR23, and RWLeu4, and the KG1 progenitor leukemia cell line. The WST-1 tetrazolium salt (10 µl) was added to well culture plates containing 100 µl of cell suspension. The plates were evaluated after 4-h of incubation. Phytic Acid had a clear cytotoxic effect on all of the tested cell lines, with an IC_{50} of 5 mmol/l after 72 h of culture.

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

Allergenicity

Sodium Phytate

A desensitization test on erythron-allergy was performed with Sodium Phytate.[52] The term erythron-allergy refers to allergic changes (i.e. allergic hemolytic anemia) that result from exposure to red blood cell phosphatide, and the red blood cell phosphatide cephalin acts as the hapten in erythron-allergy.Rabbits (number not stated) were sensitized intravenously (i.v.) with the mixture of beef red blood cell phosphatide (10 mg) and ox serum (2 cc/kg) once daily for 4 days. At approximately 3 weeks after sensitization, Sodium Phytate (10 mg) was injected once daily for 3 days. The complete antigen of red blood cell phosphatide and ox serum (P + S) was injected i.v. 2 days after the last injection of Sodium Phytate. Anemia was not observed in the peripheral blood and erythropoiesis in the bone marrow was not affected. This result indicates that Sodium Phytate inhibited erythron-allergy. It was also determined that erythron allergy is not desensitized following a single injection of 5 mg Sodium Phytate, but that erythron-allergy is prevented following a single dose of 10 mg Sodium Phytate.

Approximately 40 days after re-injection, Sodium Phytate was injected i.v. for 3 days, and P +S was injected 2 weeks later. This procedure resulted in erythron-allergy. Thus, it was demonstrated that Sodium Phytate could not prevent erythron-allergy if reinjection with complete antigen (P+S) was not performed immediately after the injection of Sodium Phytate. Furthermore, the authors noted that the desensitization test results in this study suggested that Sodium Phytate is a partial allergen (i.e., a hapten). A hapten is defined as a molecule that is incapable, by itself, of causing a cell-mediated or humoral immune response, but can, however, combine with a larger antigenic molecule (carrier). A hapten-carrier complex can stimulate antibody production and reactive T-cells.[52]

In another experiment in the preceding study, human γ-globulin was used as the transporter. A solution of the protein protein (2% in saline) was mixed with Sodium Phytate (10 mg), and this mixture was the antigen. Rabbits (number not stated) were sensitized with the antigen i.v. once daily for 4 days. There was no evidence of anemia or hematological changes after sensitization. Reinjection of the antigen i.v. once daily for 3 days, began 29 days after sensitization was observed. Soon (time period not stated) after reinjection, the red blood cell counts in the periphery began to decrease rapidly (hemolytic anemia) and were ~ 1/3 to 1/4 of the counts prior to reinjection. Furthermore, as the anemia progressed, the reticulocyte count began to increase. The author noted that the allergic changes caused by Sodium Phytate occurred as an allergic hemolytic anemia.[52]

DERMAL IRRITATION AND SENSITZATION STUDIES

Skin irritation and sensitization data on the polyol phosphates reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

CLINICAL STUDIES

Other Clinical Reports

Phytic Acid

Healthy women (15 young and 14 elderly) consumed low-Phytic Acid diets (young women: 682 mg Phytic Acid/day; elderly women: 782 mg phytate/day) or a high-Phytic Acid diet (young women: 1587 mg Phytic Acid/day; elderly women: 1723 mg Phytic Acid/day) for a period of 10 days.[53] Overt signs of toxicity were not reported in the study results. In a similar study, healthy women (14 young and 14 elderly) consumed low-Phytic Acid diets (young women: 681 mg Phytic Acid/day; elderly women: 782 mg phytate/day) or a high-Phytic Acid diet (young women: 1584mg Phytic Acid/day; elderly women: 1723 mg Phytic Acid/day) for a period of 10 days. Again, overt signs of toxicity were not reported in the study results. A considerable amount of dietary phytate was degraded in the human gut.[54]

Mannose-6-Phosphate (read-across for Sodium Mannose Phosphate)

After surgical repair of the tendon, patients were randomized to receive either a single 300 µl administration of 600 mM mannose-6-phosphate in phosphate buffered saline (pH 7.0) into the tendon sheath (13 patients), or standard care without mannose-6-phosphate (11 patients).[55] The recruited patients were under review for 26 weeks, during which time they received standardized post-operative hand therapy. Assessments of safety and performance were made by site investigators (surgeons and hand therapists) who were not party to the surgical procedure. Throughout the study, timed assessments of safety, local tolerability and performance of mannose-6-phosphate were made. Although some patients (numbers not stated) treated with mannose-6-phosphate experienced minor swelling, erythema and burning sensations, these findings were not statistically significant when the mannose-6-phosphate treatment group and the standard treatment group were compared.

SUMMARY

The safety of 10 polyol phosphates in cosmetics is reviewed in this safety assessment: According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Sodium Phytate, Phytic Acid, and Trisodium Inositol Triphosphate are reported to function as chelating agents in cosmetic products.[1] Sodium Phytate and Phytic Acid are also reported to function as oral care agents, and, Trisodium Fructose Diphosphate, as an antioxidant in cosmetic products. The remaining ingredients have the skin conditioning agent function in common, except for Xylityl Phosphate, which functions as an antiacne agent, antidandruff agent, deodorant agent, and exfoliant.

Sodium Phytate, Phytic Acid, and Trisodium Inositol Triphosphate are reported to function as chelating agents in cosmetic products. Sodium Phytate and Phytic Acid are also reported to function as oral care agents, and Trisodium Fructose Diphosphate as an antioxidant, in cosmetic products. The remaining ingredients have the skin conditioning agent function in common, except for Xylityl Phosphate, which functions as an antiacne agent, antidandruff agent, deodorant agent, and exfoliant. Functioning as an antiacne or antidandruff agent is not a cosmetic use and, therefore, the Panel will not evaluate safety in relation to those uses.

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

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

According to 2017 VCRP data, the greatest use frequency is being reported for Sodium Phytate, which is being used in 363 cosmetic products (225 of which are leave-on products). The results of a concentration of use survey conducted in 2016-2017 indicate that Phytic Acid is being used at concentrations up to2% in leave-on products (body and hand products [not spray]), which is the greatest use concentration that is being reported for the polyol phosphates reviewed in this safety assessment.

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

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

LD_{50} values of 480 mg/kg (females) and 400 to 500 mg/kg (males) were reported in an acute oral toxicity study involving F344 rats. In an acute oral toxicity study involving 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 JcI:ICR that received oral doses up to 315 mg/kg/day on gestation days 7 to 15. Groups of 8 male Wistar rats were fed dietary concentrations of 0.1% to 1% Phytic Acid for 20 days. No effects on organ weight were noted, but the concentration of T_3 in the serum was statistically significantly lower at all administered Phytic Acid concentrations. Dosing with Phytic Acid (2% in distilled water) was well-tolerated in female C7BL/6J mice treated for 70 days.

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

animals in a study in which 8 female Tg2576 mice and 10 C7BL/6J mice received Phytic Acid at a concentration of 2% in distilled water for 6 months.

Three different concentrations of 50% Phytic Acid solution (equivalent to doses of 80, 155, or 315 mg/kg/day) were administered orally to groups of 21 to 24 JcI:ICR mice on gestation days 7 to 15. No significant effects on the incidence of external or skeletal malformations were observed at any dose of Phytic Acid. The treatment of groups of 30 male albino rats (*Rattus norvegicus*) with Phytic Acid had an ameliorative effect on the pathological (i.e., degeneration with absence of spermatozoa) and hormonal alterations induced by aflatoxin B1 injection. Rat embryos cultured in 6 mg/ml mannose for 24 h displayed statistically significant inhibition of yolk-sac expansion, and were smaller and less advanced than control embryos. Irregularities in the neural groove were observed in embryos cultured in 3 mg/ml or 6 mg/ml mannose for 10 h. Results from another study (mouse embryos) suggested that the embryotoxicity caused by mannose may be due to the accumulation of mannose-6-phosphate.

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

Renal papillomas (related to calcification and necrosis of renal papillae) were observed in a very small number of male and female F344 rats in groups of 120 animals treated orally with 1.25% or 2.5% Phytic Acid in drinking water. The organ distribution of other tumor types did not differ significantly from those known to occur in F344 rats. Sodium Phytate (2% in the diet) was classified as a promoter of urinary bladder carcinogenesis. The results of animal studies indicate that Phytic Acid is antiphotocarcinogenic as well as anticarcinogenic and that Sodium Phytate is anticarcinogenic. Anti-inflammatory activity, cytotoxicity, and neuroprotective effects have also been associated with Phytic Acid treatment.

Althouth not statistically significant findings, patients treated with mannose-6-phosphate (read-across for Sodium Mannose Phosphate) have experienced minor swelling, erythema, and burning sensations. Skin irritation and sensitization data on the polyol phosphates reviewed in this safety assessment were not found in the published literature, nor were these data submitted. However, data relating to the allergenicity of Sodium Phytate were found. The results of a desensitization test involving repeated i.v. doses of Sodium Phytate (10 mg) in sensitized rabbits indicated inhibition of erythron-allergy (allergic hemolytic anemia). Also, erythron-allergy was not desensitized following a single injection of 5 mg of Sodium Phytate, but was prevented following a single injection of 10 mg of Sodium Phytate. In another i.v. dosing experiment involving rabbits sensitized with repeated injections of a 2% γ-gobulin (in saline) solution mixed with Sodium Phytate (10 mg), the results indicated that the allergic changes caused by Sodium Phytate occurred as an allergic hemolytic anemia.

Overt signs of toxicity were not reported in studies in which healthy women consumed low-Phytic Acid diets or a high-Phytic Acid diet for a period of 10 days.

DATA NEEDS/INFORMATION SOUGHT

CIR is seeking additional data on polyol phosphates described in this report as used in cosmetic formulations.

Particularly, CIR is seeking:

1. method of manufacture;
2. impurities data;
3. toxicological data, specifically dermal toxicity data on these cosmetic ingredients at use concentrations, in order to help the CIR Expert Panel assess the safety of the use of these ingredients in cosmetics;
4. dermal irritation and sensitization data, and
5. any available pertinent information that will strengthen this safety assessment.

TABLES

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

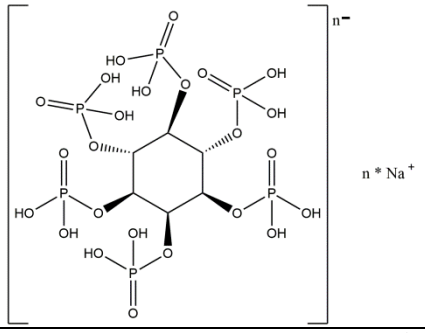
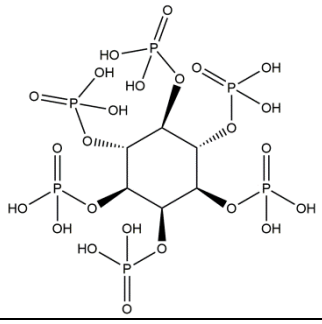
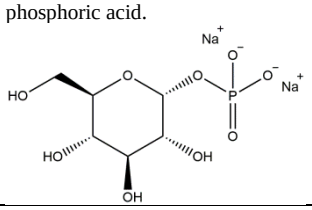
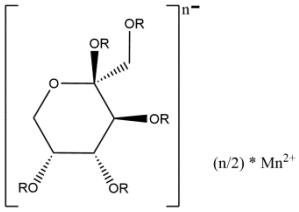
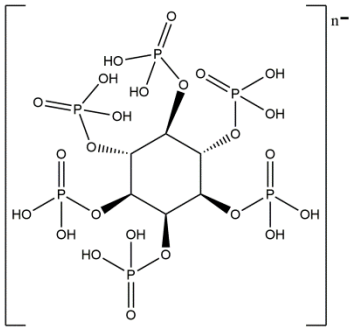
Ingredient CAS No.	Definition & Monomer Structures	Function(s)
Sodium Phytate 14306-25-3 34367-89-0	Sodium Phytate is the complex sodium salt of Phytic Acid.  	Chelating Agents; Oral Care Agents
Phytic Acid 83-86-3	Phytic Acid is the hexaphosphoric acid ester of inositol. It conforms to the formula: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

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

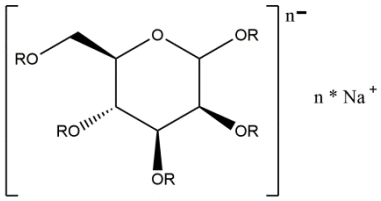
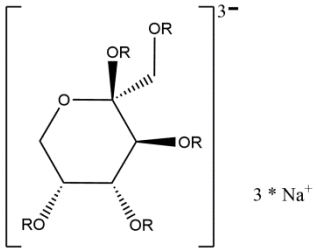
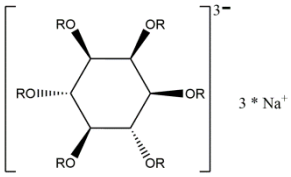
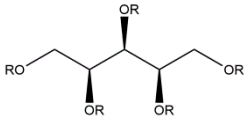
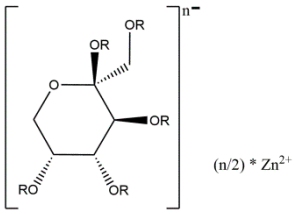
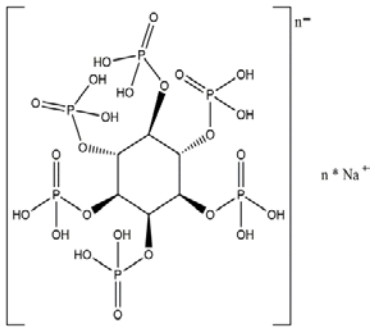
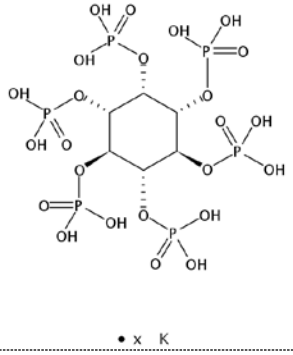
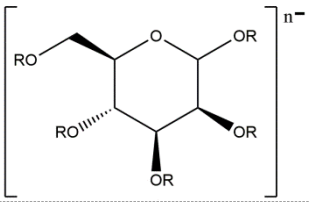
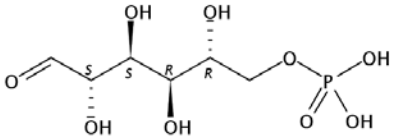
Ingredient CAS No.	Definition & Monomer Structures	Function(s)
Sodium Mannose Phosphate 70442-25-0	Sodium Mannose Phosphate is the sodium salt of a complex mixture of esters of phosphoric acid and Mannose.  *wherein R is phosphate in at least one instance and hydrogen in all other instances*	Skin-Conditioning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

Table 2. Read-across Justifications

	Target Material	Read-Across Material
Name	***Sodium Phytate***	***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)[5]	1117.12.[56]
log K_{ow} (estimated)	-6.54. [7]	Not found

Name	***Sodium Mannose Phosphate***	***Mannose-6-phosphate***
CAS No(s).	70442-25-0	3672-15-9
Structure		
read-across endpoints	• developmental and reproductive toxicity (*in vitro)* • tendon irritation/inflammation	
justification	chemical properties, physical properties and metabolism are expected to be similar for these two chemicals	
Examples:		
Formula weight (Da)	282.12 (mono-sodium mono-phosphate)[9]	260.14.[57]
log K_{ow} (estimated)	-6.38. [7]	Not found

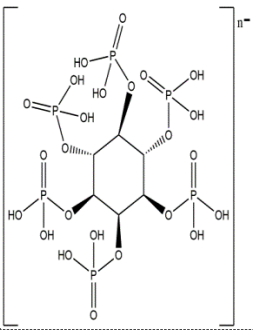
Name	***Phytin***	Phytic acid hexamagnesium salt *n*-hydrate
CAS No(s).		
Structure		Not found in the published literature
read-across endpoints	• tumor promotion	
justification	Because Phytin is defined as the calcium and magnesium salt of Phytic Acid, data on phytic acid hexamagnesium salt n-hydrate may be useful in the safety assessment of Phytin.	

Table 3. Physical and Chemical Properties of Polyol Phosphates

Property	Value	Reference
Sodium Phytate		
Physical form and/or color	Hygroscopic powder	6
Formula weight (Da)	877.86 (nonasodium)	5
Solubility	Soluble in water, with neutral reaction	5
log K_{ow}	-6.54 (est.)	7
Phytic Acid		
Physical form and/or color	Syrupy, straw-colored liquid	5
Molecular weight (Da)	660	8
Solubility	Soluble in water containing alcohol-ether mixtures; very slightly soluble in absolute alcohol and methanol; practically insoluble in anhydrous ether, benzene, and chloroform	5
Miscibility	Miscible with water, 95% alcohol, and glycerol	5
Density (g/l)	1.58	6
log K_{ow}	-1.6	8
pH (10% aqueous solution)	0.86	5
Disodium Glucose Phosphate		
Formula weight (Da)	304.10	9
log K_{ow}	-3.79 (est.)	7
Manganese Fructose Diphosphate		
Formula weight (Da)	393.04	9
log K_{ow}	-3.12 (est.)	7
Phytin		
Physical form and/or color	White, odorless powder	5
Solubility	Poor solubility in water; soluble in dilute acids	5
Formula weight (Da)	720.38 (mono-calcium mono-magnesium)	9
log K_{ow}	-10.11 (est.)	7
Sodium Mannose Phosphate		
Formula weight (Da)	282.12 (mono-sodium mono-phosphate)	9
log K_{ow}	-6.38 (est.)	7
Trisodium Fructose Diphosphate		
Formula weight (Da)	406.06	9
log K_{ow}	-9.99 (est.)	7
Trisodium Inositol Triphosphate		
Formula weight (Da)	486.04	9
log K_{ow}	-12.77 (est.)	7
Xylityl Phosphate		
Molecular weight (Da)	232.12 (monophosphate)	9
log K_{ow}	-3.23 (est.)	7
Zinc Fructose Diphosphate		
Formula weight (Da)	403.48 (monozinc)	9
log K_{ow}	-4.80 (est.)	7

Table 4. Frequency and Concentration of Use According to Duration and Type of Exposure.[11,12]

	Sodium Phytate		Phytic Acid		Sodium Mannose Phosphate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	363	0.0099-0.5	98	0.003-2	34	0.1
Duration of Use						
Leave-On	225	0.0099-0.5	69	0.003-2	31	0.1
Rinse off	131	0.025-0.3	29	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	1	0.5	NR	0.3	NR	NR
Incidental Inhalation- Sprays	1;96*	0.05-0.3*	20*	0.005-0.05*	12*	NR
Incidental Inhalation- Powders	1**	NR	NR	NR	NR	0.1**
Dermal Contact	310	0.0099-0.3	77	0.003-2	34	0.1
Deodorant (underarm)	NR	NR	1	NR	NR	NR
Hair - Non-Coloring	52	0.05-0.3	21	0.005	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	44	0.3-0.5	3	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

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

**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. Toxicokinetic 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. 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.[20]
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. 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, urinary excretion of Phytic Acid increased by 54% when compared to controls. Thus, Phytic Acid was absorbed through the epidermis and dermis, entered the blood, and increased the urinary excretion of Phytic Acid.[21]
Absorption, Distribution, Metabolism, and Excretion Studies		

Table 5. Toxicokinetic Studies

Ingredient	Animals or Subjects/Protocol	Results
Animal Studies		
[^{14}C]-Phytic Acid	Administered orally to male Sprague-Dawley rats (groups of 5)	~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).[22]
[^{3}H]-Phytic Acid	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.[23]
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.[24]
[^{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.[25] Exogenous Phytic Acid rapidly dephosphorylated to inositol.[25]
[^{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.[25]
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.[26]

Table 5. Toxicokinetic 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.[27]
Phytic Acid, Sodium Phytate, and Phytin	Seven volunteers (3 males, 4 females) were on a Phytic Acid-poor 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-poor diet, subjects became deficient in Phytic Acid; 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.[28]

Table 6. Acute Toxicity Studies

Ingredient	Animals/Protocol	Results
Oral Studies		
Phytic Acid	Jcl:ICR mice (number not stated)	LD_{50} values of 1150 mg/kg (females) and 900 mg/kg (males).[3,29]
Phytic Acid	F344 rats (number not stated)	LD_{50} values of 480 mg/kg (females) and 400 to 500 mg/kg (males).[3,30]
Intravenous Studies		
Sodium Phytate	Groups of 10 or 20 Sprague-Dawley rats or NMRI mice received i.v. doses ranging from 0.035 to 0.56 mg/g body weight at infusion rates requiring 3, 10, 2,or 40 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. [31] 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. [31]

Table 7. Short-Term Toxicity Studies

Ingredient	Animals	Protocol	Results
Oral Studies			
Phytic Acid (50% solution administered as 0%, 1.6%, 3.1%, or 6.31% aqueous solution)	Groups of 21 to 24 JcI:ICR mice (in developmental and reproductive toxicity study summarized in report)	Groups received the 50% solution as oral doses (gavage) of 0%, 1.6%, 3.1%, or 6.31% concentrations (equivalent to 0, 80, 155, or 315 mg/kg body weight/day) on gestation days 7 to 15. The dose volume administered was 10 ml/kg/day.	No maternal mortalities in control or 80 mg/kg/day group. Two of 22 dams (9.1%) in the 155 mg/kg/day group and 15 of 24 dams (62.5%) in the 315 mg/kg/day group died during the study. No significant differences in rate of maternal body weight gain reported for either dose 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. [34]
Phytic Acid (2% in distilled drinking water)	10 female wild type mice (C7BL/6J strain)	10 animals treated with Phytic Acid for 70 day period. 10 control animals received distilled drinking water	Dosing with Phytic Acid well tolerated.[36]
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. [35]
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.[32]

Table 7. Short-Term Toxicity Studies

Ingredient	Animals	Protocol	Results
Sodium Phytate (0.1% and 1% in diet)	Groups of 10 male diabetic KK mice	Groups received Phytic Acid 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.[33]

Table 8. Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Oral Studies			
Phytic Acid (2% in distilled drinking water)	8 female Tg2576 mice and 10 C7BL/6J mice	Animals treated with Phytic Acid for 6 months. Seven control Tg2576 mice and 12 control C7BL/6J mice received distilled drinking water	There were no consistent differences between animals treated with distilled drinking water or 2% Phytic Acid.[36]
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. [37]

Table 9. Developmental and Reproductive Toxicity Studies

Ingredient	Animals or Subjects/Protocol	Results
Oral Studies		
Phytic Acid (50% solution administered as 0%, 1.6%, 3.1%, or 6.31% aqueous solution)	Groups of 21 to 24 JcI:ICR mice received the 50% solution as oral doses (gavage) of 0%, 1.6%, 3.1%, or 6.31% concentrations (equivalent to 0, 80, 155, or 315 mg/kg body weight/day) on gestation days 7 to 15. The dose volume administered was 10 ml/kg/day. Fetuses removed on gestation day 18 and examined for external and skeletal anomalies.	No significant effects on the number of live fetuses, number of corpora lutea per litter, number of implantations per litter, incidence of early resorptions, and number of live fetuses per litter. Significant increase in incidence of late resorption in 80 mg/kg/day group compared to control; however, relevance of these findings is questionable because the standard deviation for the mean incidence values was larger than the actual mean (i.e., 3.8 ± 4.2). No significant effects on late resorption observed in 155 mg/kg/day and 315 mg/kg/day groups. Fetal body weights significantly decreased, in dose-dependent manner, in males dosed with Phytic Acid. Significant decrease in fetal body weight was reported in females of 155 mg/kg/day 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.[34]
Phytic Acid	Study to evaluate enhancement of aflatoxin B1-induced reproductive toxicity by Phytic Acid. Groups of 30 male albino rats (*Rattus norvegicus*): Group 1 injected with 300 µg/kg aflatoxin B1 once every 3 days for 15 days; Group 2 injected with 300 µg/kg aflatoxin B1 once every 3 days for 15 days and treated simultaneously with Phytic Acid (dose not stated) daily for another 15 days; Group 3, treated daily with Phytic Acid (40 mg/kg) for 15 days; Group 4 (control), injected with sterile phosphate buffer saline solution.	Aflatoxin B1 induced histopathological alterations in the seminiferous tubules and whole nuclei of treated-testes (degeneration in seminiferous tubules with absence of spermatozoa); testis absolute weight was significantly decreased. Treatment with Phytic Acid had marked regenerative effect upon the histopathologic features of the seminiferous tubules. Administration of Phytic Acid to aflatoxin B1-intoxicated rats induced marked ($P < 0.05$) amelioration of the reduced testosterone concentration caused by aflatoxin B1. Phytic Acid had an ameliorative effect on the pathological and hormonal alterations induced by aflatoxin B1.[38]
In Vitro Study		
mannose-6-phosphate (read-across for Sodium Mannose Phosphate)	Embryos (from C57BL/6 mice dosed orally with 3% or 10% mannose in water. The embryos were identified as *Mpi*$^{-/-}$ (both alleles of the *Mpi* gene knocked out).	Mannose was teratogenic to mouse embryos. The toxicity appears to have been due to the accumulation of mannose-6-phosphate.[39]
mannose-6-phosphate (read-across for Sodium Mannose Phosphate) resulting from administration of mannose	Rat embryos (from 9.5 days of gestation) cultured in 3 mg/ml (1.7×10^{-2} M) or 6 mg/ml (3.3×10^{-2} M) mannose for 10 h, 24 h, or 48 h.	3 mg/ml or 6 mg/ml mannose 48- h cultures displayed inhibition of expansion of the yolk sac and were smaller than the control embryos. Mannose-treated embryos also displayed delayed development, according to morphological criteria, and a range of abnormalities that included abnormalities of neural tube. Embryos cultured in 6 mg/ml mannose for 24 h displayed statistically significant inhibition of yolk-sac expansion, and were smaller and less advanced than control embryos. Abnormalities also observed in embryos cultured in 3 mg/ml or 6 mg/ml mannose for 10 h; embryos at the neural groove stage displayed irregularities in neural groove.[40]

Table 10. 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.[41]
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. [42]
Phytic Acid (2 mg/ml)	Chinese hamster ovary cells. Chromosomal aberrations assay	Non-genotoxic.[41]
Phytic Acid (high concentration [not stated])	Chinese hamster ovary cells. Chromosomal aberrations assay	Genotoxic.[3]
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.[3]

Table 11. 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.[37]
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.[43]

Table 12. Anticarcinogenicity Studies

Ingredient	Animals/Protocol	Results
Dermal Studies		
Phytic Acid (0.1 mg, 1 mg, or 5 mg dose)	Groups of 15 female Swiss albino mice in 30-week study. DMBA applied to dorsal skin weekly, immediately followed by topical application of Phytic Acid	Phytic Acid inhibited skin tumor development in dose-dependent manner.[44]
Phytic Acid (4% in cream)	8 female Crl:SKH1-*hr* hairless mice treated for 3 days with Phytic Acid (100 mg 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.[45]
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.[46]
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.[47]
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.[48]

Table 12. Anticarcinogenicity Studies

Ingredient	Animals/Protocol	Results
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.[49]

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