International Journal of Toxicology
2024, Vol. 43(Supplement 4) 78S–107S

DOI: 10.1177/10915818241259699
journals.sagepub.com/home/ijt
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# Safety Assessment of Polyol Phosphates as Used in Cosmetics

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## Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 10 polyol phosphates. 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.

## Keywords

Cosmetic Ingredient Review, Expert Panel for Cosmetic Ingredient Safety, Safety, Cosmetic Ingredient, Polyol Phosphates, 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

## Introduction

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

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

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Sodium Phytate, Phytic Acid, and Trisodium Fructose Diphosphate 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, Manganese Fructose Diphosphate and Trisodium Fructose Diphosphate are reported to function as antioxidants 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 the Panel evaluates, is available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline).

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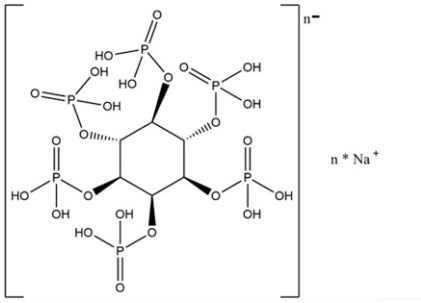
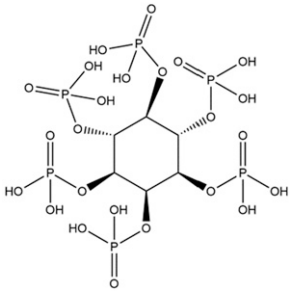
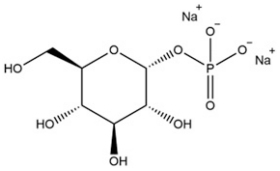
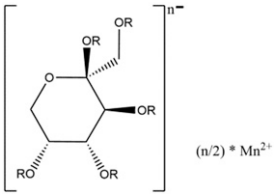
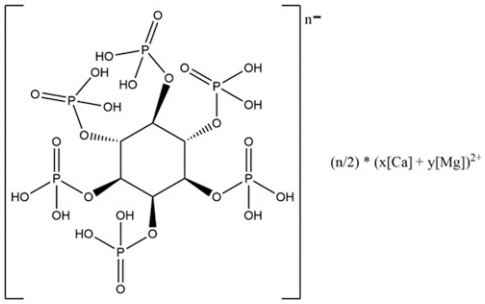
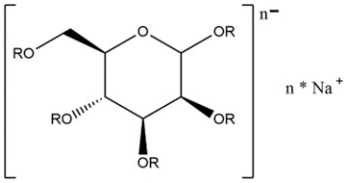
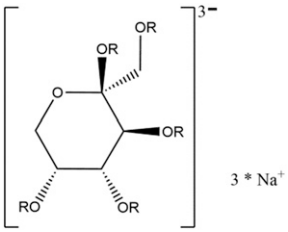
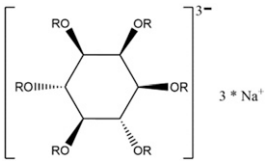
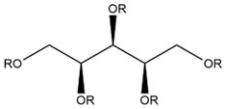
**Table 1.** Definitions, Idealized Structures, and Functions of the Ingredients in This Safety Assessment.[1; CIR Staff]

| 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 |

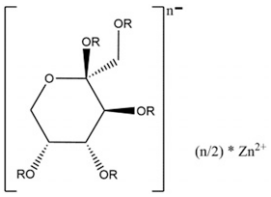
*(continued)*

**Table 1.** (continued)

| Ingredient CAS No. | Definition & Monomer Structures | Function(s) |
|---|---|---|
| Phytin 3615-82-5 | Phytin is the calcium and magnesium salt of Phytic Acid.<br>  <br> | Humectants; Skin-Conditioning Agents – Emollient; Skin-Conditioning Agents – Humectant |
| Sodium Mannose Phosphate 70442-25-0 | Sodium Mannose Phosphate is the sodium salt of a complex mixture of esters of phosphoric acid and Mannose.<br>  <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 81028-91-3 | Trisodium Fructose Diphosphate is a trisodium 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; 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><br>[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.<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 |

*(continued)*

**Table 1.** (continued)

| Ingredient CAS No. | Definition & Monomer Structures | Function(s) |
|---|---|---|
| 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 |

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 (inositol or a monosaccharide or a "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, or cyclic furanose and/or pyranose forms, like many sugars do. Some of these ingredients are naturally occurring. Indeed, Phytic Acid and other particular inositol phosphates (Figure 2) are present in practically all mammalian cells.[2]

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

### Chemical and Physical Properties

Properties of polyol phosphates are presented in Table 3.[3-7] Sodium Phytate is highly 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]

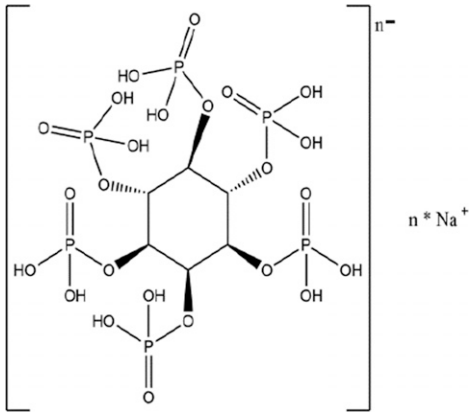
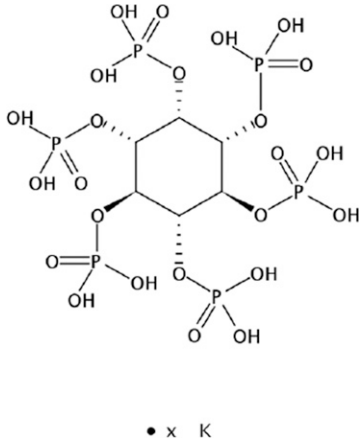
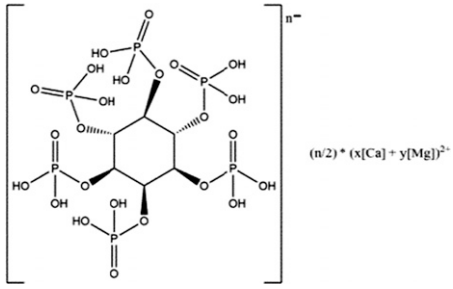
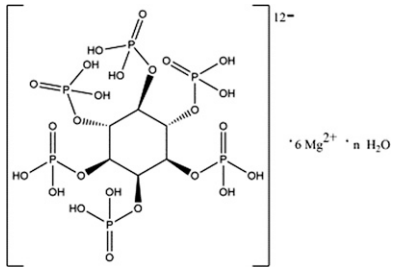
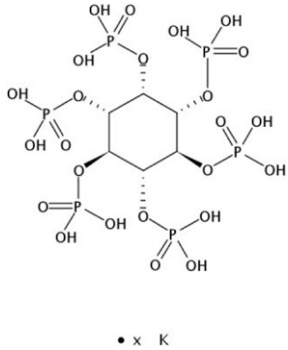
Another reported method for the production of Phytic Acid begins with the hydrochloric acid leaching of bran, which is followed by filtration, neutralization with sodium hydroxide, and water scrubbing.[11] The resulting crude phytin paste is acidified and then subjected to positive ion exchange, condensation,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

*Sodium Mannose Phosphate.* Sodium Mannose Phosphate is manufactured by enzymatic reaction from pyrophosphate and mannose.[12] The reaction medium is then stabilized by denaturing the enzyme. This step is followed by purification of the medium.

### 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]

**Table 2.** Read-Across Justifications.

| | Target Material(s) | Read-Across Source 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)[79] |
| log $K_{ow}$ (estimated) | −6.54. [5] | −26.31[80] |
| 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 | |

*(continued)*

**Table 2.** (continued)

| Name | *potassium phytate* | |
|---|---|---|
| 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) |

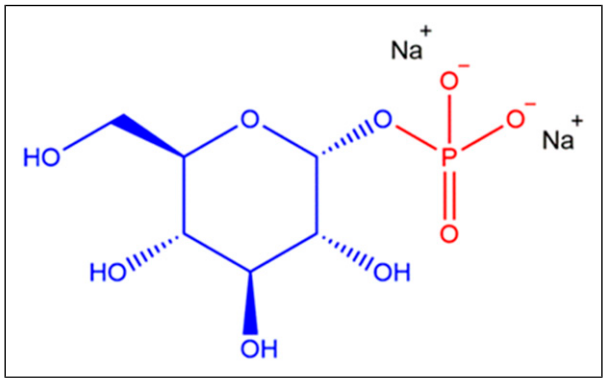



**Figure 1.** Disodium Glucose Phosphate, example of a saccharide phosphate.

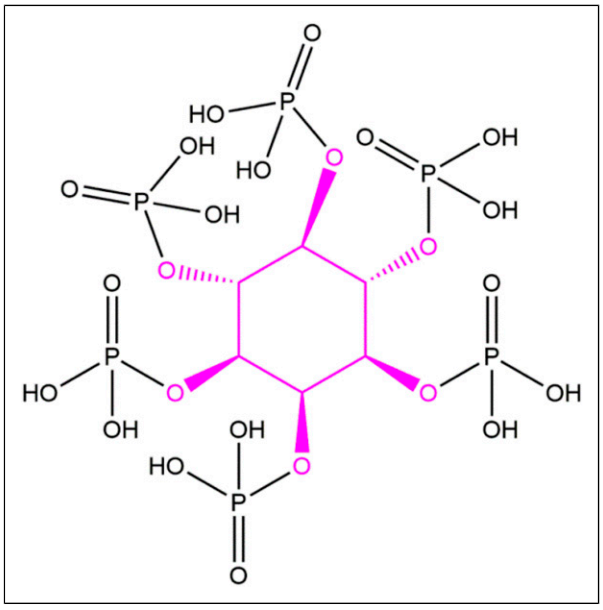



**Figure 2.** Phytic Acid, example of an inositol phosphate.

## 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 (surmised via analysis of lead sulfide precipitate; <0.002%), lead (<0.0001%), arsenic (<0.0002%), 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.[13] Results indicated that the levels of the following heavy metals were below the detection limits (≤0.0004% to ≤0.0001%): 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.

*Sodium Mannose Phosphate.* Possible impurities (0.1% to 0.5%) of Sodium Mannose Phosphate are: phosphate, sodium salt; pyrophosphate, sodium salt; sodium chloride; and magnesium and ammonium ions.[12]

# 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.[14] 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.[15]

**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) | 857.86 (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 monophosphate) | 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 (mono-zinc) | 7 |
| log $K_{ow}$ | −4.80 (est.) | 5 |

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).[14] 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.[15] 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

**Table 4.** Frequency and Concentration of Use According to Duration and Type of Exposure.[14,15]

| | 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 exposuretype uses may not equal the sum of total uses.

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.[16-19] 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.[16,17]

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.[20]

### 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."[21]

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.[22] 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

Further details for the toxicokinetic studies summarized below are presented in Table 5.

### Dermal Penetration

#### Human

*Potassium Phytate (read-across source for Sodium Phytate, Phytic Acid, and Phytin).* In a study involving 20 healthy volunteers

**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.[24] |
| 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 provided urine samples. Urine samples were collected at day 7 of treatment to evaluate phytic acid excretion (2-h urine). In phase 2, subjects continued with the Phytic Acid-poor diet and treated topically (1400 $cm^2$ area of skin, applied twice per day) with 10 g of standard moisturizing gel containing 4% potassium phytate; urine samples provided. Six control subjects received Phytic Acid-poor diet for 15 days | Following topical application of gel, an increase in the urinary excretion of Phytic Acid (54% increase) was observed over a 2-h period. On day 0, the mean urinary excretion of phytic Acid was ~0.10 mg, and had increased to a value that was between 0.15 mg and 0.2 mg by day 7. Thus, Phytic Acid was absorbed through the epidermis and dermis, entered the blood, and increased the urinary excretion of Phytic Acid.[23] |
| 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).[25] |
| [$^{3}$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.[26] |

*(continued)*

**Table 5.** (continued)

| Ingredient | Animals or Subjects/Protocol | Results |
|---|---|---|
| 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 ($5.89 \times 10^{-2}$ (standard error (SE) $5.7 \times 10^{-3}$ mg/g DM). Concentrations detected in kidneys, liver and bone were similar to each other ($1.96 \times 10^{-3}$ (SE $0.20 \times 10^{-3}$), $3.11 \times 10^{-3}$ (SE $0.24 \times 10^{-3}$), and $1.77 \times 10^{-3}$ (SE $0.17 \times 10^{-3}$) mg/g DM, respectively), and were 10-fold less than those detected in brain.[27] |
| [$^{14}$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.[28] Exogenous Phytic Acid rapidly dephosphorylated to inositol.[28] |
| [$^{14}$C]-Phytic Acid | C.B-17 SCID female mice (specific pathogen free, 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.[28] |
| 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.[29] |
| 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.[30] |
| 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.[31] |

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 was excreted into the urine. Urine samples were collected at day 7 of treatment.[23]

## *Absorption, Distribution, Metabolism, and Excretion (ADME)*

### *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.[24] 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.[25] 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.[26]

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.[27] 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.[28] 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.[29] The results of another study indicated that 1% to 10% of the total amount of Phytic Acid ingested was excreted in the urine.[30]

*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.[31] 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.[30]

*Phytate (cation not declared; read-across source 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.[32] 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.[33] 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.[34,35] Phytate degradation may result from the activities of dietary phytase, intestinal mucosal phytase, or phytase that is produced by the small intestinal microflora.[32] Mucosal phytase in the human small intestine seems to play a minor role when compared to dietary phytase for phytate hydrolysis.[36] Phytate degradation is also thought to occur in the colon, due to the action of microbial phytase originating from colonic bacteria.[35]

## Toxicological Studies

*Acute Toxicity Studies.* Additional details for the acute toxicity studies summarized below are provided 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.[9,37] $LD_{50}$ 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).[9,38]

### 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.[39] 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

**Table 6.** Acute Toxicity Studies.

| Ingredient | Animals/Protocol | Results |
|---|---|---|
| Oral Studies | | |
| Phytic Acid | Jcl:ICR mice (number not stated) | $LD_{50}$ values of 1150 mg/kg (females) and 900 mg/kg (males).[9,37] |
| Phytic Acid | F344 rats (number not stated) | $LD_{50}$ values of 480 mg/kg (females) and 400 to 500 mg/kg (males).[9,38] |
| Intravenous Studies | | |
| Sodium Phytate | Groups of 10 or 20 Sprague-Dawley rats or NMRI mice received i.v. doses ranging from 0.035 to 0.56 mg/g body weight at infusion rates ranging from 2.5 to 20 minutes. | Collectively, the data for mice demonstrate that there were no detectable effects from infusion for any of the time periods studied if the infusion rate was not more than 0.02 mg/g/min, while infusion rates above 0.1 mg/g/minute were tolerated for only 2.5 minutes, and were essentially 100% fatal when continued for 5 minutes or more. When the infusion rate was varied so that a range of doses was administered (to groups of 10 mice) within a fixed time of 7 minutes, a classical mortality rate distribution with dose was observed, yielding an $LD_{50}$ of ~0.5 mg/g. [39]<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. [39] |

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 detailed further 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.[40] 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.[41]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.[9,42] 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.[43]

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.[44] All rats that received 10% Phytic Acid and all males and 1 female that received 5% Phytic Acid died before the end of the experiment. The 108-week oral carcinogenicity study is summarized in the 'Carcinogenicity' 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.[45]

*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.[45] 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.

**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 Jcl: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.[9,42] |
| Phytic Acid (up to 10% in drinking water) | Groups of 20 (10 males, 10 females per group) F344 rats | 12-week dose range-finding study (for carcinogenicity study, summarized later in report). Test substance administered daily | All rats given 10% Phytic Acid and all males and 1 female given 5% Phytic Acid died before the end of the experiment. In groups given 1.25% or 2.5% Phytic Acid, the reduction in body weight was <10% when compared to controls.[44] |
| Phytic Acid (2% in distilled drinking water) | 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.[45] |
| 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. [43] |
| 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.[40] |
| 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.[41] |

**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 Jcl: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 ± 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.[9,42] |
| 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.[46] |

## *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.[9,42] 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.[42] 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.[46] 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.[46]

## *Genotoxicity Studies*

The genotoxicity studies summarized below are detailed further in Table 9.

### *In Vitro*

*Sodium Phytate.* The genotoxicity of a Sodium Phytate trade name material consisting of 50% water, 1% ethanol, and approximately 49% Sodium Phytate was evaluated in

**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.[48] |
| 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. [49] |
| Phytic Acid (2 mg/ml) | Chinese hamster ovary cells. Chromosomal aberrations assay | Non-genotoxic.[48] |
| Phytic Acid (high concentration [not stated]) | Chinese hamster ovary cells. Chromosomal aberrations assay | Genotoxic.[9] |
| Sodium Phytate trade name material containing 50% water, 1% ethanol, and approximately 49% Sodium Phytate (in deionized water, doses up to 4995 μg/plate) | *S. 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.[47] |
| Sodium Phytate trade name material containing 50% water, 1% ethanol, and approximately 49% Sodium Phytate (in deionized water, doses up to 5013 μg/plate) | *S. 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.[47] |
| Sodium Mannose Phosphate | *S. typhimurium* strains: TA98, TA100, TA1535, and TA1537. *Escherichia coli* strain WP2 *uvr*A. Ames test with and without metabolic activation | Non-genotoxic.[50] |
| 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. prior to harvesting cells | Non-genotoxic.[9] |

the Ames test using the following *Salmonella typhimurium* strains: TA97a, TA98, TA100, TA102, and TA1535.[47] 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.[48] In the L5178Y TK+/− mouse lymphoma assay, Phytic Acid was non-genotoxic at concentrations up to 5000 μg/ml with or without metabolic activation.[49] Also, in chromosomal aberrations assays using Chinese hamster ovary (CHO) cells, 2 mg/ml Phytic Acid was non-genotoxic,[48] 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.[50] 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 when administered intraperitoneally (i.p.) as 4 doses of 30 mg/kg or as a single 60 mg/kg dose.[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

**Table 10.** Carcinogenicity Studies.

| Ingredient | Animals/Protocol | Results |
|---|---|---|
| Oral Carcinogenicity Study | | |
| Phytic Acid (1.25% or 2.5% in drinking water) | Groups of 120 (60 males, 60 females) F344 rats treated for 108 weeks | Dose-dependent reduction in mean final body weights. Necrosis and calcification of renal papillae also reported. Renal papillomas in 3 male and 4 female rats treated with 2.5% Phytic Acid, and in 3 female rats treated with 1.25% Phytic Acid. Development of papillomas appeared to have been related to calcification and necrosis of renal papillae. Many other types of tumors developed in all groups (controls included); however, the organ distribution of the neoplasms and histological characteristics did not differ significantly from those known to occur spontaneously in the F344 strain.[44] |
| Tumor Promotion Study | | |
| Phytic Acid, Sodium Phytate, potassium phytate, or hexamagnesium phytate hydrate (similar to magnesium phytate; potential read-across for Phytin). Each chemical added to diet as 2% supplement. | Male F344 rats (15 to 16 per group). Effects of dietary Phytic Acid and its salts on promotion stage of two-stage urinary bladder carcinogenesis examined. Initiation by exposure to 0.05% N-butyl-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.[51] |

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

#### *Tumor Promotion*

*Phytic Acid, Sodium Phytate, and hexamagnesium phytate hydrate (read-across source 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.[51] 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.[52] When 8 female Crl:SKH1-*hr* hairless mice were treated with 4% Phytic Acid cream (100 mg applied to dorsum), followed by mid-wavelength ultraviolet light (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.[53]

#### *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

**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.[52] |
| 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.[53] |
| 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.[54] |
| 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.[55] |
| 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.[56] |
| 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.[57] |

antineoplastic (reduction in tumor prevalence, frequency, and size) for large intestinal cancer in a dose-dependent manner.[54]

*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.[55] 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.[56] 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 was monitored until week 31, and concomitant administration of Phytic Acid during UVB exposure caused a statistically significant decrease in the skin tumor incidence, an anti-photocarcinogenic effect.[57]

## 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.[58] 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.[59] 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.[60] Cells of a normal cell line (BALB/c 3T3 cells) exhibited no increased sensitivity towards Phytic Acid.

#### *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.[61] 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, 1% ethanol, and approximately 49% Sodium Phytate was evaluated in an in vitro skin model (reconstructed human epidermis, EpiDerm™) test for skin corrosion.[47] 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.[62] 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).[63] 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 0.49% Sodium Phytate was evaluated in a 48-h patch test (semi-occlusive patches) involving 22 subjects.[64] The dose per area 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.[65] 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 (Organization for Economic Co-operation and Development (OECD) 442d test guideline (TG), 2 experiments) for skin sensitization.[47] 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.[66] Sodium Mannose Phosphate (in dimethyl sulfoxide (DMSO)) was

**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, 1% ethanol, and approximately 49% Sodium Phytate (material was dried before testing) | Reconstructed human epidermis (in vitro skin model) | OECD 431 TG. Trade name material dried (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.[47] |
| Dried trade name material described in preceding test | Reconstructed human epidermis (in vitro skin model) | OECD 439 TG. 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.[47] |
| 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.[62] |
| 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.[63] |

*(continued)*

**Table 12.** (continued)

| 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.[65] |
| Cream containing 0.49% 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.[64] |
| Sensitization (In Vitro) | | | |
| Dried Sodium Phytate trade name material described in *in vitro* irritation tests above | LuSens cell line | OECD 442d TG. 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.[47] |
| 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.[66] |
| 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.[69] |

*(continued)*

**Table 12.** (continued)

| Test Substance | Subjects/Tissues Tested | Test Protocol | Results |
|---|---|---|---|
| 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. Occlusive 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.[68] |
| 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.[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.[67] |
| 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.[67] |
| 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.[67] |

*(continued)*

**Table 12.** (continued)

| Test Substance | Subjects/Tissues Tested | Test Protocol | Results |
|---|---|---|---|
| Moisturizer containing 5% Phytic Acid | 110 subjects | Occlusive HRIPT. A 2 cm × 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. [70] |
| Cosmetic product containing 1% Phytic Acid | 104 male and female subjects. | HRIPT. Product (~0.2 ml on 2 cm × 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.[71] |
| Cosmetic product containing 1% Phytic Acid | 98 male and female subjects | HRIPT (same as above). Product (~0.2 ml on a 2 cm × 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.[72] |
| 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.[73] |

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.[67] HRIPT results (using occlusive patches, unless otherwise stated) 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, semi-occlusive patches; 111 subjects),[67] a leave-on product containing 0.1% Sodium Phytate (undiluted, 112 subjects),[67] a rouge containing 0.19% Sodium Phytate (undiluted, 106 subjects),[68] and a topical coded product containing 1% Sodium Phytate (maximization test, 25 subjects).[69]Phytic Acid

A moisturizer containing 5% Phytic Acid was classified as a non-sensitizer in an HRIPT involving 110 subjects.[70] The skin irritation and sensitization potential of a cosmetic product

containing 1% Phytic Acid was evaluated in an HRIPT using semi-occlusive patches involving 104 male and female subjects.[71] 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.[72] In a maximization test involving 25 subjects, a face gel containing 0.25% Phytic Acid produced negative results.[73]

*Photosensitization/Phototoxicity.* A photosensitization HRIPT on a clear liquid containing 1% Sodium Phytate was performed using 25 subjects (21 females and 4 males).[74] During induction, the test substance (~40 mg) was applied for 24 h, under an occlusive patch, to a 2 cm × 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 × 2 cm) on the opposite side of the lower back. The sites were then irradiated with ½ an MED +4 J/cm2 of long-wave ultraviolet light (UVA). Reactions were scored at 48 h and 72 h after 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

*Sodium Phytate.* In the EpiOcular™ eye irritation test, negative results were reported for a cream containing 0.49% Sodium Phytate[64] 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.[47] In the reconstructed human cornea-like epithelium (RhCE) test, the same dried Sodium Phytate trade name material was classified as non-irritating,[47] and a Sodium Phytate trade name material consisting of 50% water, 1% ethanol, and approximately 49% Sodium Phytate was classified as slightly irritating in the in vitro hen's egg chorioallantoic membrane test (HET-CAM).[76]

*Phytic Acid.* Phytic Acid (50%) (vehicle not stated) was evaluated for ocular irritation potential using the EpiOcular™ tissue model in vitro toxicity testing system.[77] The $ET_{50}$ for Phytic Acid (50%) was ~9 minutes (estimated Draize ocular irritation score of >25 (moderately irritating)).

*Sodium Mannose Phosphate.* The ocular irritation potential of 3% Sodium Mannose Phosphate was evaluated in the BCOP assay using excised corneas.[78] 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.[32] No overt signs of toxicity were reported among the women in the study. 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, no overt signs of toxicity were reported for women in the study.[33]

## 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 Fructose Diphosphate 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 and Manganese Fructose Diphosphate are reported to function as antioxidants 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. Sodium Mannose Phosphate is manufactured by enzymatic reaction from pyrophosphate and mannose.

The *Food Chemicals Codex* acceptance criteria for Phytic Acid solution (aqueous solution) include: arsenic (not more

**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).[77] |
| Coded product containing 50% Sodium Phytate (in 49% water, 1% alcohol) | EpiOcular™ 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 0.49% Sodium Phytate | EpiOcular™ eye irritation test | $ET_{50}$ > 24 h (no ocular irritation potential).[64] |
| Dried Sodium Phytate (concentration not stated) trade name material | Bovine corneal opacity and permeability test (BCOP; OECD 437 TG, 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.[47] |
| 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.[47] |
| Dried Sodium Phytate (concentration not stated) trade name material | Reconstructed human cornea-like epithelium (RhCE) test (OECD 492 TG, 2 experiments). Tissues moistened with 25 μl of DPBS buffer and incubated for 30 minutes. Test material then applied (doses of 50.1 mg and 52.3 mg) for 6 h to 3-dimensional human cornea tissue model in duplicate. Tissues rinsed at end of incubation period, and cell viability was evaluated by addition of MTT, which can be reduced to formazan. Demineralized water was negative control, and methyl acetate was positive control. | Only first experiment determined to be invalid because variation between tissue replicates of the negative control too high, and, therefore, outside of range of validity. Mean value of relative tissue viability was 66.9% (in second experiment), above threshold for eye irritation potential (≤60%). Conclusion: test substance non-irritating to the eye. Positive control caused eye irritation, i.e., mean value of relative tissue viability was 42.2% (<50%).[47] |
| 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.[78] |

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. Possible impurities (0.1% to 0.5%) of Sodium Mannose Phosphate are: phosphate, sodium salt; pyrophosphate, sodium salt; sodium chloride; and magnesium and ammonium ions.

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 vs 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 four i.p. doses of 30 mg/kg or a single i.p. dose of 60 mg/kg.

The genotoxicity of a Sodium Phytate trade name material consisting of 50% water, 1% ethanol, and approximately 49% Sodium Phytate 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, 1% ethanol, and approximately 49% Sodium Phytate was evaluated in an in vitro skin model (reconstructed human epidermis, EpiDerm™) 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. 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 cream containing 0.49% Sodium Phytate was classified as having no to negligible irritation potential in a 48-h semi-occlusive patch test involving 22 subjects. 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.

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; 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.

A topical coded product containing 1% Sodium Phytate did not cause skin sensitization in a maximization test involving 25 subjects, and a rouge containing 0.19% Sodium Phytate did not cause irritation or sensitization in an HRIPT involving 106 subjects. A leave-on product containing 0.1% Sodium Phytate (undiluted) was negative for irritation and allergenicity in an occlusive HRIPT involving 112 subjects. 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 a semi-occlusive HRIPTs involving 98 and 104 subjects. A face gel containing 0.25% Phytic Acid did not induce skin sensitization in groups of 25 subjects in maximization tests.

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

A cream containing 0.49% Sodium Phytate was classified as having no ocular irritation potential in the in vitro EpiOcular™ eye irritation test. A product containing 50% Sodium Phytate was classified as a minimal to non-irritant and Phytic Acid (50%) was classified as moderately irritating in this test. The ocular irritation potential of a Sodium Phytate (concentration not stated) trade name material was also evaluated in the following in vitro assays: BCOP test, RhCE test, and HET-CAM assay. Test results indicated that the trade name material was non-irritating/non-corrosive to slightly irritating. Sodium Mannose Phosphate (3%) was a non-irritant in the in vitro BCOP assay using excised corneas.

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 following six polyol phosphates: Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate. Of these six ingredients, only Sodium Mannose Phosphate is reported to be in use. The complete list of data needs includes:

- Method of manufacture (not needed for Sodium Mannose Phosphate)
- Impurities (not needed for Sodium Mannose Phosphate)
- ADME data

While method of manufacture and impurities data on Sodium Mannose Phosphate were received, no ADME data were submitted. The Panel agreed that absorption data on this ingredient are needed to conclude on safety. Additionally, 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 discernible 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 most of the droplets/particles produced in cosmetic aerosols would not be respirable (would not enter the lungs) to any appreciable amount. However, 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 https://www.cir-safety.org/cir-findings.

## Conclusion

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

| | |
|---|---|
| Sodium Phytate | Phytin* |
| Phytic Acid | Trisodium Inositol Triphosphate* |

**Not reported to be in current use. Were the ingredients 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** | Trisodium Fructose Diphosphate** |
| Manganese Fructose Diphosphate** | Xylityl Phosphate** |
| Sodium Mannose Phosphate | Zinc Fructose Diphosphate** |

***Not reported to be in use.*

### Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 555 13th St., NW, Suite 300W, Washington, DC 20004, USA.

### Author Contributions

The articles in this supplement were sponsored by the Cosmetic Ingredient Review.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The articles in this supplement were sponsored by the Cosmetic Ingredient Review. The Cosmetic Ingredient Review is financially supported by the Personal Care Products Council.

### References

1. Nikitakis J, Kowcz A. International Cosmetic Ingredient Dictionary and Handbook Online Version (wINCI). https://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC. Last Updated 2018. Date Accessed 5-9-2018.
2. Vucenik I, Shamsuddin A. Cancer inhibition by inositol hexaphosphate (IP6) and inositol: from laboratory to clinic. *J Nutr*. 2003;133(11 Suppl 1):3778S-3784S.
3. O'Neil MJ. *The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals*. 15th ed. Cambridge, UK: Royal Society of Chemistry; 2013.
4. Lewis RJS. *Hawley's Condensed Chemical Dictionary*. 13th ed. John Wiley & Sons, Inc.; 1997.
5. United States Environmental Protection Agency (EPA). *Estimation Programs Interface Suite™ for Microsoft® Windows, v4.11*. Washington, DC, USA: United States Environmental Protection Agency; 2017.
6. Joy A, Balaji S. Drug-likeness of phytic acid and its analogues. *Open Microbiol J*. 2015;9:141-149.
7. PerkinElmer Informatics. ChemDraw® 17. 2017.
8. United States Pharmacopeial Convention. *Food Chemicals Codex*. 10th ed. Rockville, MD: The United States Pharmacopeial Convention; 2016.
9. Tsuno Food Industrial Co., Ltd. GRAS exemption claim for phytic acid (50% solution). https://authorzilla.com/bzeK9/gras-notice-000381-phytic-acid.html. Last Updated 2011. Date Accessed 10-6-2017.
10. Saad N, Esa N, Ithnin H, et al. Optimization of optimum condition for phytic acid extraction from rice bran. *Afr J Plant Sci*. 2011;5(3):168-176.
11. Anonymous. Flow chart for phytic acid production. Unpublished data submitted by the Personal Care Products Council on 1-25-2018. 2018:1
12. Anonymous. Method of manufacture and impurities - Sodium Mannose Phosphate. Unpublished data submitted by Personal Care Products Council. 2018.
13. Anonymous. Evaluation of heavy metals in phytic acid (50%). Unpublished data submitted by the Personal Care Products Council on 1-25-2018. 2017:1-3.
14. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program – Frequency of Use of Cosmetic Ingredients. College Park, MD: 2018. Obtained under the Freedom of Information

Act from CFSAN; requested as "Frequency of Use Data" January 3, 2018; received February 5, 2018).
15. Personal Care Products Council. Concentration of use by FDA product category: Cyclic Polyol Phosphates. Unpublished data submitted by the Personal Care Products Council on 10-4-2017. 2017:1-2.
16. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.
17. Bremmer HJ, Prud'homme de Lodder LCH, van Engelen JGM. Cosmetics Fact Sheet: to assess the risks for the consumer. 2020. Updated version for ConsExpo 4 https://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.
18. Rothe H. Special aspects of cosmetic spray evaluation. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C. 2011.
19. Johnsen MA. The influence of particle size. *Spray Technol Mark*. 2004;14(11):24-27. https://www.spraytechnology.com/index.mv?screen=backissues
20. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. https://ec.europa.eu/growth/tools-databases/cosing/. Last Updated 2017. Date Accessed 6-8-2017.
21. United States Food and Drug Administration (FDA). Agency response letter GRAS Notice No. GRN 000381, dated 6-4-2012. https://web.archive.org/web/20171031000421/. https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm313045.htm. Last Updated 2017. Date Accessed 10-6-2017.
22. Sarkar R, Garg V, Bansal S, et al. Comparative evaluation of efficacy and tolerability of glycolic acid, salicylic mandelic acid, and phytic acid combination peels in melasma. *Dermatol Surg*. 2016;42(3):384-391.
23. Grases F, Isern B, Perello J, et al. Absorption of myo-inositol hexakisphosphate ($InsP_6$) through the skin in humans. *Pharmazie*. 2006;61(7):652.
24. Grases F, Perello P, Isern B, et al. Study of the absorption of myo-inositol hexakisphosphate ($InsP_6$) through the skin. *Biol Pharm Bull*. 2005;28(4):764-767.
25. Nahapetian A, Young V. Metabolism of (14)C-phytate in rats: effect of low and high dietary calcium intakes. *J Nutr*. 1980;110(7):1458-1472.
26. Sakamoto K, Vucenik I, Shamsuddin A. [3H] Phytic Acid ( inositol hexaphosphate) is absorbed and distributed to various tissues in rats. *J Nutr*. 1993;123(4):713-720.
27. Grases F, Simonet B, Prieto R, et al. Phytate levels in diverse rat tissues: influence of dietary phytate. *Br J Nutr*. 2001;86(2):225-231.
28. Eiseman J, Lana J, Guoa J, et al. Pharmacokinetics and tissue distribution of inositol hexaphosphate in C.B17 SCID mice bearing human breast cancer xenografts. *Metab Clin Exp*. 2011;60:1465-1474.
29. Shamsuddin AM. Metabolism and cellular functions of $IP_6$: a review. *Anticancer Res*. 1999;19(5A):3733-3736.
30. Grases F, L'lobera A. Determination of phytic acid in urine by ICP atomic emission spectrometry. *Analyt Lett*. 1996;29:1193-1199.
31. Grases F, Simonet B, Vucenik I, et al. Absorption and excretion of orally administered inositol hexaphosphate ($IP_6$ or phytate) in humans. *Biofactors*. 2001;15(1):53-61.
32. Joung H, Jeun B, Li S, et al. Fecal phytate excretion varies with dietary phytate and age in women. *J Am Coll Nutr*. 2007;26(3):295-302.
33. Kim J, Woodhouse L, King J, et al. Relationships between fecal phytate and mineral excretion depend on dietary phytate and age. *Br J Nutr*. 2009;102(6):835-841.
34. Sandberg A, Hasselblad C, Hasselblad K. The effect of wheat bran on the absorption of minerals in the small intestine. *Br J Nutr*. 1982;48:185-191.
35. Schlemmer U, Jany K, Berk A, et al. Degradation of phytate in the gut of pigs - pathway of gastrointestinal inositol phosphate hydrolysis and enzymes involved. *Arch Anim Nutr*. 2001;55:255-280.
36. Sandberg A, Andersson H. Effect of dietary phytase on the digestion of phytate in the stomach and small intestine of humans. *J Nutr*. 1988;118:469-473.
37. Fujitani T, Yoneyama M, Kabashima J-I, et al. Acute toxicity of phytic acid and sodium phytate to mice. *Tokyo Toritsu Eisei Kenkyu Nenpo [Ann.Rep.Tokyo Metr.Res.Lab PH]*. 1987;38:368-370.
38. Ichikawa H, Ohishi S, Takahashi O, et al. Studies on acute oral toxicities of phytic acid and sodium phytate in rat. *Tokyo Toritsu Eisei Kenkyu Nenpo [Ann.Rep.Tokyo Metr.Res.Lab PH]*. 2017;38:371-376.
39. Gersonde K, Weiner M. The influence of infusion rate on the acute intravenous toxicity of phytic acid, a calcium-binding agent. *Toxicology*. 1982;22(4):279-286.
40. Onomi S, Okazaki Y, Katayama T. Effect of dietary level of phytic acid on hepatic and serum lipid status in rats fed a high-sucrose diet. *Biosci Biotechnol Biochem*. 2004;68(6):1379-1381.
41. Lee S-H, Park H, Chun H-K, et al. Dietary phytic acid lowers the blood glucose level in diabetic KK mice. *Nutr Res*. 2006;26(9):474-479.
42. Ogata A, Ando H, Kubo Y, et al. Teratological studies of phytic acid in icr mice. *Tokyo Toritsu Eisei Kenkyusho Nempo*. 1987;38:377-381.
43. Szkudelski T. Phytic acid-induced metabolic changes in the rat. *J Anim Physiol Anim Nutr*. 2005;89(11 and 12):397-402.
44. Hiasa Y, Kitahori Y, Morimoto J, et al. Carcinogenicity study in rats of phytic acid 'Daiichi', a natural food additive. *Fd Chem Toxic*. 1992;30(2):117-125.
45. Anekonda T, Wadsworth T, Sabinc R, et al. Phytic acid as a potential treatment for Alzheimer's pathology: evidence from animal and in vitro models. *J Alzheim Dis*. 2011;23:21-35.
46. Abu El-Saad A, Mahmoud H. Phytic acid exposure alters aflatoxin B1-induced reproductive and oxidative toxicity in albino rats (*Rattus norvegicus*). *Alternat Med*. 2007;6(3):331-341.

47. Laus GmbH. Summaries of studies of sodium phytate. Unpublished data submitted by the Personal Care Products Council on 2-8-2018. 2018.
48. Ishidate M Jr., Sofuni T, Yoshikawa K, et al. Primary mutagenicity screening of food additives currently used in Japan. *Food Chem Toxicol*. 1984;62:623-636.
49. Whitakker P, Seifried H, San R, et al. Genotoxicity of iron chelators in L5178Y mouse lymphoma cells. *Environ Mol Mutagen*. 2001;38(4):347-356.
50. Charles River Laboratories Skokie, LLC. *Salmonella-E. coli*/Mammalian microsome reverse mutation assay (Sodium Mannose Phosphate). Unpublished data submitted by the Personal Care Products Council on 5-21-2018:1-49.
51. Takaba K, Hirose M, Ogawa K, et al. Modifications of N-butyl-N-(4-hydroxybutyl)nitrosamine-initiated urinary bladder carcinogenesis in rats by phytic acid and its salts. *Food Chem Toxicol*. 1994;32(6):499-503.
52. Gupta K, Singh J, Bharathi R. Suppression of DMBA-induced mouse skin tumor development by inositol hexaphosphate and its mode of action. *Nutr Cancer*. 2003;46(1):66-72.
53. Williams K, Kolappaswamy K, DeTolla L, et al. Protective effect of inositol hexaphosphate against UVB damage in HaCaT cells and skin carcinogenesis in SKH1 hairless mice. *Comp Med*. 2011;61(1):39-44.
54. Ullah A, Shamsuddin A. Dose-dependent inhibition of large intestinal cancer by inositol hexaphosphate in F344 rats. *Carcinogenesis*. 1990;11(12):2219-2222.
55. Hirose M, Hoshiya T, Akagi K, et al. Inhibition of mammary gland carcinogenesis by green tea catechins and other naturally occurring antioxidants in female Sprague-Dawley rats pretreated with 7,12-dimethylbenz[α]anthracene. *Cancer Lett*. 1994;83(1-2):149-156.
56. Ishikawa TNY, Zarkovic M, Shamsuddin A. Inhibition of skin cancer by $IP_6$ in vivo: initiation-promotion model. *Anticancer Res*. 1999;19(5A):3749-3752.
57. Midorikawa K, Murata M, Oikawa S, et al. Protective effect of phytic acid on oxidative DNA damage with reference to cancer chemoprevention. *Biochem Biophys Res Commun*. 2001;288(2 November 2001):552-557.
58. Kumar M, Reddy B, Babu S, et al. Antiinflammatory and antiulcer activities of phytic acid in rats. *Indian J Exp Biol*. 2004; 42(2):179-185.
59. Deliliers G, Servida F, Fracchiolla N, et al. Efffect of inositol hexaphosphate (IP6) on human normal and leukemic hematopoietic cells. *Br J Hematol*. 2002;117(3):577-587.
60. Norhaizan M, Ng S, Norashareena M, et al. Antioxidant and cytotoxicity effect of rice bran phytic acid as an anticancer agent on ovarian, breast, and liver cancer cell lines. *Mal J Nutr*. 2011; 17(3):367-375.
61. Al HS, Hassan M, Saha S, et al. Dietary phytate intake inhibits the bioavailability of iron and calcium in the diets of pregnant women in rural Bangladesh: a cross-sectional study. *BMC Nutrition*. 2016;2(24):1-10.
62. Consumer Product Testing Co. The MatTek corporation EpiDerm™ skin model *in vitro* toxicity testing system: phytic acid (50%). Unpublished data submitted by the Personal Care Products Council on 1-25-2018. 2004:1-5.
63. Institute for In Vitro Sciences, Inc. Skin irritation test (SIT) using the EpiDerm™ skin model (3% sodium mannose phosphate). Unpublished data submitted by the Personal Care Products Council on 5-21-2018. 2016:1-14.
64. Anonymous. Summaries of studies on a product containing Sodium Phytate. Unpublished data submitted by the Personal Care Products Council on 1-23-2018. 2018:1
65. Anonymous. Clinical evaluation report: human patch test (product containing 0.25% phytic acid). Unpublished data submitted by the Personal Care Products Council on 4-24-2018. 2010:1
66. Anonymous. KeratinoSens™ assay: test report on D-mannose-6-phosphate (INCI: Sodium Mannose Phosphate). Unpublished data submitted by the Personal Care Products Council on 5-21-2018. 2016:1-17.
67. Personal Care Products Council. Summaries of HRIPTs of products containing Sodium Phytate. Unpublished data submitted by the Personal Care Products Council on 3-6-2018. 2018:1-4.
68. Anonymous. Human repeated insult patch test with challenge (rouge containing 0.19% sodium phytate). Unpublished data submitted by the Personal Care Products Council on 5-8-2018. 2012:1-7.
69. KGL, Inc. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (clear liquid containing 1% Sodium Phytate). Unpublished data submitted by the Personal Care Products Council on 4-24-2018. 2009:1-11.
70. Hill Top Research, Inc. Human repeat insult patch test of a moisturizer containing 5% phytic acid. Unpublished data submitted by the Personal Care Products Council on 4-23-2018. 1995:1-17.
71. Essex Testing Clinic, Inc. Clincial safety evaluation repeated insult patch test (product containied 1% phytic acid). Unpublished data submitted by the Personal Care Products Council on 5-7-2018. 2012:1-13.
72. Essex Testing Clinic, Inc. Clinical safety evaluation repeated insult patch test (product contained 1% phytic acid). Unpublished data submitted by the Personal Care Products Council on 5-7-2018. 2011:14-25.
73. KGL, Inc. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (face gel containing 0.25% phytic acid). Unpublished data submitted by the Personal Care Products Council on 4-24-2018. 2011:1-9.
74. KGL, Inc. An assessment of the photosensitization potential of two topical coded test products using a human photocontact allergenicity assay (clear liquid contains 1% sodium phytate). Unpublished data submitted by the Personal Care Products Council on 4-24-2018. 2009:1-13.
75. MB Research Laboratories. MatTek EpiOcular™ MTT viability assay (coded procduct R1109837 contains 50% sodium phytate in 49% water, 1% alcohol). Unpublished data

submitted by the Personal Care Products Council on 4-24-2018. 2009:1-12.
76. Labor L + S AG. Hen's egg chorioallantoic membrane test (HET-CAM) on sodium phytate. Unpublished data submitted by the Personal Care Products Council on 2-8-2018. 2018.
77. Consumer Product Testing Co. The MatTek Corporation Epi-OcularTM tissue model in vitro toxicity testing system: phytic acid (50%). Unpublished data submitted by the Personal Care Products Council on 1-25-2018. 2004:1-5.
78. Institute for In Vitro Sciences, Inc. Bovine corneal opacity and permeability assay (3% sodium mannose phosphate). Unpublished data submitted by the Personal Care Products Council on 5-21-2018. 2017:1-13.
79. Chemical Book, Inc. Potassium phytate. https://www.chemicalbook.com/ChemicalProductProperty_EN_CB4515162.htm. Last Updated 2016.
80. United States Environmental Protection Agency (EPA). EPISuite™ - Estimation Program Interface v4.11 - EPA. 2017.