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Safety Assessment of Phosphoric Acid and Its Salts as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Phosphoric Acid and its salts (31 ingredients), which are reported to function as buffering agents, corrosion inhibitors, chelating agents, and pH adjusters in cosmetic products. The Panel reviewed data relating to the safety of these ingredients and concluded that Phosphoric Acid and its salts are safe in the present practices of use and concentration in cosmetics when formulated to be nonirritating.

Keywords

safety, cosmetics, phosphoric acid, salts

Introduction

The safety of the following 31 ingredients, as used in cosmetics, is reviewed in this safety assessment:

Phosphoric Acid	Disodium Pyrophosphate	Sodium Metaphosphate
Ammonium Phosphate	Magnesium Hydrogen Phosphate	Sodium Polyphosphate
Dicalcium Phosphate	Magnesium Phosphate	Sodium Phosphate
Calcium Dihydrogen Phosphate	Metaphosphoric Acid	Sodium Trimetaphosphate
Calcium Phosphate	Pentapotassium Triphosphate	Tetrapotassium Pyrophosphate
Calcium Potassium Sodium Phosphate	Pentasodium Triphosphate	Tetrasodium Pyrophosphate
Calcium Pyrophosphate	Phosphate Buffered Saline	Tricalcium Phosphate
Diammonium Phosphate	Potassium Metaphosphate	Trimagnesium Phosphate
Dicalcium Phosphate Dihydrate	Potassium Phosphate	Trisodium Phosphate
Dipotassium Phosphate	Potassium Polyphosphate	
Disodium Phosphate	Sodium Hexametaphosphate	

According to the web based-*International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the functions of these ingredients in cosmetic products include buffering agents, corrosion inhibitors, chelating agents, and pH adjusters.[1]

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Three of the phosphate salt ingredients included in this safety assessment, that is, Sodium Metaphosphate, Sodium Trimetaphosphate, and Sodium Hexametaphosphate, have been previously reviewed by the Expert Panel for Cosmetic Ingredient Safety (Panel).[2] In 2001, the Panel concluded that these ingredients are safe for use in cosmetics when formulated to avoid skin irritation.

Chemistry

Definition and Structure

The definitions, structures, and functions in cosmetics of Phosphoric Acid and its salts are presented in Table 1.

Phosphoric Acid and its salts all share the same phosphate core in common. Except for Phosphoric Acid and Metaphosphoric Acid, the ingredients in this report are either alkaline earth metal (Periodic Table column I or II) salts or ammonium salts of a phosphoric acid. These ingredients are related to each other as inorganic phosphates, with varying cation identity and degree of protonation (Figure 1). This group comprises phosphate salts for which property differences are attributable primarily to having different cation(s). Characterizing these differences in one report that addresses all of these ingredients is more informative than attempting to assess the safety of these salts in separate reports that each addresses only one ingredient.

Phosphoric Acid is a polyprotic acid which is deprotonated to mono-, di-, and triphosphates with rising pH.

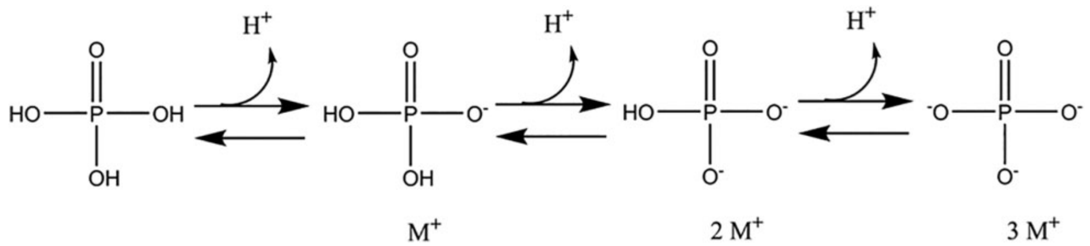

Figure 1. Phosphoric Acid and the orthophosphates (dihydrogen phosphate, hydrogen phosphate, and phosphate).

However, Phosphoric Acid and phosphate salts also exist as dimers and trimers of phosphate, *pyro-* and *meta-* respectively. Accordingly, these ingredients vary by the identity of associated cations, degree of protonation, *and* in the number of phosphate repeat units (ie, 1 repeat is *ortho-*, 2 repeats is *pyro-*, and 3 repeats is *meta-*; Figure 2).

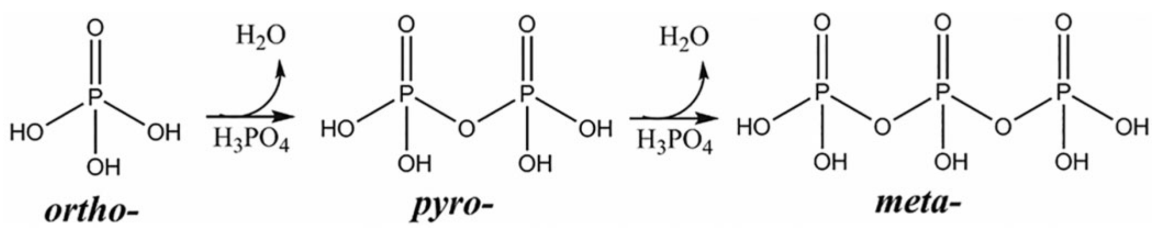

Figure 2. Dehydration of phosphoric acids, from ortho- to pyro- to meta-phosphoric acid.

As some of the *Dictionary* names for these ingredients vary from the customary names and may be confusing, systematic or common names have been added to Table 1. However, elsewhere in this report only the *Dictionary* ingredient name is used.

Chemical and Physical Properties

These ingredients range from colorless crystalline solids to white amorphous powders. The water solubilities of these ingredients are pH dependent (Table 2).

Method of Manufacture

Acids

Phosphoric Acid. Phosphoric Acid is manufactured by the wet process or the furnace (thermal) process. In the wet process, Phosphoric Acid is produced directly from phosphate ores and is said to be of low purity.[3] This process is used mostly for the production of fertilizers. In the thermal or furnace process, phosphoric acid is produced from elemental phosphorus. This process is used in the production of phosphoric acid for uses other than fertilizer production, such as metal treatment, refractories, catalysts, and use in food and beverages.

Ammonium Salts

Ammonium Phosphate. In the process for manufacturing Ammonium Phosphate, a one-to-one ratio of ammonia (NH_3) and Phosphoric Acid (H_3PO_4) is reacted, and the resulting slurry of Ammonium Phosphate is solidified in a granulator.[4]

Diammonium Phosphate. In the manufacture of Diammonium Phosphate, each stoichiometric equivalent of

Phosphoric Acid is neutralized by approximately 2 equivalents of ammonia.[5]

Sodium Salts

Disodium Phosphate. Disodium Phosphate is prepared by the ignition of Dicalcium Phosphate.[6]

Sodium Metaphosphate. Sodium Metaphosphate is prepared by dehydration of sodium orthophosphates.[6]

Sodium Polyphosphate. Sodium phosphate monobasic hydrate was used to prepare Sodium Polyphosphate with a degree of polymerization (D_p) lower than $\approx$ 500.[7] Sodium phosphate monobasic hydrate was heated to 700 °C for 1, 3, or 9 hours, and the melt was then quenched on a copper plate. To fraction the Sodium Polyphosphate glass, the frit was ground and dissolved in deionized water to yield a 10% (w/v) Sodium Polyphosphate solution. The solution was stirred, fractioned by serial dilution with acetone, and then centrifuged to collect the precipitate. Sodium Polyphosphate with a $D_p > 500$ was obtained from an ion-exchange process on a potassium polyphosphate crystalline phase.

Tetrasodium Pyrophosphate. Tetrasodium Pyrophosphate is produced by molecular dehydration of dibasic Sodium Phosphate at 500 °C.[6]

Pentasodium Triphosphate. Pentasodium Triphosphate is prepared by the molecular dehydration of mono- and disodium phosphates.[6]

Potassium Salts

Potassium Metaphosphate. Potassium Metaphosphate is obtained by the fusion of monopotassium phosphates.[8] It is also prepared by dehydration of Potassium Phosphate.[6]

Potassium Phosphate. Food-grade potassium phosphates have been prepared by the neutralization of Phosphoric Acid with potassium hydroxide at 50 °C to 60 °C.[9]

Potassium Polyphosphate. Potassium Polyphosphate can be obtained by heating monopotassium orthophosphate to any temperature above 150 °C.[10]

Calcium Salts

Calcium Pyrophosphate. Calcium Pyrophosphate can be obtained by a solid state reaction (870 °C and normal atmosphere) from a mixture of Tricalcium Phosphate and Phosphoric Acid.[11] It can also be prepared by ignition of Dicalcium Phosphate.[6]

Dicalcium Phosphate. Commercial Dicalcium Phosphate is not a chemically discrete entity but is a mixture of varying amounts of dicalcium and monocalcium phosphates, Phosphoric Acid, calcium carbonate, and impurities, depending on the origin of the raw material and procedures employed in its industrial production.[12]

Tricalcium Phosphate. Tricalcium Phosphate has been produced by a calcination process (at high temperatures of 1500 °C-1600 °C) that is preceded by the grinding and mixing of phosphate rock and sodium carbonate and the addition of Phosphoric Acid to the reaction mixture.[13]

Magnesium Salts

Magnesium Phosphate. Magnesium Phosphates have been prepared by adding a magnesium nitrate solution into mixed solutions of potassium hydroxide and Phosphoric Acid at temperatures of 29 °C to 95 °C.[14]

Composition/Impurities

Phosphoric Acid. According to the *Food Chemicals Codex* specification for this chemical, the following limits for inorganic impurities in Phosphoric Acid have been established: arsenic ($\leq$3 mg/kg), cadmium ($\leq$3 mg/kg), fluoride ($\leq$10 mg/kg), and lead ($\leq$3 mg/kg).[15]

Ammonium Salts

Ammonium Phosphate. According to the *Food Chemicals Codex* specification for Ammonium Phosphate, the acceptance criteria for this chemical indicate that it contains not less than 96% Ammonium Phosphate and not more than 100% Ammonium Phosphate. The following limits for inorganic impurities in Ammonium Phosphate have been established: arsenic ($\leq$3 mg/kg), fluoride ($\leq$10 mg/kg), and lead ($\leq$4 mg/kg).[15] According to another source, iron and aluminum have been mentioned as Ammonium Phosphate impurities.[4]

Diammonium Phosphate. According to the *Food Chemicals Codex* specification for Diammonium Phosphate, the acceptance criteria for this chemical indicate that it contains not less than 96% Diammonium Phosphate and not more than 100% Diammonium Phosphate. The following limits for inorganic impurities in Diammonium Phosphate have been established: arsenic ($\leq$3 mg/kg), fluoride ($\leq$10 mg/kg), and lead ($\leq$ 4 mg/kg).[15]

Sodium Salts

Sodium Hexametaphosphate. Sodium Hexametaphosphate contains 10 to 12 repeating pyrophosphate subunits.[16]

Sodium Phosphate. According to the *Food Chemicals Codex* specification for Sodium Phosphate, the acceptance criteria for this chemical are not less than 98% Sodium Phosphate and not more than 103% Sodium Phosphate on the dried basis, and the following limits for inorganic impurities have been established: arsenic ($\leq$3 mg/kg), fluoride ($\leq$0.005%), and lead ($\leq$4 mg/kg).[15]

Sodium Polyphosphate. According to the *Food Chemicals Codex* specification for Sodium Polyphosphate, the acceptance criteria for phosphorus pentoxide content range from 60% to 71%, and the following limits for inorganic impurities have been established: arsenic ($\leq$3 mg/kg), fluoride ($\leq$0.005%), and lead ($\leq$4 mg/kg).[15]

Trisodium Phosphate. According to the *Food Chemicals Codex* specification for Trisodium Phosphate, the acceptance criteria for this chemical are not less than 97% Trisodium Phosphate (anhydrous and monohydrate forms), calculated on the ignited basis, and not less than 90% Trisodium Phosphate (dodecahydrate), calculated on the ignited basis. The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤0.005%), and lead (≤4 mg/kg).[15]

Potassium Salts

Dipotassium Phosphate. According to the *Food Chemicals Codex* specification for Dipotassium Phosphate, the acceptance criteria for this chemical indicate that it contains not less than 98% Dipotassium Phosphate, on the dried basis. The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤10 mg/kg), and lead (≤2 mg/kg).[15] According to another source, heavy metal (as lead, 0.0006%) and arsenic (0.00005%) impurities have been reported for Dipotassium Phosphate.[17]

Potassium Metaphosphate. According to the *Food Chemicals Codex* specification for Potassium Metaphosphate, the acceptance criteria for this chemical are not less than 59% phosphorus pentoxide and not more than 61% phosphorus pentoxide. The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤10 mg/kg), and lead (≤2 mg/kg).[15]

Potassium Phosphate. According to the *Food Chemicals Codex* specification for Potassium Phosphate, the acceptance criteria for this chemical indicate that it contains not less than 98% Potassium Phosphate, on the dried basis. The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤10 mg/kg), and lead (≤2 mg/kg).[15]

Potassium Pyrophosphate. According to the *Food Chemicals Codex* specification for Potassium Pyrophosphate, the acceptance criteria for this chemical indicate that it contains not less than 95% Potassium Pyrophosphate. The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤10 mg/kg), and lead (≤2 mg/kg).[15]

Calcium Salts

Calcium Dihydrogen Phosphate. According to another source, Calcium Dihydrogen Phosphate may contain a trace amount of Phosphoric Acid as an impurity.[6]

Calcium Phosphate. Calcium Phosphate is approximately 96% pure, usually containing an excess of calcium oxide.[6]

Dicalcium Phosphate. Commercial Dicalcium Phosphate is not a chemically discrete entity but is a mixture of varying amounts of dicalcium and monocalcium phosphates, Phosphoric Acid, calcium carbonate, and impurities, depending on the origin of the raw material and procedures employed in its industrial production.[12]

According to the *Food Chemicals Codex* specification for Dicalcium Phosphate, the acceptance criteria for this chemical indicate that it contains not less than 97% Dicalcium Phosphate and not more than 105% Dicalcium Phosphate (anhydrous or dehydrate form). The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤0.005%), and lead (≤2 mg/kg).[15]

Tricalcium Phosphate. According to the *Food Chemicals Codex* specification for Tricalcium Phosphate, the acceptance criteria for this chemical indicate that it contains not less than 34% calcium and not more than 40% calcium. The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤0.0075%), and lead (≤2 mg/kg).[15]

Magnesium Salts

Magnesium Hydrogen Phosphate. According to the *Food Chemicals Codex* specification for Magnesium Hydrogen Phosphate, the acceptance criteria for this chemical indicate that it is not less than 96% pure, on the ignited basis. The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤25 mg/kg), and lead (≤2 mg/kg).[15]

Trimagnesium Phosphate. According to the *Food Chemicals Codex* specification for Trimagnesium Phosphate, the acceptance criteria for this chemical indicate that it is not less than 98% pure. The following limits for inorganic impurities have been established: arsenic (≤3 mg/kg), fluoride (≤25 mg/kg), and lead (≤2 mg/kg).[15]

Use

Cosmetic

The safety of Phosphoric Acid and its salts included in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetic 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. Use concentration data are submitted by Industry in response to surveys conducted by the Personal Care Products Council (Council) of maximum reported use concentrations, by product category. Collectively, the use frequency and use concentration data indicate that 22 of the 31 ingredients in this safety assessment are currently being used in cosmetic products (see Tables 3A-C). According to these data, the following 9 ingredients are not reported as being used in cosmetics:

Calcium Potassium Sodium Phosphate	Phosphate Buffered Saline
Magnesium Hydrogen Phosphate	Potassium Polyphosphate
Magnesium Phosphate	Sodium Polyphosphate
Metaphosphoric Acid	Sodium Trimetaphosphate
Pentapotassium Triphosphate	

According to 2016 VCRP data, the greatest reported use frequency is for Phosphoric Acid (489 formulations, mostly rinse-off products), followed by Dicalcium Phosphate (327 formulations, mostly leave-on products; Tables 3A-C).[18] The results of a concentration of use survey provided in

2015 indicate that Dicalcium Phosphate Dihydrate has the highest maximum concentration of use; it is used at concentrations up to 49% in rinse-off products (dentifrices; Tables 3A-C).[19]

The highest maximum ingredient use concentration in leave-on products (10% in eye shadow) is being reported for Dicalcium Phosphate. In some cases, reported uses appear in the VCRP database, but concentrations of use data were not provided; the opposite is also true. For example, according to the VCRP, Tetrapotassium Pyrophosphate and Calcium Pyrophosphate are being used in 95 and 3 cosmetic products, respectively; however, use concentration data on these ingredients were not provided in the concentration of use survey. Furthermore, use concentration data on Calcium Phosphate were provided in the concentration of use survey; however, use frequency data were not reported in the VCRP data.

Cosmetic products containing Phosphoric Acid or its salts may be applied to the skin and hair or, incidentally, may come in contact with the eyes (eg, Dicalcium Phosphate at maximum use concentrations up to 10% in eye area cosmetics) and mucous membranes (eg, Dicalcium Phosphate Dihydrate at maximum use concentrations up to 49% in dentifrices). Additionally, some of these ingredients are being used in products that may result in incidental ingestion. For example, Dicalcium Phosphate Dihydrate is being used in dentifrices at maximum use concentrations up to 49%, and Dicalcium Phosphate is being used in lipstick at maximum use concentrations up to 10%. Products containing these ingredients 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.

Phosphoric Acid is used in aerosol hair sprays at concentrations of <0.01% and in pump hair sprays at concentrations up to 0.26%. The following other ingredients are also used in hair sprays: Potassium Phosphate (pump hair sprays up to 0.09%) and Sodium Phosphate (pump hair sprays up to 0.000014%). The following ingredients are used in face powders: Dicalcium Phosphate (up to 2.2%), Diammonium Phosphate (up to 0.00046%), Dicalcium Phosphate Dihydrate (up to 2.2%), Sodium Metaphosphate (up to 0.25%), and Sodium Phosphate (up to 0.086%). 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.[20-23] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[20,21] Additionally, Phosphoric Acid is used in dusting and talcum powders at concentrations up to 0.00001%, and Tricalcium Phosphate is used in dusting and talcum powders at concentrations up to 10%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[24-26]

Non-Cosmetic

Phosphoric Acid and Phosphates. The FDA has determined that the following 20 ingredients included in this report are direct food additives that are generally recognized as safe (GRAS):[27]

Phosphoric Acid	Pentasodium Triphosphate
Ammonium Phosphate	Potassium Phosphate
Calcium Dihydrogen Phosphate	Potassium Pyrophosphate
Calcium Phosphate	Sodium Hexametaphosphate
Calcium Pyrophosphate	Sodium Metaphosphate
Diammonium Phosphate	Sodium Phosphate
Dicalcium Phosphate	Sodium Trimetaphosphate
Dipotassium Phosphate	Tetrasodium Pyrophosphate
Disodium Phosphate	Trimagnesium Phosphate
Magnesium Hydrogen Phosphate	Trisodium Phosphate

Additionally, the FDA has determined that potassium polymetaphosphate, chemically similar to one or more ingredients on the preceding list, is a GRAS direct food additive.

Acids

Phosphoric Acid. Phosphoric Acid is used in the manufacture of the following: phosphate salts, superphosphate fertilizers, detergents, activated carbon, animal feed, ceramics, dental cement, pharmaceuticals, soft drinks, gelatin, rust inhibitors, wax, and rubber latex.[3] Use in the following other processes has also been reported: electropolishing, engraving, photoengraving, lithograving, metal cleaning, sugar refining, and water treatment.

Metaphosphoric Acid. In dentistry, Metaphosphoric Acid is used to make zinc oxyphosphate cement.[6] It is also used as a reagent in chemical analysis.

Ammonium Salts

Ammonium Phosphate. In agriculture, Ammonium Phosphate has been an important granular fertilizer for many years.[4] Ammonium Phosphate is also used in dry chemical fire extinguishers, which are commonly found in offices, schools, and homes. The extinguisher spray disperses finely powdered Ammonium Phosphate, which coats the fuel and rapidly smothers the flame.

Diammonium Phosphate. Diammonium Phosphate is a complex fertilizer that contains 2 major nutrients, nitrogen and phosphorus.[28] Additionally, Diammonium Phosphate is used in fireproofing textiles, paper, wood, vegetable fibers, and dentifrices.[6]

Sodium Salts

Disodium Phosphate. Disodium Phosphate is used as an emulsifier and buffer in foods, and in the manufacture of enamels, ceramics, detergents, and boiler compounds.[6]

Disodium Pyrophosphate. Disodium Pyrophosphate is used chiefly in baking powders.[6]

Pentasodium Triphosphate. Pentasodium Triphosphate is used as a preservative, sequestrant, and texturizer in foods, and as whitening agent in toothpaste; it is also used in water softeners and detergents.[6]

Sodium Hexametaphosphate. Sodium Hexametaphosphate is an antitartar ingredient in toothpaste and is known to remove stains.[16]

Sodium Phosphate. Sodium phosphate products have been used for bowel cleansing prior to medical procedures such as colonoscopy. The FDA is aware of reports of acute phosphate nephropathy that are associated with such usages.[29] Acute phosphate nephropathy is a form of acute kidney injury that is associated with deposits of calcium phosphate crystals in the renal tubules, which may result in permanent renal function impairment. In response, FDA requires that the manufacturer of 2 oral sodium phosphate products (prescription only) for bowel cleansing add a Boxed Warning to the labeling for these products. The FDA has also stated that, in light of the risk of acute phosphate nephropathy, over-the-counter (OTC) laxative oral sodium phosphate products should not be used for bowel cleansing.

Sodium Phosphate is also used in baking powders and as dry acidulant and sequestrant for foods.[6]

Sodium Polyphosphate, Sodium Trimetaphosphate, and Tetrasodium Pyrophosphate. Blended phosphates (usually ortho and glassy polyphosphates) are used in municipal water treatment as part of scale-control and corrosion-control programs in the United States, because these compounds bind calcium carbonate, iron, magnesium, and manganese.[30] Sodium Polyphosphate, Sodium Trimetaphosphate, and Tetrasodium Pyrophosphate are some of the chemicals that are found in the phosphate blends. Sodium Trimetaphosphate is also used in detergent processing and as a crosslinking agent for starch in foods and pharmaceuticals.[6]

Tetrasodium Pyrophosphate is also used in processed meat products, as an emulsifier in cheese, and as a color preservative in soybean paste.[31] Other uses include: sequestrant, dispersant, deflocculant, detergent builder, and component of solid or liquid fertilizers.[32] Tetrasodium Pyrophosphate is one of the anticalculus components of most tartar control dentifrices that are marketed.[33]

The US Environmental Protection Agency (EPA) has established an exemption from the requirement of a tolerance for residues of Tetrasodium Pyrophosphate when used as an inert ingredient in pesticide formulations applied to growing crops only.[34]

Trisodium Phosphate. Trisodium Phosphate is used in photographic developers, in detergent mixtures, and in the manufacture of paper.[6]

Potassium Salts

Dipotassium Phosphate. Dipotassium Phosphate is used as a buffering agent in antifreeze, nutrient in the culturing of antibiotics, ingredient of instant fertilizers, and as a sequestrant in the preparation of nondairy powdered coffee creams.[6]

Potassium Phosphate. Potassium Phosphate is used as a buffering agent in pharmaceuticals.[6]

Tetrapotassium Pyrophosphate. Blended phosphates (usually ortho and glassy polyphosphates) are used in municipal water treatment as part of scale-control and corrosion-control programs in the United States, because these compounds bind calcium carbonate, iron, magnesium, and manganese.[30] Sodium Polyphosphate, Sodium Trimetaphosphate, and Tetrasodium Pyrophosphate are some of the chemicals that are found in the phosphate blends. Sodium Trimetaphosphate is also used in detergent processing and as a crosslinking agent for starch in foods and pharmaceuticals.[6]

Calcium Salts

Calcium Phosphate. Calcium Phosphate has been used as an adjuvant (ie, a material that can increase the humoral or cellular immune response to an antigen) for simultaneous immunizations with diphtheria, tetanus, polio, Bacillus Calmette-Guérin, yellow fever, measles and hepatitis B vaccines, with hepatitis B and DTP-polio vaccines, and immunization with allergens.[35] It has also been used in the manufacture of fertilizers, Phosphoric Acid, P compounds, milk-glass, polishing and dental powders, porcelains, and pottery.[6]

Calcium Phosphate is an active ingredient in antacid OTC drug products that are GRAS and effective.[36]

Calcium Pyrophosphate. One form of Calcium Pyrophosphate has been used clinically as a bone-graft extender, because it bonds with host bone.[37] It is also used in dentifrices and in the production of ceramic ware and glass.[6]

Dicalcium Phosphate. Dicalcium Phosphate is used chiefly in animal feeds and is also used as a mineral supplement in cereals and other foods.[6]

Dicalcium Phosphate Dihydrate. Dicalcium Phosphate Dihydrate is a cleaning and polishing agent that is specifically used in dentifrices that contain monofluorophosphate.[38] As an abrasive, this ingredient assists in the removal of dental stains and deposits that form on tooth surfaces.

The FDA has determined that there are inadequate data to establish general recognition of the safety and effectiveness of Dicalcium Phosphate Dihydrate as an active ingredient in anticaries OTC drug products.[36]

Tricalcium Phosphate. Tricalcium Phosphate, described as a porous ceramic material, is used in bone transplantation surgery.[39] It acts as a scaffold for bone ingrowth, undergoing progressive degradation, and replacement by bone. Most often, it is used in granule or powder form during surgery.

Tricalcium Phosphate is an active ingredient in antacid OTC drug products, and FDA has established a maximum daily dosage limit of 24 grams for Tricalcium Phosphate in these products.[40]

Magnesium Salts

Magnesium Hydrogen Phosphate and Trimagnesium Phosphate. The FDA has determined that Magnesium Hydrogen Phosphate and Trimagnesium Phosphate are GRAS as a direct human food ingredients.[41]

Toxicokinetics

Phosphorus (as phosphate) is an essential constituent of all known protoplasms, and its content is uniform across most plant and animal tissues.[42] According to the 1994 US Department of Agriculture survey of food intake of individuals, values for the mean daily phosphorus intake from food were 1495 mg (males, $\geq$ 9 years) and 1024 mg (females, $\geq$ 9 years). In both sexes, intakes decreased at age $\geq$ 51 years.

Structurally, phosphorus occurs as phospholipids, which constitute a major component of most biological membranes, and as components as nucleotides and nucleic acids. The total phosphorus concentration in whole blood is 13 mmol/L (40 mg/dL), most of which is in the phospholipids of red blood cells and plasma lipoproteins. Approximately 1 mmol/L (3.1 mg/dL) is present as inorganic phosphate (P_i), which is a tiny fraction of body phosphorus (<0.1%). In adults, P_i makes up approximately 15 mmol (465 mg) of body phosphorus and is located mainly in the blood and extracellular fluid. Phosphate enters the P_i pool during absorption from the diet and resorption from bone and is the primary source from which cells of all tissues derive both structural and high-energy phosphate.[42] Furthermore, most of the urinary phosphorus and hydroxyapatite mineral phosphorus are derived from the P_i.

Phosphates are absorbed from the gastrointestinal tract, and the transport of phosphate from the lumen is an active, energy-dependent process; vitamin D stimulates phosphate absorption.[43] At physiologic pH (7.4), extracellular phosphate is present primarily as the Disodium Phosphate and Sodium Phosphate (4:1). Once absorbed, phosphate combines with calcium to form Dicalcium Phosphate in bones and teeth.[30] Free orthophosphate is the primary form by which dietary P_i is absorbed. When phosphate ion is ingested in very large amounts, most of the phosphate ion uptake from the gut is eliminated in the feces.[44] According to another source, approximately two-thirds of the ingested phosphate is absorbed from the gastrointestinal tract in adults, and absorbed phosphate is almost entirely excreted in the urine.[43]

Animal

Phosphoric Acid. Phosphoric Acid dissociates and is then absorbed as phosphate and hydronium ions through mucous membranes.[45]

Sodium Salts

Sodium Hexametaphosphate. Sodium Hexametaphosphate is converted to Sodium Phosphate in the stomach.[46]

After hexametaphosphate was administered to rats and rabbits by stomach tube, no more than trace amounts of labile phosphate were found in the urine.[8,47]

Sodium Polyphosphate. Ingested polyphosphates are degraded by phosphatase enzymes to monophosphates.[30] The short- and long-chain polyphosphates are absorbed intact only to a very limited extent, if at all, and the larger molecules are hydrolyzed by phosphatases (present in the gut) to monophosphates.[48]

In an animal study (number and species not stated), 10% to 30% of administered Sodium Polyphosphate was absorbed as monophosphate, and small amounts of oligophosphates were found in the urine.[8] In another experiment in which labeled Sodium Polyphosphate was administered to rats, the chemical was not absorbed as such, but was taken up, after hydrolysis, as monophosphate and diphosphate. In 18 hours, 40% of the dose was hydrolyzed and absorbed.[8,49]

Potassium Salts

Potassium Metaphosphate. In an animal study (species and number not stated), 10% to 30% of administered Potassium Metaphosphate was absorbed as monophosphate, and small amounts of oligophosphates were found in the urine.[50] Study details were not provided.

When radiolabeled (radiolabel not specified), Potassium Metaphosphate was administered orally to rats, approximately half of the radioactivity was recovered from the feces, mainly as polymeric phosphate. Only a small percentage of the dose was found in the urine, in the form of monophosphate.[50]

Human

Sodium Salts

Sodium Phosphate. In a pharmacokinetic analysis, 45 mL of a laxative containing 30 g of Sodium Phosphate was administered to 13 normal volunteers.[51-53] The subjects were divided into the following 2 groups: group 1 (median weight = 60 kg) and group 2 (median weight = 119.2 kg). Serum and urine electrolytes were measured for 12 hours. Hydration was maintained by monitoring the weight, fluid intake, and total body water. Markedly elevated serum phosphate levels were observed in group 1 compared to group 2. The normalized area under the phosphate versus time curve was much higher in group 1 (1120 $\pm$ 190 mg/dL·min) than in group 2 (685 $\pm$ 136 mg/dL· min); $P < 0.001$was reported for this comparison. The urinary excretion of calcium was significantly lower in group 1 (mean = 16.4 $\pm$ 7.6 mg), compared to group 2 (mean = 39.2 $\pm$ 7.8 mg); $P < 0.001$ was reported for this comparison. The results of this study demonstrated that lower body-weight individuals develop prolonged high serum phosphate levels after ingesting Sodium Phosphate. The authors noted that individuals of lower body weight are at risk for acute phosphate nephropathy when they use colonoscopy preparations containing Sodium Phosphate.

Calcium Salts

Tricalcium Phosphate. The absorption of ingested Tricalcium Phosphate was evaluated in 10 women. The subjects ingested

Tricalcium Phosphate (1200 mg) after fasting for 12 hours.[54,55] Calcium and phosphorus absorption were determined by the post-load rise in urinary calcium and phosphate, respectively, above baseline. A statistically significant increase in urinary calcium excretion ($P < 0.001$) was observed during the 2 to 4 hours post-load period, and a statistically significant increase in serum calcium ($P < 0.02$) was observed at 4 hours post-load. Statistically significant increases in urinary phosphate excretion ($P < 0.001$) and serum phosphorus ($P < 0.001$) were also reported.

Toxicology

Calcium Phosphate

The English abstract of a Japanese publication on the safety of a Calcium Phosphate bone paste was available.[56] The following series of tests was performed: acute toxicity, pyrogenicity, hemolysis, intracutaneous reactivity, sensitization, genotoxicity, and cytotoxicity. The authors noted that there was no evidence of abnormal or toxic effects in any of these tests. The abstract does not include pertinent details relating to study results.

Single Dose (Acute) Toxicity

Animal

Dermal. *Phosphoric Acid and Salts*: Results of acute dermal studies for Phosphoric Acid and its salts are presented in Table 6. In studies involving rabbits, an LD_{50} of 2740 mg/kg and an $LD_{50} > 3160$ mg/kg were reported for Phosphoric Acid. For ammonium salts of phosphoric acid, the reported LD_{50} was > 5000 mg/kg (rats) and ranged from > 7940 mg/kg to > 10000 mg/kg (rabbits). LD_{50} values ranging from > 300 mg/kg to > 7940 mg/kg (rabbits) were reported for sodium salts of phosphoric acid. The dermal administration of potassium salts of phosphoric acid to rabbits resulted in reported LD_{50} values ranging from > 300 mg/kg to > 10000 mg/kg. LD_{50} values ranging from > 300 mg/kg to > 7940 mg/kg were reported for calcium salts of phosphoric acid. Reported LD_{50} values ranging from > 2000 mg/kg to > 7940 mg/kg were reported for magnesium salts of phosphoric acid.

Oral. *Phosphoric Acid and Salts*: Acute oral LD_{50} values for Phosphoric Acid and its salts are presented in Table 5. In studies involving rats, the LD_{50} for Phosphoric Acid ranged from 1530 mg/kg to 4400 mg/kg. The LD_{50} for Phosphoric Acid in rabbits was 2740 mg/kg. The oral LD_{50} for the ammonium salts of phosphoric acid in studies involving rats ranged from 3250 mg/kg (Ammonium Phosphate) to > 25100 mg/kg (Diammonium Phosphate). Sodium salts of phosphoric acid were administered to rats, mice, hamsters, and guinea pigs in acute oral toxicity studies, and the LD_{50} ranged from 1300 mg/kg (Tetrasodium Pyrophosphate [mice]) to 10600 mg/kg (Sodium Trimetaphosphate [rats]). For potassium salts of phosphoric acid administered orally in studies involving rats or mice, the acute oral LD_{50} ranged from 1000 mg/kg (Tetrapotassium Pyrophosphate [mice]) to 7100 mg/kg (Potassium Phosphate [rats]). In acute oral toxicity studies on calcium salts of phosphoric acid involving rats or mice, the reported LD_{50} ranged from 2170 mg/kg (Calcium Phosphate [rats]) to > 10000 mg/kg (Calcium Pyrophosphate [rats]). The reported LD_{50} for Magnesium Phosphate in studies involving rats ranged from > 1000 mg/kg (Magnesium Phosphate) to > 10000 mg/kg (Trimagnesium Phosphate).

Inhalation. *Phosphoric Acid and Salts*: Acute inhalation toxicity data on Phosphoric Acid and its sodium, potassium, and calcium salts are presented in Table 4. At the highest lethal concentrations tested, Phosphoric Acid caused tracheal lesions in rabbits, rats, and mice, but not in guinea pigs. Due to its hygroscopic nature, Phosphoric Acid aerosols will combine with water molecules in the air within the human tracheobronchial tree, which increases the aerodynamic diameter of the particles of the aerosol. This effect is known as hygroscopic growth. As a result, the deposition characteristics of these aerosols change as they pass through the respiratory tract, which will affect the total deliverable dose in the lungs after inhalation.[45] Overall, the data suggest that the sodium, potassium, and calcium salts of Phosphoric Acid exhibit a low potential for inhalation toxicity.

According to one publication, Phosphoric Acid caused moderate to acute inhalation toxicity in mice.[57] Pertinent details were not included in this BIBRA Toxicity Profile abstract on phosphoric acid and common inorganic phosphates.

Short-Term, Subchronic, and Chronic Toxicity Studies

Oral. The results of short-term, subchronic, and chronic oral toxicity studies on Phosphoric Acid and its salts are summarized in Table 7. In the longest duration feeding study on Phosphoric Acid, a no-observed-effect level (NOEL) of 338 mg/kg/d was reported for rats that received concentrations up to 0.75% in the diet for 1 year. The average weight of the parathyroid glands (only parameter assessed) was 235% of control values in rabbits that received oral doses of Diammonium Phosphate up to 700 mg/kg/d for up to 16 months. Kidney damage (nephrocalcinosis) was a common pathological finding in repeated oral dose toxicity studies involving sodium and potassium salts of Phosphoric Acid. There were basically no adverse effects in rats/monkeys fed calcium salts of Phosphoric Acid in the diet.

Developmental and Reproductive Toxicity

Reproductive and developmental toxicity data on ammonium, sodium, potassium, and calcium salts of Phosphoric Acid are presented in Table 8. Teratogenicity was assessed primarily using rats and mice; however, rabbits and hamsters were also used. These salts did not produce teratogenic effects in vivo, and the highest dose tested was 1500 mg/kg/d Diammonium Phosphate (in rats) for 35 days. However, the following salts of Phosphoric Acid were teratogenic to chick embryos: Tetrasodium Pyrophosphate (injection of 5 mg/egg), Sodium Hexametaphosphate (injection of 0.5-10 mg/egg), Sodium Phosphate (injection of 0.5-10 mg/egg), Potassium Phosphate (injection of

10 mg/egg), Calcium Phosphate (injection of 2.5 mg/egg), and Tricalcium Phosphate (injection of 2.5 mg/egg). Information relating to whether or not pH was measured or controlled in the eggs was not found.

Genotoxicity

The in vitro and in vivo genotoxicity data on Phosphoric Acid and its ammonium, sodium, potassium, and calcium salts are presented in Table 9. The in vitro tests included the Ames/*Salmonella* mutagenicity assay (with and without metabolic activation), the *Saccharomyces cerevisiae* mutagenicity assay (with and without metabolic activation), the chromosome aberrations assay (Chinese hamster fibroblasts), and the in vitro cytogenetics assay (human lung cells). The in vivo tests included the dominant lethal test (rats), host-mediated assay (mice), and the mouse translocation test. Phosphoric Acid and its ammonium, sodium, potassium, and calcium salts did not produce positive responses in in vitro or in vivo genotoxicity assays.

Carcinogenicity

Animal

Acids

Phosphoric Acid. According to one source, no carcinogenic potential was demonstrated in limited feeding studies involving rats treated with Phosphoric Acid or several of its salts. However, in rodents treated orally, several phosphates have been shown to promote the effects of known carcinogenicity.[57] Pertinent details were not included in this BIBRA Toxicity Profile abstract on phosphoric acid and common inorganic phosphates.

Sodium Salts

Disodium Phosphate and Tetrasodium Pyrophosphate. An oral feeding study involving groups of 10 male and 10 female rats fed various concentrations of a mixed preparation (33% Potassium Metaphosphate + 67% Tetrasodium Pyrophosphate [in Sherman diet]) was conducted.[8,58] The following diets were fed to the rats:

- 0.5% commercial preparation (effective concentration [Potassium Metaphosphate] = 0.5% × 33% = 0.17%; effective concentration [Tetrasodium Pyrophosphate] = 0.5% × 67% = 0.34%)
- 1% commercial preparation (effective concentration [Potassium Metaphosphate] = 1% × 33% = 0.33%; effective concentration [Tetrasodium Pyrophosphate] = 1% × 67% = 0.67%)
- 5% commercial preparation (effective concentration [Potassium Metaphosphate] = 5% × 33% = 1.7%; effective concentration [Tetrasodium Pyrophosphate] = 5% × 67% = 3.4%)

From each dietary group, second and third generations were produced and feeding was continued. For all dietary groups, the tumor incidence was not greater than that observed in control animals. Additional study details were not provided.

Pentasodium Triphosphate. Groups of weanling rats of the Rochester strain (number not stated) were maintained on a diet supplemented with 0.05%, 0.5%, or 5% Pentasodium Triphosphate for 2 years.[59] The carcinogenesis indexes were similar to the frequencies expected for aging rats and did not vary among dietary groups.

Sodium Hexametaphosphate. Groups of weanling rats (males and females; number and strain not stated) were fed a diet containing 0.05%, 0.5%, or 5% Sodium Hexametaphosphate for 2 years.[59] There was no correlation between the dietary level of Sodium Hexametaphosphate and tumor incidence.

Sodium Trimetaphosphate. A diet containing 0.1%, 1%, or 10% Sodium Trimetaphosphate was fed to groups of weanling rats (number and strain not stated) for 2 years. There was no correlation between the dietary level of Sodium Trimetaphosphate and tumor incidence.[59]

Sodium Metaphosphate. Calcium sodium metaphosphate (CSM) fiber is a man-made inorganic fiber composed of condensed polyphosphate chains in a specific crystal lattice.[60] Male and female Fischer 344 rats (80/sex/group) were exposed (inhalation) to CSM fiber 6 h/d, 5 d/wk at target-exposure levels of 0, 1, 5, or 25 mg/m^3 (corresponding to 0, 27, 80, and 513 fibers/mL, respectively) for 24 months. At 3 and 12 months, 10 rats/sex/group were killed and, at 18 and 24 months, 5 rats/sex/group were killed. Additionally, 5 rats/sex/group were removed from exposure at 18 months and maintained for a 6-month recovery period. No increase in tumors (benign or malignant) was observed in this study.

Tumor Promotion

Potassium Salts

Dipotassium Phosphate. In a tumor promotion study involving groups of 20 uninephrectomized male rats, the following diets were used[17,61]:

- Group I: 1000 ppm *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN) diet (2 weeks) + 50000 ppm Dipotassium Phosphate diet (18 weeks)
- Group II: Basal diet (2 weeks) + 50000 ppm Dipotassium Phosphate (18 weeks)
- Group III: 1000 ppm EHEN diet (2 weeks) + the basal diet (18 weeks)
- Group IV: Basal diet (20 weeks)

The rats were fed EHEN (1000 ppm) in the diet for 2 weeks, and the left kidney was removed at week 3. After nephrectomy, the rats were fed Dipotassium Phosphate (50000 ppm) in the diet for 18 weeks (from week 3 to week 20). A control group of 20 rats received basal diet only after EHEN administration and nephrectomy. The mean relative kidney weight per body weight in group I was significantly greater when compared to group III. Additionally, the mean kidney weight in group II was significantly greater when compared to group IV. The numbers of simple hyperplastic foci and adenomatous hyperplastic foci in group I animals were statistically significantly greater ($P < 0.05$) when compared to group III. The incidence of renal cell tumors was 30% in group I. Nephropathy, lymphocyte accumulation, hyaline droplets in proximal convoluted tubular cells, and dilatation of the proximal convoluted tubular cells were observed in the cortex of group I and group II animals. Calcification was observed in the renal medulla and cortex of groups I and II. It was concluded that Dipotassium Phosphate promoted the development of renal tubular cell tumors. The authors noted that the results documented in this study clearly suggest a link between toxicity-dependent proliferation and promoting ability.

In a medium-term bioassay for renal tumorigenesis, the feeding of male Wistar rats with 5% potassium dibasic phosphate in the diet promoted the development of preneoplastic lesions.[62] These study results were obtained from the limited details found in the English abstract of a Japanese publication.

Phosphate. A study was performed to elucidate the potential effects of high dietary phosphate (P_i) on the development of lung cancer.[63] The first experiment involved 2 groups of male K-*ras*^{LA1} mice (9 per group). One group received an AIN93-based diet containing 0.5% P_i (normal P_i), and the other group received the same diet fortified with 1% P_i (high P_i). Both diets were fed to the mice for 4 weeks, after which the animals were killed. Blood samples were obtained and necropsy was performed. Tumor lesions of lung surfaces were counted and the diameter of each lesion was measured. A lobe of the left lung was prepared for histopathological examination and immunohistochemistry. The diet containing 1% P_i increased lung tumor progression and growth, when compared with the diet containing 0.5% P_i. Histopathological examination results showed that pulmonary tumor progression was markedly stimulated by 1% P_i in the diet. The number and size (at least 1.5 mm in diameter) of lung surface tumor lesions (adenomas) increased significantly ($P < 0.05$). P_i (1%) in the diet also had the following effects: (1) increased the sodium-dependent inorganic phosphate transporter-2b protein levels in the lungs; (2) stimulated pulmonary protein kinase B (Akt; known to regulate cell cycle progression) activity, while suppressing (a) the protein levels of tumor suppressor phosphatase and tensin homolog deleted on chromosome 10 and (b) the Akt binding partner carboxyl-terminal modulator protein, resulting in facilitated cap-dependent protein translation; and (3) significantly ($P < 0.05$) stimulated cell proliferation in the lungs of K-*ras*^{LA1} mice.

In a second study (urethane-induced lung cancer model), A/J mice were injected intraperitoneally with urethane (1 mg/g body weight) in saline. At 4-week postinjection, the mice were divided into 2 groups (7 mice per group) and fed 1% P_i and 0.5% P_i in the diet, respectively, for 4 weeks. The effect of high dietary P_i on lung tumorigenesis was confirmed in this experiment. P_i (1%) in the diet statistically significantly increased ($P < 0.05$) tumor development. Both the mean number of tumors and the mean tumor diameter (at least 1 mm in diameter) increased statistically significantly ($P < 0.05$). Histopathological examination results also showed that pulmonary tumor progression was stimulated. The authors noted that the results of this study indicate that high dietary P_i strongly activated Akt signaling and increased lung tumorigenesis.[63]

Other Relevant Studies

Cytotoxicity

Calcium Phosphate and Dicalcium Phosphate Dihydrate. The cytotoxicity of the following mixture was evaluated using a mouse L-929 cell suspension: Tricalcium Phosphate (90%; α-) and Dicalcium Phosphate Dihydrate (10%) in a solution containing chondroitin sulfate (5%) and sodium succinate (12%).[64] Cell morphology was evaluated at 24 hours; the affected area of the cell layer was determined using microscopy. Contracted cells, rounded cells with dark nuclei, and broken cells were considered damaged cells. A very low degree of cytotoxicity (mild cytotoxicity) was observed.

Calcium Pyrophosphate. The cytotoxicity of Calcium Pyrophosphate was studied using Chinese hamster ovary K-1 cells.[11] Cytotoxicity potential was determined quantitatively by cytolethality (expressed as the cytotoxicity index [$IC_{50\%}$]) using a colony suppression assay. The $IC_{50\%}$ is defined as the concentration that is necessary to kill half of the cell population or the concentration that suppresses colony formation to 50% of the control value. Phenol solution (0.02%) and alumina extracts served as positive and negative controls, respectively. Calcium Pyrophosphate was not cytotoxic ($IC_{50\%} = 100$). The positive and negative controls performed as expected.

Dermal Irritation and Sensitization Studies

Skin irritation and sensitization data on Phosphoric Acid and its ammonium, sodium, potassium, calcium, and magnesium salts are presented in Table 10. A broad range of reactions (from irritation/no irritation [Phosphoric acid and salts] to irritating/corrosive [Phosphoric Acid] effects) reported for phosphoric acid or its salts at concentrations within and outside of the range of those used in cosmetic products. Phosphoric acid was an irritant at concentrations as low as 2.5%; however, the pH of the test substance was low, pH of 2.1.67 The corrosive effect of Phosphoric Acid was observed at concentrations ranging from 17.5% (pH of 0.6-0.2) to 100%.[48,65] The sodium salts were nonirritating (Sodium Phosphate)50 to moderately irritating (Disodium Phosphate),[48] and the potassium and calcium salts were nonirritating (Potassium Phosphate and Dicalcium Phosphate)[48] to mildly irritating (Dipotassium Phosphate and Calcium Phosphate)50 to rabbit skin. The ammonium salts (Ammonium Phosphate and Diammonium Phosphate) were nonirritating to mildly irritating to rabbit skin.[48] The magnesium salts of Phosphoric Acid (Magnesium Phosphate and Trimagnesium Phosphate) were nonirritating to the skin of rabbits.[48] Pentasodium Triphosphate (50% solution) and Sodium Metaphosphate (1% solution) were mildly irritating to the skin of human subjects.[30] Phosphoric Acid was not sensitizing in human subjects,[48,66] and Sodium Phosphate (10% in propylene glycol) was not sensitizing in the local lymph node assay.[67]

Ocular Irritation

Animal

Ocular irritation data on phosphoric acid and its ammonium, sodium, potassium, calcium, and magnesium salts are presented in Table 11. Phosphoric Acid was corrosive to the eyes of rabbits at concentrations in the 70% to 85% range[48,68,69] but was nonirritating at concentrations of 10% and 17%.[65,68] None of the salts of Phosphoric Acid was found to be corrosive to the eyes of rabbits. However, ocular irritation was observed; for example, Tetrasodium Pyrophosphate was irritating at a concentration of 10% and Trisodium Phosphate was irritating at concentrations of 10% and 15%.[30,48]

Mucosal Irritation

Human

Phosphoric Acid. Phosphoric Acid (50%) was applied to the gingival tissue and teeth of 26 orthodontic patients.[3] The 90-s contact period for the acid was followed by rinsing. No demonstrable test substance-related effect on treated tissues was observed during the 7-day observation period.

Tetrasodium Pyrophosphate and Tetrapotassium Pyrophosphate. Some nonprescription dentifrices, particularly pyrophosphate-based tartar control toothpastes, may be irritating to oral tissues.[33] The following clinical observations were made in patients (number not stated) at a dental clinic who frequently uses tartar control toothpastes containing Tetrasodium Pyrophosphate and/or Tetrapotassium Pyrophosphate: pale gingival tissues, mucosal sloughing, small blisters, dryness of oral tissues, and/or free-gingival-margin erythema. Subjective symptoms included a painful, burning sensation of oral tissues (most commonly gingival mucosa); a generalized, nonspecific sensitivity or odd feeling to teeth and/or soft tissues; and sensations of "itchy" oral tissues. Patient complaints averaged approximately 5 per week over a 2-year period. Amelioration of the patients' chief symptoms occurred rapidly upon switching to a nontartar control toothpaste.

Clinical Reports

Calcium Pyrophosphate

The articular deposition of Calcium Pyrophosphate (Calcium Pyrophosphate deposition disease) is a common age-related phenomenon. Frequently, this disease is asymptomatic and unassociated with structural joint damage.[70,71] Acute attacks of synovitis, resulting in pseudogout, are observed.[72] These attacks are often provoked by local trauma or surgery and commonly involve the knee, and, less often, the wrist, hip, shoulder, and elbow.

Sodium Phosphate

A systematic review of adverse event reports relating to oral Sodium Phosphate (used for bowel cleansing prior to colonoscopy) was performed.[73] Fifty-eight publications of significant events in 109 patients who used Sodium Phosphate were identified. Between January of 2006 and December of 2007, the most commonly reported findings were electrolyte disturbances, renal failure, and colonic ulceration. The number of cases of renal failure reported to FDA during this period was 171.

A retrospective study of renal adverse event reports was performed using the FDA Adverse Event Reporting System, a voluntary reporting system available for public access.[74] A total of 2097223 files (year 2004-2008 and the first 9 months of 2009) from FDA's website were examined. Of the 178 patients (71% women) on sodium phosphate tablets identified, an increasing number of renal adverse drug reactions (ADRs) associated with tablet preparations were reported each year. In 2006, 9 of 74 (12%) renal ADRs were reported to be from ingesting tablets; results for subsequent year were as follows: 40 of 181 (22%; 2007), 46 of 148 (31%; 2008), and 60 of 795 (7.55%; 2009). The mean weight for women with renal complications from tablet preparations was 68.57 $\pm$ 1.78 kg, statistically significantly lower than the national average weight of 74 $\pm$ 0.5 kg for the same age-group ($P = 0.003$) in the National Health and Nutrition Examination Survey. It was concluded that renal ADRs from sodium phosphate tablets were more common in women with a mean body weight lower than the national average weight.

In more recent studies, 10 adult cases of acute phosphate nephropathy, associated with acute renal failure, following administration of a Sodium Phosphate preparation before colonoscopy, and a case series of 3 children with severe hyperphosphatemia and hypocalcemia after the use of Sodium Phosphate-containing laxatives were reported.[75,76] Acute renal failure due to phosphate nephropathy following bowel cleansing with an oral Sodium Phosphate solution was reported in another patient.[77] Electron microscopy of a kidney biopsy sample revealed membranous glomerulonephritis and Calcium Phosphate deposits were observed in tubular cells and in tubules. Phosphate remained elevated for 11 days; other electrolyte levels were normal. A biopsy taken only 2 months before the acute kidney disease showed no sign of the Calcium Phosphate deposits in the second biopsy. It was concluded that the phosphate load given to the patient was responsible for the biopsy findings.

Epidemiology

Acids

Phosphoric acid. In the 1980s, a large population-based case-control study in Montreal was performed to explore the possible associations among hundreds of occupational substances and multiple cancer sites,[78] and an analysis of the occupational information collected in this study (focusing on renal cell cancer) was subsequently performed.[78] In this study, the following individuals were interviewed: 142 male patients with pathologically confirmed renal carcinoma; 1900 controls with cancer at other sites; and 533 population-based controls. Logistic regression results for exposure to selected substances were presented, including the following 2 sets of odds ratios (ORs):

(1) OR_1 (95% CI): ORs (adjusted for respondent status, age, smoking, and body mass index [BMI]) and 95% CI; (2) OR_2 (95% CI): ORs (adjusted for respondent status, age, smoking, BMI, and occupational confounders) and 95% CI. The authors concluded that there was evidence of excess risk for renal cell carcinoma following workplace exposure to Phosphoric Acid, as indicated by the following ORs: The OR_1 value reported for phosphoric acid was 3.4 (1.3-9.2), and an OR_2 value of 2.4 (0.8-7.0) was reported.[78]

In the International Agency for Research on Cancer (IARC) monograph on occupational exposures to mists and vapors from sulfuric acid and other inorganic acids (including Phosphoric Acid), several questionable epidemiological studies in the phosphate fertilizer manufacturing industry showed excess lung cancer; but, IARC did not classify Phosphoric Acid as carcinogenic.[79] However, IARC did conclude that occupational exposure to strong inorganic acid mists containing sulfuric acid is carcinogenic to humans.

Phosphates. Cancer morbidity and mortality were studied in a population of employees of phosphate ore mining and processing operations in Central Florida.[80] The workers involved in the study were employed by participating phosphates companies between 1950 and 1979, and the study population consisted of 3541 male employees who had worked for 6 months or more. Based upon an industrial hygiene analysis, only drying/shipping, chemical/fertilizer, and maintenance job categories were found to have the potential for exposure to high levels of dust, chemical fumes, or radiation. Cancer incidence was traced using questionnaires confirmed by medical records and by tumor registry searches. Standardized incidence ratios were calculated. To estimate the study population's risk in relation to general rates in the United States, standardized mortality ratios (SMRs) adjusted for age and calendar time were calculated. The SMRs were tested for statistical significance at the 0.05 level using the Poisson distribution. Statistically significant elevations in lung cancer (SMR = 1.62) and emphysema were observed when compared to rates in the United States. For workers employed over a period of 20 years, there was a dose-response trend of increasing lung cancer risk with increasing duration of employment (SMR = 2.48, with 20 years of employment). There was no evidence of excess lung cancer risk among employees who were hired after 1960. The authors noted that multivariate analyses and internal comparisons of risk by job type were consistent with a hypothesis of occupationally related lung cancer, but that the small numbers prevented firm conclusions.

Risk Assessment

Phosphates, Diphosphates, and Polyphosphates

Oral. Phosphates, diphosphates (ie, pyrophosphates), and polyphosphates (eg, metaphosphates) were evaluated by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives.[81] A maximum tolerable daily intake (MTDI) of 70 mg/kg was determined, based on the lowest concentration of phosphorus (6600 mg/d) that caused nephrocalcinosis in rats. "The MTDI is expressed as phosphorus and applies to the sum of phosphates naturally present in food and the phosphates derived from use of these food additives." The FAO/WHO Expert Committee considered establishing an average daily intake to be inappropriate because phosphorus (as phosphates) is an essential nutrient and an unavoidable constituent of food. The Federation of American Societies for Experimental Biology estimate of MTDI of phosphates in man is also 70 mg/kg.[82]

Inhalation

Phosphoric Acid. The EPA calculated an inhalation reference concentration (RfC) of 1×10^{-2} mg/m^3 for Phosphoric Acid (the critical effect is bronchiolar fibrosis).[83] Development of an inhalation RfC involves evaluating toxic effects inside the respiratory system (port-of-entry effects) and outside the respiratory system (extrarespiratory effects). In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects over a lifetime of exposure. The calculated RfC for Phosphoric Acid is based on inhalation toxicity data summarized in the Repeated Dose Toxicity Section of this safety assessment.[84] Based on the histologic lesions in the tracheobronchiolar region, 180 mg/m^3 was the LOAEL, and 50 mg/m^3 was the NOAEL in this study.

Summary

The safety of 31 ingredients, Phosphoric Acid and its salts, as used in cosmetics is reviewed in this safety assessment. The functions of these ingredients in cosmetic products frequently include buffering agents, corrosion inhibitors, chelating agents, and pH adjusters.

According to the 2016 VCRP data, the greatest reported use frequency is for Phosphoric Acid (489 formulations, mostly rinse-off), followed by Dicalcium Phosphate (327 formulations, mostly leave-on). Lower use frequencies were reported for the remaining salts. The results of a concentration of use survey provided in 2015 indicate that Dicalcium Phosphate Dihydrate has the highest maximum concentration of use; it is used at concentrations up to 49% in rinse-off products (dentifrices).

Phosphoric Acid ionizes and is then absorbed as phosphate and hydronium ions through mucous membranes. Some of the phosphate and hydronium ions are conjugated in the liver and then excreted in the urine. Following the absorption of phosphates from the gastrointestinal tract, phosphate combines with calcium to form calcium hydrogen orthophosphate in bones and teeth. Free orthophosphate is the primary form by which dietary P_i is absorbed. In general, approximately two-thirds of the ingested phosphate is absorbed from the gastrointestinal tract in adults, and absorbed phosphate is almost entirely excreted in the urine.

In acute inhalation toxicity studies, at the highest lethal concentrations, Phosphoric Acid caused tracheal lesions in rabbits, rats, and mice, but not in guinea pigs. Overall, the data suggest that the sodium, potassium, and calcium salts exhibit a low potential for inhalation toxicity. The EPA has calculated an inhalation RfC of 0.01 mg/m^3 for Phosphoric Acid, based on the results from 2 parallel 13-week inhalation toxicity studies involving rats. In general, the RfC is an estimate of a daily inhalation exposure of the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime.

In acute oral toxicity studies involving rats, the LD_{50} for Phosphoric Acid ranged from 1530 mg/kg to 4400 mg/kg. The oral LD_{50} for Phosphoric Acid in rabbits was 2740 mg/kg. The oral LD_{50} for the ammonium salts of Phosphoric Acid in studies involving rats ranged from 5750 mg/kg (Ammonium Phosphate) to > 25100 mg/kg (Diammonium Phosphate). Sodium salts of Phosphoric Acid were administered to rats, mice, hamsters, and guinea pigs in acute oral toxicity studies, and LD_{50} values ranged from 1300 mg/kg (Tetrasodium Pyrophosphate [mice]) to 10600 mg/kg (Sodium Trimetaphosphate [rats]). For potassium salts of Phosphoric Acid administered orally in studies involving rats or mice, acute oral LD_{50} values ranged from 1000 mg/kg (Tetrapotassium Pyrophosphate, involving mice) to 7100 mg/kg (Potassium Phosphate [rats]). In acute oral toxicity studies on calcium salts of Phosphoric Acid involving rats or mice, LD_{50} values ranged from 2170 mg/kg (Calcium Phosphate [rats]) to > 10000 mg/kg (Calcium Pyrophosphate [rats]). LD_{50} values for Magnesium Phosphate in studies involving rats ranged from > 1000 mg/kg (Magnesium Phosphate) to > 10000 mg/kg (Trimagnesium Phosphate).

The feeding of Phosphoric Acid at concentrations up to 0.75% in the diet of rats for 52 weeks yielded an NOEL of 338 mg/kg/d. An NOAEL of 105 mg/kg/d was reported in a study in which sheep received doses of Phosphoric Acid up to 211 mg/kg/d for 70 days. An NOAEL of 250 mg/kg/d was reported for groups of rats that received Diammonium Phosphate at doses up to 1500 mg/kg/d for 35 days. The average weight of the parathyroid glands (only parameter assessed) was 235% of control values in rabbits that received oral doses of Diammonium Phosphate up to 700 mg/kg/d for up to 16 months.

A study of rats fed Disodium Phosphate or Disodium Pyrophosphate (up to 5% in the diet) for 100 days resulted in an LOEL (renal histopathology) of < 2571 mg/kg/d (Disodium Phosphate) and an LOEL (renal histopathology) = 450 mg/kg/d (Disodium Pyrophosphate). When Disodium Phosphate, Pentasodium Triphosphate, or Tetrasodium Pyrophosphate was administered to rats at concentrations up to 5% in the diet for 39 weeks, an LOEL of 495 mg/kg/d was reported. Of the NOELs determined in rat studies, the highest NOEL (338 mg/kg/d) was reported in a study in which rats were fed Phosphoric Acid at concentrations up to 0.75% in the diet daily for > 52 weeks. The highest NOAEL (2623 mg/kg/d) was reported in a study in which rats were fed Dipotassium Phosphate at concentrations up to 5.1% in the diet daily for 150 days. In studies involving dogs, an NOAEL of 100 mg/kg/d was reported for the following sodium salts, each of which was administered orally at a dose of 100 mg/kg/d for 30 days: Pentasodium Triphosphate, Sodium Polyphosphate/Sodium Hexametaphosphate, and Sodium Trimetaphosphate. Kidney damage (nephrocalcinosis) was a common finding in repeated dose oral toxicity studies involving sodium salts of Phosphoric Acid. The feeding of commercial preparations, to rats, containing effective concentrations of up to 3.4% Tetrasodium Pyrophosphate and 1.7% Potassium Metaphosphate also resulted in nephrocalcinosis.

When potassium salts of Phosphoric Acid were fed in the diet of rats at concentrations ranging from 0.6% to 10%, nephrocalcinosis/nephrotoxicity was observed at concentrations of 5% (Tetrapotassium Pyrophosphate [daily doses; number of days not stated]) and 10% (Tetrapotassium Pyrophosphate [daily doses; number of days not stated] or Dipotassium Phosphate [8 weeks]). Nephrocalcinosis was also observed in dogs that were fed a diet providing Dipotassium Phosphate at a dose of 800 mg/kg/d. There were basically no adverse findings in rats/monkeys fed calcium salts of Phosphoric Acid in the diet (up to 0.8% calcium and 1.30% phosphorus). The same was true for rats that received Dicalcium Phosphate or Tricalcium Phosphate at doses up to 1000 mg/kg/d.

In acute dermal toxicity studies involving rabbits, an LD_{50} of 2740 mg/kg and an LD_{50} > 3160 mg/kg were reported for Phosphoric Acid. For ammonium salts of Phosphoric Acid, the dermal LD_{50} for rats was > 5000 mg/kg (rats) and ranged from > 7940 mg/kg to > 10000 mg/kg for rabbits. Dermal LD_{50} values ranging from > 300 mg/kg to > 7940 mg/kg (rabbits) were reported for sodium salts of Phosphoric Acid. The dermal administration of potassium salts of Phosphoric Acid to rabbits resulted in dermal LD_{50} values ranging from > 300 mg/kg to > 10000 mg/kg. Dermal LD_{50} values ranging from > 300 mg/kg to > 7940 mg/kg were reported for calcium salts of Phosphoric Acid. LD_{50} values ranging from > 2000 mg/kg to > 7940 mg/kg were reported for magnesium salts of Phosphoric Acid.

The teratogenicity of ammonium, sodium, potassium, and calcium salts of Phosphoric Acid was assessed primarily using rats and mice; however, rabbits and hamsters were also used. These salts did not produce teratogenic effects in vivo, and the highest dose tested was Diammonium Phosphate at 1500 mg/kg/d for 35 days. However, the following salts of Phosphoric Acid were teratogenic to chick embryos: Tetrasodium Pyrophosphate (injection of 5 mg/egg), Sodium Hexametaphosphate (injection of 0.5-10 mg/egg), Sodium Phosphate (injection of 0.5-10 mg/egg), Potassium Phosphate (injection of 10 mg/egg), Calcium Phosphate (injection of 2.5 mg/egg), and Tricalcium Phosphate (injection of 2.5 mg/egg).

Both in vitro and in vivo genotoxicity data on Phosphoric Acid and its ammonium, sodium, potassium, and calcium salts are available. The in vitro tests included the Ames/*Salmonella* mutagenicity assay (with and without metabolic activation), the *S cerevisiae* mutagenicity assay (with and without metabolic activation), the chromosome aberrations assay (Chinese hamster fibroblasts), and the in vitro cytogenetics assay (human lung cells). The in vivo tests included the dominant lethal test (rats), host-mediated assay (mice), and the mouse translocation test. Phosphoric Acid and its ammonium, sodium, potassium, and calcium salts did not produce positive responses in in vitro or in vivo genotoxicity assays.

In an oral carcinogenicity study, rats were fed mixtures containing up to 1.7% Potassium Metaphosphate and up to 5% Tetrasodium Pyrophosphate. Feeding was continued through the second and third generations produced. For all dietary groups, the tumor incidence was similar to control animals. When groups of rats were fed Pentasodium Triphosphate or Sodium Hexametaphosphate at concentrations up to 5% for 2 years, there was no correlation between concentration in the diet and tumor incidence. The same was true for rats fed a diet containing up to 10% Sodium Trimetaphosphate.

The results of a study on high dietary P_i intake and the development of lung cancer in mice indicated that high dietary P_i strongly activated Akt signaling and increased lung tumorigenesis

In a population-based case-control study, workplace exposure to Phosphoric Acid produced some evidence of excess risk of renal cell carcinoma. Furthermore, in an IARC monograph on occupational exposure to Phosphoric Acid and other inorganic acids, there were several questionable epidemiological studies of the phosphate fertilizer manufacturing industry that showed excess lung cancer. However, IARC did not classify Phosphoric Acid as carcinogenic. Dipotassium Phosphate, given in the diet (containing the carcinogen, EHEN) of male rats, promoted the development of renal tumors.

Skin irritation and sensitization data on Phosphoric Acid and its ammonium, sodium, potassium, calcium, and magnesium salts are available, and a broad range of reactions (nonirritating to corrosive) have been reported. Phosphoric Acid was classified as nonirritating or corrosive. Phosphoric acid was an irritant at concentrations as low as 2.5%; however, the pH of the test substance was low, pH of 2.1. The corrosive effect of Phosphoric Acid was observed at concentrations ranging from 17.5% (pH of 0.6-0.2) to 100%, but 19% Phosphoric Acid was nonirritating. The sodium salts were nonirritating to moderately irritating, and the potassium and calcium salts were nonirritating to mildly irritating to rabbit skin. The magnesium salts of Phosphoric Acid were nonirritating to the skin of rabbits. Pentasodium Triphosphate and Sodium Metaphosphate were mildly irritating to the skin of human subjects. Phosphoric Acid was a nonsensitizer in human subjects, and Sodium Phosphate was a nonsensitizer in the local lymph node assay.

Phosphoric Acid was corrosive to the eyes of rabbits at concentrations in the 70% to 85% range, but was nonirritating at concentrations of 10% and 17%. None of the salts of Phosphoric Acid was found to be corrosive to the eyes of rabbits. However, ocular irritation was observed; for example, Tetrasodium Pyrophosphate was irritating at a concentration of 10% and Trisodium Phosphate was irritating at concentrations of 10% and 15%.

Renal failure has resulted from the use of sodium phosphate-containing colonoscopy preparations. Other case reports have indicated that some nonprescription dentifrices, particularly pyrophosphate-based tartar control toothpastes, may be irritating (erythema, burning, and mucosal sloughing) to oral tissues. The clinical findings relate to tartar control toothpastes containing Tetrasodium Pyrophosphate and/or Tetrapotassium Pyrophosphate.

Discussion

The Panel noted the broad range of results (from irritation/no irritation to irritating/corrosive effects) reported for Phosphoric Acid or its salts at concentrations within and outside of the range of those used in cosmetic products. The results of a concentration of use survey provided by the Council in 2015 indicate that Dicalcium Phosphate Dihydrate has the highest maximum concentration of use; it is used at concentrations up to 49% in rinse-off products (dentifrices). Phosphoric acid was an irritant at concentrations as low as 2.5%; however, the pH of the test substance was low, pH of 2.1. The corrosive effect of Phosphoric Acid was observed at concentrations ranging from 17.5% (pH of 0.6-0.2) to 100%. For salts of Phosphoric Acid, skin irritation was observed at concentrations ranging from 1% to 50% and ocular irritation was observed at concentrations as low as 10% and 15%.

The Panel noted that test animals fed high concentrations of Phosphoric Acid in the diet exhibited renal damage and evidence of the tumor-promoting potential of Phosphoric Acid. The oral exposures to Potassium Phosphate in one of these studies promoted the development of kidney tumors initiated by treatment with a potent renal carcinogen. The Panel also discussed animal studies on Potassium Phosphate indicating that this salt was not associated with renal damage or cancer, and one epidemiological study suggesting an association between occupational exposures to Phosphoric Acid and kidney and lung cancer. The Panel concluded that renal toxicity and tumor promotion would not be expected from exposures to cosmetic products containing phosphoric acid or its salts, because such exposures can reasonably be anticipated to be substantially lower than those associated with adverse effects in these studies.

Concern about heavy metals that may be present in salts of Phosphoric Acid was expressed by the Panel. They stressed that the cosmetics industry should continue to use current good manufacturing practices to limit impurities in the ingredient before blending into cosmetic formulations.

The Panel discussed the issue of incidental inhalation exposure from propellant and pump hair sprays and face powders. The Panel considered inhalation toxicity data and pertinent data indicating that incidental inhalation exposures to these ingredients in such cosmetic products would not cause adverse health effects, including acute inhalation toxicity data on Phosphoric Acid and its salts and data characterizing the potential for these ingredients to cause acute and repeated dose oral toxicity, and ocular or dermal irritation or sensitization. The Panel noted that droplets/particles from spray and loose-powder cosmetic products would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Conclusion

The Panel concluded that the following 31 ingredients are safe in the present practices of use and concentration in cosmetics as described in this safety assessment, when formulated to be nonirritating.

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Phosphoric Acid	Disodium Pyrophosphate	Sodium Metaphosphate
Ammonium Phosphate	Magnesium Hydrogen Phosphate*	Sodium Polyphosphate*
Dicalcium Phosphate	Magnesium Phosphate*	Sodium Phosphate
Calcium Dihydrogen Phosphate	Metaphosphoric Acid*	Sodium Trimetaphosphate*
Calcium Phosphate	Pentapotassium Triphosphate	Tetrapotassium Pyrophosphate
Calcium Potassium Sodium Phosphate*	Pentasodium Triphosphate*	Tetrasodium Pyrophosphate
Calcium Pyrophosphate	Phosphate Buffered Saline*	Tricalcium Phosphate
Diammonium Phosphate	Potassium Metaphosphate	Trimagnesium Phosphate
Dicalcium Phosphate Dihydrate	Potassium Phosphate	Trisodium Phosphate
Dipotassium Phosphate	Potassium Polyphosphate*	
Disodium Phosphate	Sodium Hexametaphosphate	

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

Author Contribution

Johnson, W. contributed to conception and design; contributed to acquisition, analysis, and interpretation; and drafted the manuscript. Heldreth, B. contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; and critically revised the manuscript. Boyer, I., Bergfeld, W., Belsito, D., Hill, R., Klaassen, C., Liebler, D., Marks, J., Shank, R., Slaga, T., Snyder, P., and Gill, L. contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Declaration of Conflicting Interests

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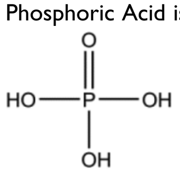
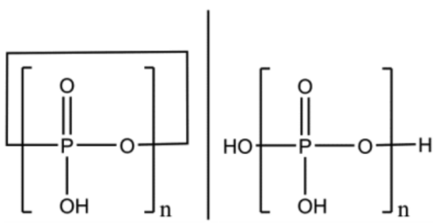
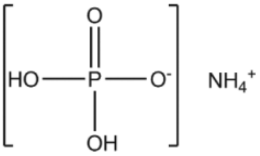
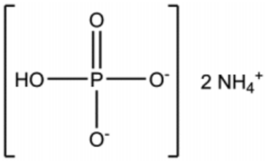
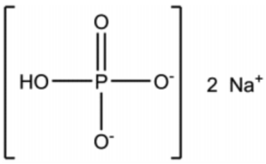
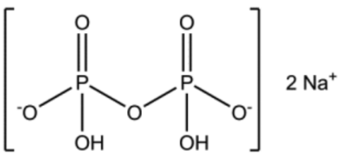
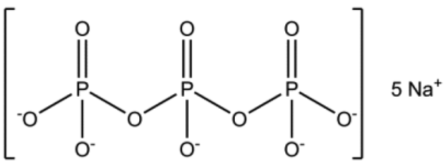
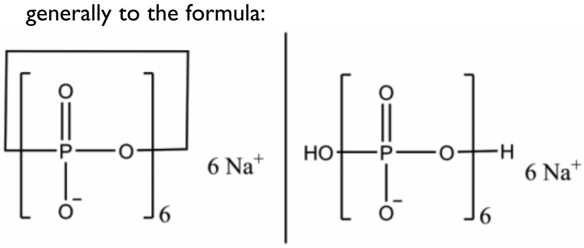
Table 1. Definitions, Structures, and Functions of the Ingredients in This Safety Assessment.[1,6]

Ingredient/CAS No.	Definition and Structure	Function
Acids		
Phosphoric Acid 7664-38-2	Phosphoric Acid is the inorganic acid that conforms to the formula:  [Commonly called orthophosphoric acid]	Fragrance Ingredients, pH Adjusters
Metaphosphoric Acid 10343-62-1 37267-86-0	Metaphosphoric Acid is the inorganic acid that conforms to the formula:  ["Metaphosphoric" is a term used for a series of condensed protonated phosphates prepared by dehydration of orthophosphates; differing reaction conditions lead to various cyclic	pH Adjusters

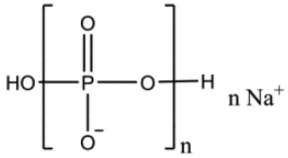
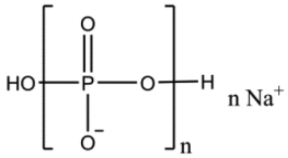
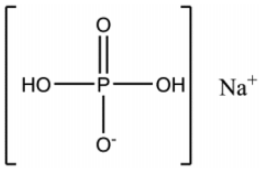
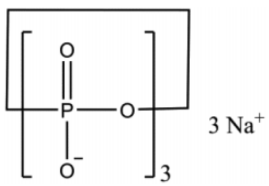
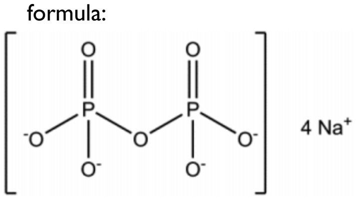
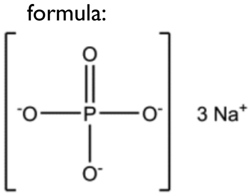
(continued)

Table 1. (continued)

Ingredient/CAS No.	Definition and Structure	Function
	or linear polymeric structures. True metaphosphates, with the general formula, $(MHPO_3)n$, are cyclic polymers. Commonly "n" is 3.]	
Ammonium Salts		
Ammonium Phosphate 7722-76-1	Ammonium Phosphate is an inorganic salt that conforms to the formula:  [Commonly called ammonium dihydrogen orthophosphate]	Buffering Agents, Oral Care Agents, pH Adjusters
Diammonium Phosphate 7783-28-0	Diammonium Phosphate is the inorganic salt that conforms to the formula:  [Commonly called ammonium hydrogen orthophosphate]	Buffering Agents, Corrosion Inhibitors, Oral Care Agents
Sodium Salts		
Disodium Phosphate 10140-65-5 7558-79-4 7782-85-6	Disodium Phosphate is the inorganic salt that conforms to the formula:  [Commonly called disodium hydrogen orthophosphate]	Buffering Agents, Corrosion Inhibitors, Fragrance Ingredients, pH Adjusters
Disodium Pyrophosphate 7758-16-9	Disodium Pyrophosphate is the inorganic salt that conforms generally to the formula:  [Commonly called disodium dihydrogen pyrophosphate]	Buffering Agents, Chelating Agents, Corrosion Inhibitors, pH Adjusters
Pentasodium Triphosphate 7758-29-4	Pentasodium Triphosphate is the inorganic salt that conforms to the formula:  [Commonly called pentasodium metaphosphate]	Chelating Agents, pH Adjusters
Sodium Hexametaphosphate 10124-56-8 10361-03-2 68915-31-1	Sodium Hexametaphosphate is the inorganic salt that conforms generally to the formula:  [The name, Sodium Hexametaphosphate, has been used for both the cyclic hexamer and for a mixture of soluble Sodium Phosphate polymers also known as sodium polymetaphosphate.]	Chelating Agents, Corrosion Inhibitors, Fragrance Ingredients

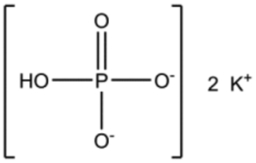
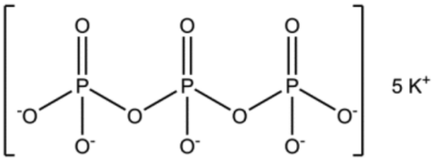
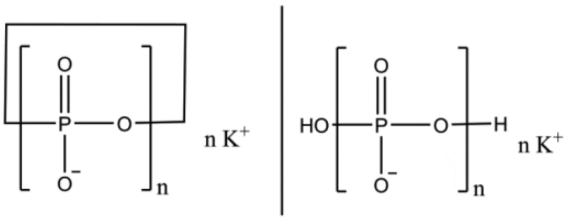
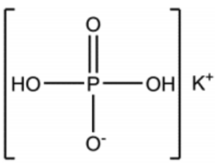
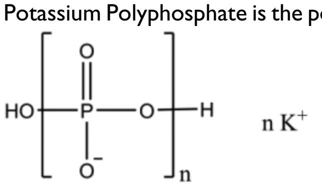
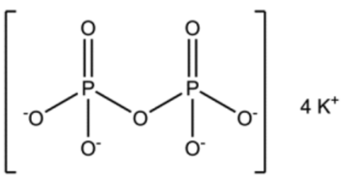
(continued)

Table 1. (continued)

Ingredient/CAS No.	Definition and Structure	Function
Sodium Metaphosphate 10361-03-2 50813-16-6	Sodium Metaphosphate is a linear Sodium Polyphosphate that conforms generally to the formula:  ["Metaphosphate" is a term used for a series of condensed inorganic phosphates prepared by dehydration of orthophosphates; differing reaction conditions lead to various cyclic or linear polymeric structures. In contrast with the definition of this ingredient, true metaphosphates, with the general formula, $(MPO_3)n$, are cyclic polymers. Commonly "n" is 3.]	Chelating Agents, Oral Care Agents
Sodium Polyphosphate 68915-31-1	Sodium Polyphosphate is a mixture of the sodium salts of Polyphosphoric Acid. 	Chelating Agents
Sodium Phosphate 7558-80-7 7632-05-5	Sodium Phosphate is the inorganic salt that conforms to the formula:  [Commonly referred to as sodium orthophosphate]	Buffering Agents
Sodium Trimetaphosphate 7785-84-4	Sodium Trimetaphosphate is the inorganic salt that conforms to the formula:  ["Metaphosphate" is a term used for a series of condensed inorganic phosphates prepared by dehydration of orthophosphates; differing reaction conditions lead to various cyclic or linear polymeric structures. True metaphosphates, with the general formula, $(MPO_3)n$, are cyclic polymers and "n" is 3.]	Buffering Agents, Chelating Agents, pH Adjusters
Tetrasodium Pyrophosphate 7722-88-5	Tetrasodium Pyrophosphate is the inorganic salt that conforms to the formula: 	Buffering Agents, Chelating Agents, Corrosion Inhibitors, Oral Care Agents, pH Adjusters
Trisodium Phosphate 7601-54-9	Trisodium Phosphate is the inorganic salt that conforms to the formula:  [Commonly referred to as trisodium orthophosphate]	Chelating Agents, pH Adjusters

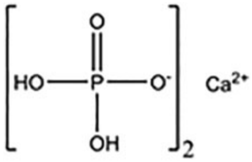
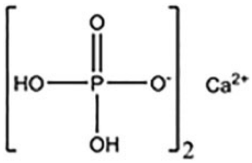
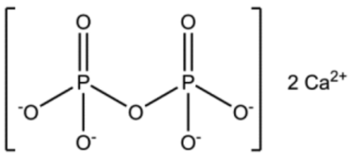
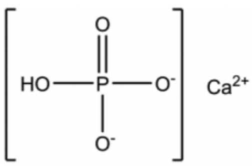
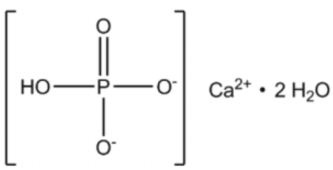
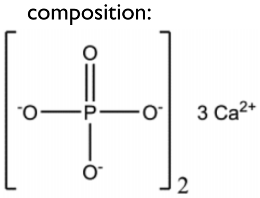
(continued)

Table 1. (continued)

Ingredient/CAS No.	Definition and Structure	Function
Potassium Salts		
Dipotassium Phosphate 7758-11-4	Dipotassium Phosphate is the inorganic salt that conforms generally to the formula:  [Commonly called dipotassium hydrogen orthophosphate]	Corrosion Inhibitors, pH Adjusters
Pentapotassium Triphosphate 13845-36-8	Pentapotassium Triphosphate is the inorganic salt that conforms to the formula:  [Commonly called pentapotassium metaphosphate]	Chelating Agents, pH Adjusters
Potassium Metaphosphate 7790-53-6	Potassium Metaphosphate is the potassium salt of Metaphosphoric Acid.  ["Metaphosphate" is a term used for a series of condensed inorganic phosphates prepared by dehydration of orthophosphates; differing reaction conditions lead to various cyclic or linear polymeric structures. True metaphosphates, with the general formula, $(MPO_3)n$, are cyclic polymers. Commonly "n" is 3.]	Surfactants—Cleansing Agents
Potassium Phosphate 16068-46-5 7778-77-0	Potassium Phosphate is the inorganic salt that conforms generally to the formula:  [Commonly called potassium dihydrogen orthophosphate]	pH Adjusters
Potassium Polyphosphate 68956-75-2	Potassium Polyphosphate is the potassium salt of Polyphosphoric Acid. 	Chelating Agents
Tetrapotassium Pyrophosphate 7320-34-5	Tetrapotassium Pyrophosphate is the inorganic salt that conforms to the formula: 	Buffering Agents, Chelating Agents, Corrosion Inhibitors, Oral Care Agents, pH Adjusters

(continued)

Table 1. (continued)

Ingredient/CAS No.	Definition and Structure	Function
Calcium Salts		
Calcium Dihydrogen Phosphate 7758-23-8	Calcium Dihydrogen Phosphate is the inorganic salt that conforms to the formula: [Commonly called calcium dihydrogen orthophosphate] 	pH Adjusters
Calcium Phosphate 10103-46-5	Calcium Phosphate is the inorganic salt that conforms to the formula:  [Though a representative structure is drawn (commonly called calcium dihydrogen pyrophosphate), the actual ratio of phosphate (with various degrees of protonation) to calcium is unknown, as is the form of phosphate, for this ingredient]	Abrasives, Buffering Agents, Bulking Agents, Oral Care Agents
Calcium Pyrophosphate 7790-76-3	Calcium Pyrophosphate is the inorganic salt that conforms to the formula:  [Commonly called dicalcium pyrophosphate]	Abrasives, Buffering Agents, Bulking Agents, Oral Care Agents
Dicalcium Phosphate 7757-93-9	Dicalcium Phosphate is the inorganic salt that conforms to the formula:  [Commonly called calcium hydrogen orthophosphate]	Abrasives, Opacifying Agents, Oral Care Agents
Dicalcium Phosphate Dihydrate 7789-77-7	Dicalcium Phosphate Dihydrate is the inorganic salt that conforms to the formula:  [Commonly called calcium hydrogen orthophosphate dihydrate]	Abrasives, Opacifying Agents, Oral Care Agents
Tricalcium Phosphate 7758-87-4	Tricalcium Phosphate is the inorganic salt that consists of a variable mixture of Calcium Phosphates having the approximate composition:  [Commonly called tricalcium orthophosphate]	Abrasives, Fragrance Ingredients, Opacifying Agents, Oral Care Agents

(continued)

Table 1. (continued)

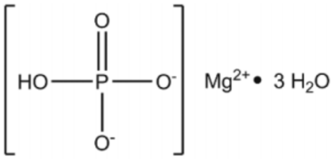
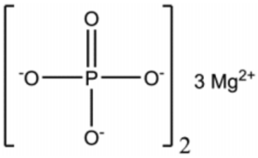
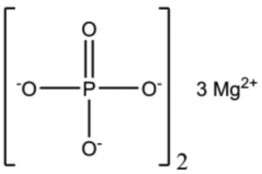
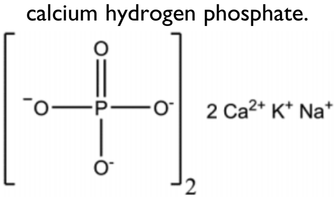
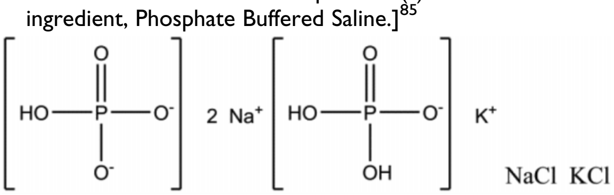
Ingredient/CAS No.	Definition and Structure	Function
Magnesium Salts		
Magnesium Hydrogen Phosphate 7782-75-4	Magnesium Hydrogen Phosphate is the inorganic salt that conforms to the formula:  [Commonly called magnesium hydrogen orthophosphate trihydrate]	Anticaking Agents
Magnesium Phosphate 10043-83-1	Magnesium Phosphate is the inorganic salt that conforms to the formula:  [Though a representative structure is drawn (commonly called trimagnesium orthophosphate), the actual ratio of phosphate (with various degrees of protonation) to magnesium is unknown, as is the form of phosphate (ie, ortho, pyro, or meta), for this ingredient]	Dispersing Agents—Nonsurfactant
Trimagnesium Phosphate 7757-87-1	Trimagnesium Phosphate is the inorganic salt that conforms to the formula:  [Commonly called trimagnesium orthophosphate]	Bulking Agents, Opacifying Agents
Multication Salts		
Calcium Potassium Sodium Phosphate 131862-42-5	Calcium Potassium Sodium Phosphate is the inorganic salt produced by the reaction of sodium carbonate, potassium carbonate, and calcium hydrogen phosphate.  [Commonly called dicalcium potassium sodium orthophosphate]	Abrasives, Anticaries Agents, Antimicrobial Agents, Oral Care Agents
Phosphate Buffered Saline	Phosphate Buffered Saline is a phosphate buffered solution containing a physiological concentration of inorganic salt. [It is an aqueous solution containing phosphate and chloride salts of sodium, potassium, calcium, or magnesium (or some combination thereof). For example, Phosphate Buffered Saline (PBS) solutions, by 1 protocol, may contain: 137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, and 1.8 mM KH_2PO_4. However, no submission has been received that indicates which protocol(s) utilized in the cosmetic ingredient, Phosphate Buffered Saline.][85] 	Solvents

Table 2. Properties of Phosphoric Acid and Its Salts.[6]

Property	Value	Background Information
	Phosphoric Acid	
Form	Unstable orthorhombic crystals or clear, syrupy liquid	
% Composition	H (3.09%), O (65.31%), and P (31.61%)	
Formula weight	97.99	
Density	1.8741 (100% solution)	
Solubility	Miscible with water and alcohol. Soluble in 8 vols of a 3:1 ether: alcohol mixture	
Melting point	42.35 °C (orthorhombic crystals)	Becomes anhydrous at 150°. Changes to Metaphosphoric Acid when heated above 300°.
	Metaphosphoric Acid	
Form	Transparent, glass-like solid, or soft silky masses; hygroscopic	Volatilizes at red heat
% Composition	H (1.26%), O (60.01%), and P (38.7%)	
Formula weight	79.98	
Solubility	Very slowly soluble in cold water, slowly changing to H_3PO_4. Soluble in alcohol	
	Ammonium Phosphate	
Form	Odorless crystals or white crystalline powder	Stable in air
% Composition	H (5.26%), N (12.18%), O (55.64%), and P (26.93%)	
Density	1.80	
Formula weight	115.02	
Solubility	1 g dissolves in ~ 2.5 mL water; slightly soluble in alcohol; practically insoluble in acetone	
Boiling point	376.1 °C	
Melting point	193.3 °C	
	Calcium Dihydrogen Phosphate	
Form	Monohydrate, large, shining, triclinic plates, crystalline powder, or granules	Nonhygroscopic when pure, but traces of impurities such as H_3PO_4 cause material to be deliquescent. Loses H_2O at 100°. Decomposes at 200°
% Composition	Ca (17.12%), H (1.72%), O (54.69%), and P (26.47%)	
Density	2.220	
Formula weight	234.05	
Solubility	Moderately soluble in water; soluble in dilute HCl or HNO_3 or acetic acid	
	Calcium Pyrophosphate	
Form	Polymorphous crystals or powder	
% Composition	Ca (31.55%), O (44.07%), and P (24.38%)	
Density	3.09	
Formula weight	254.10	
Solubility	Practically insoluble in water; soluble in dilute HCl or HNO_3	
	Diammonium Phosphate	
Form	Odorless crystals or crystalline powder	Gradually loses approximately 8% NH_3 upon exposure to air
% Composition	H (6.87%), N (21.21%), O (48.46%), and P (23.45%)	
Formula weight	132.06	
Solubility	1 g dissolves in 1.7 mL water; practically insoluble in alcohol and acetone	

(continued)

Table 2. (continued)

Property	Value	Background Information
	Dicalcium Phosphate	
Form	Triclinic crystals	At red heat, dehydrated to Calcium Pyrophosphate
% Composition	Ca (29.46%), H (0.74%), O (47.04%), and P (22.76%)	
Formula weight	136.06	
Solubility	Soluble in 3 N HCl or 2 N HNO_3; practically insoluble in water and alcohol	
	Dicalcium Phosphate Dihydrate	
Form	Monoclinic crystals	Loses water of crystallization slowly below 100°. Dehydration at red heat to Calcium Pyrophosphate
Density	2.31	
Solubility	Slightly soluble in dilute acetic acid; soluble in dilute HCl or HNO_3; practically insoluble in water and alcohol	
	Dipotassium Phosphate	
Form	White, hydroscopic granules	Converted into pyrophosphate by ignition
% Composition	H (0.58%), K (44.90%), O (36.74%), and P (17.78%)	
Formula weight	174.17	
Solubility	Very soluble in water; slightly soluble in alcohol	
	Disodium Phosphate	
Form	Hygroscopic powder	On exposure to air, will absorb from 2 to 7 mols H_2O, depending on the humidity and temperature
% Composition	H (0.71%), Na (32.39%), O (45.08%), and P (21.82%)	
Formula weight	141.96	
Solubility	Soluble in water; insoluble in alcohol	
	Disodium Pyrophosphate	
Form	White fused masses or powders	Decomposes at 220°
% Composition	H (0.91%), Na (20.72%), O (50.46%), and P (27.91%)	
Solubility	Soluble in water	
	Magnesium Hydrogen Phosphate	
Form	White crystalline powder	
% Composition	H (0.84%), Mg (20.21%), O (53.21%), and P (25.75%)	
Density	2.13	
Formula weight	120.28	
Solubility	Soluble in dilute acids; slightly soluble in water	
	Magnesium Phosphate	
Form	White powder	
% Composition	H (1.85%), Mg (11.13%), O (58.64%), and P (28.38%)	
Formula weight	218.28	
Solubility	Soluble in water	
	Pentasodium Triphosphate	
Form	Slightly hygroscopic granules	Reverts to the orthophosphate with prolonged heating
% Composition	Na (31.25%), O (43.49%), and P (25.26%)	
Formula weight	367.86	
Solubility	Soluble in water	
	Potassium Metaphosphate	
Form	White, monoclinic crystals	
Density	2.45	

(continued)

Table 2. (continued)

Property	Value	Background Information
Solubility	Soluble in aqueous solutions of alkali metal (except potassium) salts; insoluble in water	
	Potassium Phosphate	
Form	Colorless crystals or white, granular powder	At 400°, loses H_2O, forming metaphosphate
% Composition	H (1.48%), K (28.73%), O (47.03%), and P (22.76%)	
Density	2.34	
Formula weight	136.08	
Solubility	Soluble in water; practically insoluble in alcohol	
	Potassium Polyphosphate	
Form	White, monoclinic crystals	
Density	2.45	
Solubility	Soluble in aqueous solutions of alkali metals (except potassium) salts; insoluble in water	
	Sodium Hexametaphosphate	
		The name, Sodium Hexametaphosphate, has been used for both the cyclic hexamer and for a mixture of soluble Sodium Phosphate polymers
	Sodium Metaphosphate	
		The name, Sodium Metaphosphate, is used for a series of condensed inorganic phosphates prepared by the dehydration of sodium orthophosphates
	Sodium Phosphate	
% Composition	H (1.68%), Na (19.16%), O (53.34%), and P (25.82%)	
Formula weight	119.98	
	Sodium Polyphosphate	
Form	Clear, hygroscopic glass	Depolymerizes in aqueous solution to form Sodium Trimetaphosphate and sodium orthophosphates
Solubility	Soluble in water	
Melting point	628 °C	
	Sodium Trimetaphosphate	
Form	White crystals or white, crystalline powder	Hydrolyzes to sodium tripolyphosphate (Pentasodium Triphosphate) in dilute alkaline solution
% Composition	Na (22.55%), O (47.07%), and P (30.38%)	
Density	2.49	
Solubility	Soluble in water	
	Tetrapotassium Pyrophosphate	
% Composition	K (47.34%), O (33.90%), and P (18.75%)	
Formula weight	330.33	
Solubility	Soluble in water; insoluble in alcohol	
	Tetrasodium Pyrophosphate	
Form	Crystals	Hydrolyzes to orthophosphate in aqueous solution
% Composition	Na (34.58%), O (42.12%), and P (23.30%)	
Density	2.534	
Formula weight	265.90	
Solubility	Soluble in water	

(continued)

Table 2. (continued)

Property	Value	Background Information
	Tricalcium Phosphate	
Form	Amorphous powder	
% Composition	Ca (38.76%), O (41.27%), and P (19.97%)	
Density	3.14	
Formula weight	310.17	
Solubility	Readily soluble in 3 N HCl and 2 $NHNO_3$; practically insoluble in water, alcohol, and acetic acid	
	Trimagnesium Phosphate	
% Composition	Mg (27.74%), O (48.69%), and P (23.57%)	
Formula weight	262.85	
	Trisodium Phosphate	
% Composition	Na (42.07%), O (39.04%), and P (18.89%)	Crystallizes with 8 and 12 mols H_2O
Formula weight	163.94	

Table 3A. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[18,19]

	Phosphoric Acid		Ammonium Phosphate		Diammonium Phosphate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	489	0.000004-9	1	0.6	3	0.00046-5
Duration of Use						
Leave-On	168	0.000004-1.2	1	NR	NR	0.00046
Rinse off	311	0.00005-9	NR	0.6	3	5
Diluted for (bath) Use	10	0.34	NR	NR	NR	NR
Exposure Type						
Eye Area	7	NR	NR	NR	NR	NR
Incidental Ingestion	2	0.0003-0.21	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	0.001-0.26	NR	NR	NR	NR
Incidental Inhalation- Powders	NR	0.00001	NR	NR	NR	0.00046
Dermal Contact	154	0.000004-2.7	NR	NR	1	0.00046
Deodorant (underarm)	NR	0.068	NR	NR	NR	NR
Hair—Non-Coloring	123	0.00023-5.9	1	0.6	1	NR
Hair-Coloring	101	0.07-9	NR	NR	1	5
Nail	45	0.00049-0.1	NR	NR	NR	NR
Mucous Membrane	109	0.00005-0.34	NR	NR	NR	NR
Baby Products	NR	0.00001	NR	NR	NR	NR
	Disodium Phosphate		Disodium Pyrophosphate		Pentasodium Triphosphate	
Totals/Conc. Range	280	0.000054-2.9	15	0.05-0.3	43	0.25-9.3
Duration of Use						
Leave-On	94	0.000054-1.2	NR	NR	3	0.25-9.3
Rinse off	176	0.000055-2.9	15	0.05-0.3	23	1.1
Diluted for (bath) Use	10	0.04-0.2	NR	NR	17	6-9
Exposure Type						
Eye Area	16	0.00095-1	NR	NR	NR	NR
Incidental Ingestion	1	0.5	8	NR	22	1.1
Incidental Inhalation- Sprays	NR	0.02-0.3	NR	NR	NR	NR
Incidental Inhalation—Powders	NR	0.00095-1.2**	NR	NR	NR	1**
Dermal Contact	132	0.000054-1.7	NR	NR	17	1-9
Deodorant (underarm)	NR	0.03	NR	NR	NR	NR
Hair—Non-Coloring	21	0.000055-2	NR	NR	NR	NR

(continued)

Table 3A. (continued)

	Phosphoric Acid		Ammonium Phosphate		Diammonium Phosphate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Hair-Coloring	75	0.0025-2.9	7	0.05-0.3	NR	NR
Nail	NR	NR	NR	NR	NR	0.25-9.3
Mucous Membrane	48	0.04-0.5	8	NR	39	1.1-9
Baby Products	NR	NR	NR	NR	NR	NR
	Sodium Hexametaphosphate		Sodium Metaphosphate		Sodium Phosphate	
Totals/Conc. Range	89	0.09-3	45	0.01-9.6	87	0.0000015-2.6
Duration of Use						
Leave-On	74	0.1-3	42	0.01-9.6	52	0.0000015-2
Rinse off	12	0.09-1.5	3	0.01-0.2	35	0.00007-2.6
Diluted for (bath) Use	3	NR	NR	0.03-0.5	NR	NR
Exposure Type						
Eye Area	19	NR	7	0.03-0.1	9	0.00007-0.5
Incidental Ingestion	2	NR	NR	0.14	7	0.25-0.55
Incidental Inhalation- Sprays	NR	NR	NR	0.04*	NR	0.000014
Incidental Inhalation- Powders	NR	0.1-3	NR	0.25	NR	0.00015-0.086
Dermal Contact	48	0.09-3	34	0.01-9.6	45	0.0000015-2.6
Deodorant (underarm)	NR	NR	NR	0.029	NR	0.099
Hair—Non-Coloring	NR	NR	NR	0.01-0.05	6	0.000014-2
Hair-Coloring	NR	NR	NR	0.15	1	NR
Nail	NR	NR	NR	0.03	NR	NR
Mucous Membrane	5	1.5	2	0.03-0.5	15	0.0032-2.6
Baby Products	NR	NR	NR	NR	1	0.00015

Table 3B. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[18,19]

	Sodium Phosphate, Monobasic		Tetrasodium Pyrophosphate		Trisodium Phosphate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	31	NR	118	0.0000014-6	25	0.00045
Duration of Use						
Leave-On	11	NR	17	0.03-3	13	0.00045-7
Rinse off	20	NR	101	0.0000014-6	12	0.05-1.7
Diluted for (bath) Use	NR	NR	NR	NR	NR	0.08
Exposure Type						
Eye Area	1	NR	2	NR	5	0.00045
Incidental Ingestion	NR	NR	8	0.4-2	5	NR
Incidental Inhalation- Sprays	NR	NR	NR	NR	NR	NR
Incidental Inhalation—Powders	NR	NR	NR	<0.1-1**	NR	7**
Dermal Contact	21	NR	42	0.0000014-3	9	0.00045-7
Deodorant (underarm)	NR	NR	NR	<0.01	NR	NR
Hair—Non-Coloring	1	NR	NR	0.000014-0.04	NR	0.25-0.5
Hair-Coloring	NR	NR	63	0.02-6	2	0.18 -1.7
Nail	1	NR	1	0.03	6	3.7
Mucous Membrane	16	NR	8	0.0000014-2	6	0.08
Baby Products	NR	NR	NR	NR	NR	NR
	Dipotassium Phosphate		Potassium Metaphosphate		Potassium Phosphate	
Totals/Conc. Range	31	0.002-1.8	NR	0.11	107	0.0000000014-0.9
Duration of Use						
Leave-On	10	0.002-0.3	NR	NR	61	0.0000000014-0.9
Rinse off	21	0.033-1.8	NR	0.11	45	0.00007-0.68
Diluted for (bath) Use	NR	NR	NR	NR	1	0.06

(continued)

Table 3B. (continued)

	Sodium Phosphate, Monobasic		Tetrasodium Pyrophosphate		Trisodium Phosphate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	16	0.033-0.4	NR	NR	23	0.006-0.56
Incidental Ingestion	NR	NR	NR	NR	2	0.000007
Incidental Inhalation—Sprays	NR	NR	NR	NR	NR	0.00065-0.08
Incidental Inhalation—Powders	NR	0.002-0.3**	NR	NR	NR	0.0000000014-0.01**
Dermal Contact	27	0.002-0.47	NR	0.11	65	0.0000000014-0.9
Deodorant (underarm)	NR	NR	NR	NR	NR	0.07
Hair—Non-Coloring	1	NR	NR	NR	1	0.000003-0.6
Hair-Coloring	NR	1.8	NR	NR	4	0.2
Nail	NR	NR	NR	NR	1	NR
Mucous Membrane	1	0.05-0.066	NR	0.11	9	0.000007-0.06
Baby Products	NR	NR	NR	NR	NR	NR
	Tetrapotassium Pyrophosphate		Calcium Dihydrogen Phosphate		Calcium Phosphate	
Totals/Conc. Range	95	NR	4	NR	NR	0.0001
Duration of Use						
Leave-On	5	NR	1	NR	NR	0.0001
Rinse off	90	NR	3	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	23	NR	3	NR	NR	NR
Incidental Inhalation—Sprays	NR	NR	NR	NR	NR	NR
Incidental Inhalation—Powders	NR	NR	NR	NR	NR	NR
Dermal Contact	69	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	0.0001
Mucous Membrane	23	NR	3	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 3C. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[18,19]

	Calcium Pyrophosphate		Dicalcium Phosphate		Dicalcium Phosphate Dihydrate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	3	NR	327	0.000099-47.7	16	0.58-49
Duration of Use						
Leave-On	1	NR	322	0.04-10	11	0.58-6.8
Rinse off	2	NR	5	0.000099-47.7	5	49
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	24	0.042-10	6	0.58
Incidental Ingestion	2	NR	222	0.3-47.7	9	6.8-49
Incidental Inhalation—Sprays	NR	NR	NR	NR	NR	NR
Incidental Inhalation—Powders	NR	NR	14	0.04-2.2	NR	2.2
Dermal Contact	NR	NR	89	0.04-10	6	0.58-2.2
Deodorant (underarm)	NR	NR	NR	0.49	NR	NR
Hair—Non-Coloring	1	NR	NR	0.000099	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR

(continued)

Table 3C. (continued)

	Calcium Pyrophosphate		Dicalcium Phosphate		Dicalcium Phosphate Dihydrate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Mucous Membrane	2	NR	218	0.3-47.7	9	6.8-49
Baby Products	NR	NR	NR	NR	NR	NR
	Tricalcium Phosphate		**Trimagnesium Phosphate**			
Totals/Conc. Range	33	NR	1	NR		
Duration of Use						
Leave-On	31	NR	NR	NR		
Rinse off	2	NR	1	NR		
Diluted for (bath) Use	NR	NR	NR	NR		
Exposure Type						
Eye Area	NR	NR	NR	NR		
Incidental Ingestion	2	NR	1	NR		
Incidental Inhalation—Sprays	NR	NR	NR	NR		
Incidental Inhalation—Powders	26	0.099**-10	NR	NR		
Dermal Contact	30	NR	NR	NR		
Deodorant (underarm)	NR	0.4	NR	NR		
Hair—Non-Coloring	NR	NR	NR	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	2	NR	1	NR		
Baby Products	7	0.12	NR	NR		

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for (Bath) Use Product Uses.
*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
**It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 4. Acute Inhalation Toxicity.

Ingredient	Animals	Results
	Acids	
Phosphoric Acid (generated from pure red phosphorus ignited in an air stream). Target concentrations of smoke ranged from 111 to 6731 mg/m^3 as Phosphoric Acid	New Zealand white rabbits (groups of 10), Porton strain rats (groups of 9 to 12), Porton strain mice (group of 20 or 50), and Dunkin-Hartley guinea pigs (groups of 10 or 20)	LC_{50}s (1-h exposure): 5337 mg/m^3 (rabbits), 3846 mg/m^3 (rats), 856 mg/m^3 (mice), and 193 mg/m^3 (guinea pigs). Lesions in larynx and trachea in all groups, except for guinea pigs.[65,68]
	Sodium Salts	
Disodium Pyrophosphate	Rats	LC_{50} (4-h exposure) > 0.58 mg/L air.[48]
Pentasodium Triphosphate	Rats	LC_{50} (4-h exposure) > 0.39 mg/L air.[48]
Sodium Polyphosphate/Sodium Hexametaphosphate	Rats	LC_{50} (4-h exposure) > 3.9 mg/L air.[48]
Sodium Phosphate	Rats	LC_{50} (4-h exposure) > 0.83 mg/L air.[48]
	Potassium Salts	
Tetrapotassium Pyrophosphate	Rats	LC_{50} (4-h exposure) > 1.1 mg/L air.[48]
	Calcium Salts	
Calcium Dihydrogen Phosphate	Rats (5 males and 5 females)	LC_{50} (4-h exposure) ≥ 2.6 mg/L air.[86,87]
Dicalcium Phosphate	Wistar rats (5 males and 5 females)	LC_{50} (4-h exposure) > 2.6 mg/L air.[67]

Table 5. Acute Oral Toxicity Studies.

Ingredient	Test Concentration	Animals (number stated, if available from source)	Results
		Acids	
Phosphoric Acid	Not stated	Rats	LD_{50} = 1530 mg/kg.[3,68]
Phosphoric Acid	Not stated	Sprague-Dawley rats (12 females)	LD_{50} ≈ 2000 mg/kg.[68]
Phosphoric Acid	75%-85% solution	Rats	LD_{50} = 3160 mg/kg.[48]
Phosphoric Acid	85% solution	Rats	LD_{50} = 3380 mg/kg.[48]
Phosphoric Acid	85% solution	Sprague-Dawley albino rats (males and females)	LD_{50} = 3500 mg/kg.[68,69]
Phosphoric Acid	80% solution	Sprague-Dawley albino rats (males and females)	LD_{50} = 4200 mg/kg.[68,69]
Phosphoric Acid	75% solution	Sprague-Dawley albino rats (males and females)	LD_{50} = 4400 mg/kg.[68,69]
Phosphoric Acid		Rabbits	LD_{50} = 2740 mg/kg.[3]
		Ammonium Salts	
Ammonium Phosphate		Rats	LD_{50} >1000 mg/kg.[48]
Ammonium Phosphate		Rats	LD_{50} = 3250 mg/kg.[88]
Ammonium Phosphate		Rats	LD_{50} = 5750 mg/kg.[48]
Ammonium Phosphate		Rats	LD_{50} > 2000 mg/kg.[88]
Diammonium Phosphate		Rats	LD_{50} > 1000 mg/kg.[48]
Diammonium Phosphate		Rats	LD_{50} > 2000 mg/kg.[88]
Diammonium Phosphate		Rats	LD_{50} = 6500 mg/kg.[48]
Diammonium Phosphate		Rats	LD_{50} > 25100 mg/kg.[48]
		Sodium Salts	
Disodium Phosphate		Rats	LD_{50} = 5950 mg/kg.[48]
Disodium Pyrophosphate		Rats	LD_{50} > 1000 mg/kg.[48]
Disodium Pyrophosphate		Rats	LD_{50} = 1690 mg/kg.[8]
Disodium Pyrophosphate		Rats	LD_{50} = 3600 mg/kg.[48]
Disodium Pyrophosphate		Rats	LD_{50} > 4000 mg/kg.[48,89]
Disodium Pyrophosphate		Mice	LD_{50} = 3350 mg/kg.[8]
Disodium Pyrophosphate		Hamsters	LD_{50} = 1660 mg/kg.[8]
Pentasodium Triphosphate		Rats	LD_{50} = 1700 mg/kg.[8]
Pentasodium Triphosphate		Rats	LD_{50} = 5010 mg/kg.[48]
Pentasodium Triphosphate		Mice	LD_{50} = 2380 mg/kg.[8]
Pentasodium Triphosphate		Rabbits	LD_{50} = 2500 mg/kg.[8]
Sodium Hexametaphosphate		Rats	LD_{50} = 2400 mg/kg.[8]
Sodium Hexametaphosphate		Mice	LD_{50} = 3700 mg/kg.[8]
Sodium Polyphosphate/Sodium Hexametaphosphate		Rats	LD_{50} = 2400 mg/kg.[48]
Sodium Polyphosphate/Sodium Hexametaphosphate		Rats	LD_{50} = 2900 mg/kg.[48,90]
Sodium Polyphosphate/Sodium Hexametaphosphate		Rats	LD_{50} > 10000 mg/kg.[48]
Sodium Polyphosphate/Sodium Hexametaphosphate		Mice	LD_{50} = 3700 mg/kg.[8]
Sodium Phosphate		Rats	LD_{50} = 4100 mg/kg.[8]
Sodium Phosphate		Rats	LD_{50} = 7100 mg/kg.[48]
Sodium Phosphate		Rats	LD_{50} = 8390 mg/kg.[48,66]
Sodium Phosphate		Mice	LD_{50} > 3700 mg/kg.[48,8]
Sodium Phosphate		Guinea pigs	LD_{50} > 2000 mg/kg.[48,89]
Sodium Trimetaphosphate		Rats	LD_{50} = 10600 mg/kg.[48]
Tetrasodium Pyrophosphate		Rats	LD_{50} = 1380 mg/kg.[8]
Tetrasodium Pyrophosphate		Rats (female)	LD_{50} = 1825 mg/kg.[48]
Tetrasodium Pyrophosphate		Rats (male)	LD_{50} = 2150 mg/kg.[48]
Tetrasodium Pyrophosphate		Rats	LD_{50} = 3770 mg/kg.[48]
Tetrasodium Pyrophosphate		Rats	LD_{50} = 1380 mg/kg.[8]
Tetrasodium Pyrophosphate (∼ 67%) and Potassium Metaphosphate (∼ 33%)		Rats	LD_{50} = 4000 mg/kg.[8]

(continued)

Table 5. (continued)

Ingredient	Test Concentration	Animals (number stated, if available from source)	Results
Tetrasodium Pyrophosphate	200 mg/mL suspension in distilled water	Sprague-Dawley rats (females, groups of 5)	No clinical signs or necropsy findings. $LD_{50} > 2000$ mg/kg.[30,91]
Tetrasodium Pyrophosphate		Mice	$LD_{50} = 1300$ mg/kg.[8]
Trisodium Phosphate		Rats	$LD_{50} > 2000$ mg/kg.[48,92]
Trisodium Phosphate		Rats	$LD_{50} = 4100$ mg/kg.[48]
Trisodium Phosphate		Rats	$LD_{50} = 4150$ mg/kg.[48]
Trisodium Phosphate		Rats (female)	$LD_{50} < 5000$ mg/kg.[48]
Trisodium Phosphate	20% solution	Rats	$LD_{50} = 6500$ mg/kg.[48,93]
Trisodium Phosphate		Rats	$LD_{50} = 7800$ mg/kg.[48]
		Potassium Salts	
Dipotassium Phosphate		Rats	$LD_{50} > 500$ mg/kg.[48]
Dipotassium Phosphate		Rats	$LD_{50} > 1000$ mg/kg.[48]
Dipotassium Phosphate(liquid)		Rats	$LD_{50} = 4810$ mg/kg.[48]
Dipotassium Phosphate		Rats	$LD_{50} = 5700$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Rats (male)	$LD_{50} > 1000$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Rats	$LD_{50} = 2980$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Rats	$LD_{50} = 3160$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Rats	$LD_{50} = 3550$ mg/kg.[48]
Tetrapotassium Pyrophosphate	Solution (concentration not stated)	Rats	$LD_{50} = 2440$ mg/kg.[48]
Tetrapotassium Pyrophosphate	Solution (concentration not stated)	Rats	$LD_{50} < 5000$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Mice	$LD_{50} = 1000$ mg/kg.[48,94]
Dipotassium Phosphate		Mice	$LD_{50} = 1700$ mg/kg.[48,95]
Pentapotassium Triphosphate		Rats (male)	$LD_{50} > 1000$ mg/kg.[48]
Potassium Phosphate		Rats (male)	$LD_{50} > 4640$ mg/kg.[48]
Potassium Phosphate		Rats	$LD_{50} = 7100$ mg/kg.[48]
Potassium Phosphate		Rats	$LD_{50} = 2820$ mg/kg.[8]
Potassium Phosphate		Mice	$LD_{50} = 1700$ mg/kg.[48,96]
Potassium Phosphate		Mice	$LD_{50} \approx 3200$ mg/kg.[8]
		Calcium Salts	
Calcium Dihydrogen Phosphate (in distilled water)		Female Sprague-Dawley rats (groups of 3)	$LD_{50} > 2000$ mg/kg.[86,87]
Calcium Dihydrogen Phosphate		Female Sprague-Dawley rats (groups of 5)	$LD_{50} > 10000$ mg/kg.[86,87]
Calcium Dihydrogen Phosphate		Albino rabbits (5 males and 5 females)	$LD_{50} > 2000$ mg/kg.[87]
Calcium Phosphate		Rats	$LD_{50} > 1000$ mg/kg.[48]
Calcium Phosphate		Rats	$LD_{50} = 2170$ mg/kg.[48]
Calcium Phosphate		Rats (female)	$LD_{50} = 3986$ mg/kg.[48]
Calcium Phosphate		Rats (male)	$LD_{50} > 5000$ mg/kg.[48]
Calcium Phosphate		Mice	$LD_{50} = 4600$ mg/kg.[8]
Dicalcium Phosphate		6 Sprague-Dawley rats (female)	$LD_{50} \geq 2000$ mg/kg.[67]
Dicalcium Phosphate		Rats	$LD_{50} = 7100$ mg/kg.[48]
Dicalcium Phosphate		Rats	$LD_{50} > 7940$ mg/kg.[48]
Dicalcium Phosphate		10 Sprague-Dawley rats (female)	$LD_{50} > 10000$ mg/kg.[67]
Dicalcium Phosphate		Mice	$LD_{50} \approx 1700$ mg/kg.[17]
Tricalcium Phosphate		Rats	$LD_{50} > 5000$ mg/kg.[48]
Tricalcium Phosphate		Sprague-Dawley rats (female, groups of 3)	$LD_{50} > 2000$ mg/kg.[55]
Calcium Pyrophosphate		Rats	$LD_{50} > 10000$ mg/kg.[48]
		Magnesium Salts	
Magnesium Phosphate		Rats	$LD_{50} > 1000$ mg/kg.[48]
Magnesium Phosphate		Rats	$LD_{50} > 4640$ mg/kg.[48]
Magnesium Phosphate		Rats	$LD_{50} > 5000$ mg/kg.[48]
Trimagnesium Phosphate		Rats	$LD_{50} > 10000$ mg/kg.[48]
Magnesium Phosphate	Solution (concentration not stated)	Rabbits	$LD_{50} > 2000$ mg/kg.[48]

Table 6. Acute Dermal Toxicity Studies.

Ingredient	Test Concentration/ Dose	Animals (number stated, if available from source)	Results
Acids			
Phosphoric Acid	85% solution	New Zealand white rabbits (males and females; groups of up to 2)	$LD_{50} > 1260$ mg/kg.[68]
Phosphoric Acid		Rabbits	$LD_{50} = 2740$ mg/kg.[48,66]
Phosphoric Acid	75% and 80% solutions	New Zealand white rabbits (males and females; groups of up to 2)	$LD_{50} > 3160$ mg/kg.[68]
Phosphoric Acid	85% solution	Rabbits	$LD_{50} > 2000$ mg/kg.[48]
Ammonium Salts			
Ammonium Phosphate		Rats	$LD_{50} > 5000$ mg/kg.[88]
Ammonium Phosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Diammonium Phosphate		Rats	$LD_{50} > 5000$ mg/kg.[88]
Diammonium Phosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Diammonium Phosphate		Rabbits	$LD_{50} > 10000$ mg/kg.[48]
Diammonium Phosphate		Rats	$LD_{50} > 5000$ mg/kg.[97]
Sodium Salts			
Disodium Phosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Disodium Pyrophosphate		Rabbits	$LD_{50} > 300$ mg/kg.[98]
Disodium Pyrophosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Pentasodium Triphosphate		Rabbits	$LD_{50} = 4640$ mg/kg.[48]
Pentasodium Triphosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Sodium Phosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Sodium Polyphosphate/Sodium Hexametaphosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Tetrasodium Pyrophosphate		20 Sprague-Dawley rats	No clinical signs or necropsy findings. $LD_{50} > 2000$ mg/kg.[31]
Tetrasodium Pyrophosphate		Rabbits	$LD_{50} > 2000$ mg/kg.[48]
Tetrasodium Pyrophosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Trisodium Phosphate		Rabbits	$LD_{50} > 300$ mg/kg.[98]
Trisodium Phosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Potassium Salts			
Dipotassium Phosphate		Rabbits	$LD_{50} > 300$ mg/kg.[48]
Dipotassium Phosphate(liquid)		Rabbits	$LD_{50} > 5000$ mg/kg.[48]
Dipotassium Phosphate		Rabbits	$LD_{50} > 5000$ mg/kg.[48]
Pentapotassium Triphosphate		Rabbits	$LD_{50} > 4640$ mg/kg.[48]
Potassium Phosphate		Rabbits	$LD_{50} > 4640$ mg/kg.[48]
Potassium Phosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Rabbits	$LD_{50} > 2000$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Rabbits	$LD_{50} > 4640$ mg/kg.[48]
Tetrapotassium Pyrophosphate (liquid)		Rabbits	$LD_{50} > 5000$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Tetrapotassium Pyrophosphate		Rabbits	$LD_{50} > 10000$ mg/kg.[48]
Calcium Salts			
Calcium Dihydrogen Phosphate	2000 mg/kg	Rabbits (5 males and 5 females)	Severe erythema and mild edema. $LD_{50} > 2000$ mg/kg.[86]
Calcium Phosphate		Rabbits	$LD_{50} > 300$ mg/kg.[98]
Calcium Phosphate		Rabbits	$LD_{50} > 2000$ mg/kg.[48]
Calcium Pyrophosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Dicalcium Phosphate	2000 mg/kg	Stauffland albino rabbits (5 males and 5 females)	$LD_{50} > 2000$ mg/kg.[67]
Dicalcium Phosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]
Tricalcium Phosphate		Rabbits	$LD_{50} > 2000$ mg/kg.[48]
Magnesium Salts			
Magnesium Phosphate	Solution (concentration not stated)	Rabbits	$LD_{50} > 2000$ mg/kg.[48]
Magnesium Phosphate		Rabbits	$LD_{50} > 4640$ mg/kg.[48]
Trimagnesium Phosphate		Rabbits	$LD_{50} > 7940$ mg/kg.[48]

Table 7. Repeated Dose Oral Toxicity Studies.

Ingredient	Test Concentration/Dose	Animals (number stated, if available from source)	Results
		Acids	
Phosphoric Acid	Oral doses (by gavage) of 0, 125, 250, or 500 mg/kg/d for 42 d (males) and 40 to 42 d (females)	Sprague-Dawley rats (13/sex/dose)	2 females of 500 mg/kg/d group died. NOAEL = 250 mg/kg/d.[65,68]
Phosphoric Acid	Up to 0.75% in diet (338 mg/kg/d*) for > 52 wk	Rats	NOEL = 338 mg/kg/d*. [48,89]
Phosphoric Acid	0, 35, 105, or 211 mg/kg/d for 70 d	Sheep	NOAEL = 105 mg/kg/d.[99]
		Ammonium Salts	
Diammonium Phosphate	Oral doses (by gavage) of 0, 250, 750, or 1500 mg/kg/d (7 d/wk) for 35 d	Rats (groups of 10 [5 males and 5 females/group])	Histological examination of stomach revealed submucosal inflammation (not dose-dependent) at all doses. NOAEL = 250 mg/kg/d.[88,100]
Diammonium Phosphate	Increasing oral doses (in drinking water) of 300 to 700 mg/kg/d for 5 to 16 mo	10 Rabbits (females)	Average weight of parathyroid glands (only parameter assessed) was 235% of control values.[97]
		Sodium Salts	
Disodium Phosphate	10% in diet for 24 h to 72 h	Rats	Histological and histochemical changes in the kidneys.[8,101]
Disodium Phosphate	1.8%, 3%, and 5% in modified Sherman diet for 6 mo	Young rats (groups of 34 to 36)	Significant decrease in growth and kidney damage (nephrocalcinosis) at dietary concentrations of 3% and 5%. Normal growth and slight increase (statistically significant) in kidney weight at 1.8% in the diet.[8,102]
Disodium Phosphate	0%, 1.1%, 1.8%, 3%, or 5% in diet (0, 495, 810, 1350, and 2250 mg/kg/d*) for 39 wk	Rats	Slight kidney calcification. LOEL = 495 mg/kg/d*.[8,48,103]
Disodium Phosphate	1%, 2.5%, and 5% in Sherman diet for 16 wk	Rats	Severe kidney damage in 5% dietary group (number of animals not stated). Hypertrophy and hemorrhage of the stomach (number of animals not stated).[8,104]
Disodium Phosphate	5% Disodium Phosphate in the diet for 1 month (2571 mg/kg/d)	Weanling rats	Renal tubular necrosis. LOEL < 2571 mg/kg/d (assuming that 0.35 kg rat consumes18 g food/d)[30,90]
Disodium Phosphate	1%, 2.5%, or 5% in diet containing 0.6% calcium and 0.5% phosphorus for 100 d	20 rats per sex	Renal histopathology, decreased renal function, and increased kidney weight in all dietary groups. LOEL for 5% in diet = 2571 mg/kg/d (assuming that 0.35 kg rat consumed 18 g food per d).[30,104]
Disodium Pyrophosphate	1%, 2.5%, or 5% in basal diet (contained 0.6% calcium and 0.5% phosphorus) for 100 d	Groups of 20 rats per sex	Renal histopathology, decreased renal function, and increased kidney weight in all groups except 1% dietary group. LOEL for 1% dietary group = 450 mg/kg/d (assuming that 0.35 kg rat consumes18 g food/d).[30,104]
Pentasodium Triphosphate	0%, 0.2%, 2%, or 10% (0, 103, 900, and 5143 mg/kg/d*) for 30 d	Rats	NOEL = 103 mg/kg/d. (Extrapolated from level of chemical in diet, assuming 0.35 kg rat eats 18 g food/d.)[90]
Pentasodium Triphosphate	0%, 0.2%, 2%, or 10% (0, 90, 900, and 4500 mg/kg/d*) for 30 d	Rats	NOEL = 90 mg/kg/d (Extrapolated from level of chemical in diet, assuming 0.35 kg rat eats 18 g food/d.)[90]
Pentasodium Triphosphate	1% solutions (pH of 5) of 3%, and 5% Pentasodium Triphosphate (effective concentrations of 0.03% and 0.05% [14 and 23 mg/kg/d]*, respectively) in Sherman diet for 24 wk	Groups of rats (36 males, 36 females/group)	Growth retardation at 0.05% in diet. Temporary growth retardation at 0.03% in diet. Nephrocalcinosis at both concentrations.[8,102,105,106]
Pentasodium Triphosphate	0%, 1.1%, 1.8%, 3%, and 5% (0, 495, 810, 1350, and 2250 mg/kg/d*) for 39 wk	Rats	LOEL = 495 mg/kg/d*.[48,103]
Pentasodium Triphosphate	1.8%, 3%, and 5% (pH of 5 for each) (810, 1350, 2250 mg/kg/d*) in Sherman diet for 24 wk	Groups of rats (36 males, 36 females/group)	Growth retardation at 5% in diet, temporary growth retardation at 3% in diet, and normal growth at 1.8% in diet. Nephrocalcinosis at 1.8%, 3%, or 5% in diet. Extent of kidney damage less at test substance pH of 5 than at pH 9.5.[8,102,105,106]

(continued)

Table 7. (continued)

Ingredient	Test Concentration/Dose	Animals (number stated, if available from source)	Results
Pentasodium Triphosphate	0.05%, 0.5%, or 5% in diet (23, 225, 2250 mg/kg/d*) for 2 yr	Weanling rats (groups of 50 males and 50 females)	Growth reduction only at 5% in diet (significant in males; slight in females). Smaller number (not stated) of rats fed 5% in diet survived. Low grade of anemia and increased kidney weight only at 5% in diet. NOEL = 225 mg/kg/d*.[8,90]
Pentasodium Triphosphate	Oral dose rate of 0.1 g/kg/d for 1 month (1 dog). 2 other dogs dosed similarly for 1 month, and dose had increased to 4 g/kg/d by end of 5-month period	3 dogs	Kidney tubule damage in dogs receiving higher doses. No treatment-related changes in dog dosed with 0.1 g/kg/d only.[8]
Pentasodium Triphosphate	0 and 100 mg/kg/d for 30 d	Dogs	NOAEL = 100 mg/kg/d.[90]
Sodium Hexametaphosphate	0.9% and 35% in diet for up to 150 d. Control group: diet containing 0.4% P and 0.5% Ca	Groups of 12 male rats	Kidney weight significantly heavier in 30% dietary group (possibly due to high salt load on kidneys), when compared to control. No histopathological abnormalities in either group.[8,107]
Sodium Hexametaphosphate	0.2%, 2%, or 10% in diet for 1 month	Groups of 5 weanling male rats	Increased relative kidney weight and renal tubular necrosis at 120% in diet. Dietary no-effect-level of 0.2% in diet (equivalent to 103 mg/kg/d, assuming that 0.35 kg rat consumes 18 g food/d).[30,90]
Sodium Hexametaphosphate	0.05%, 0.5%, or 5% in diet (23, 225, 2250 mg/kg/d*) for 2 yr	Groups of 50 male and 50 female weanling rats	Calcification and increased kidney weight (not significant changes) in 5% dietary group. High mortality in all groups (unrelated to dietary concentration).[8]
Sodium Hexametaphosphate	1% in diet (450 mg/kg/d*) containing iron (1000 ppm) and iodine (30 ppm) for 9 mo. Control group: unfortified salt diet	8 Wistar/NIN rats	No gross bone abnormality. Normal histology of kidneys and parathyroid gland in test and control groups.[108]
Sodium Hexametaphosphate	Oral dose rate of 0.1 g/kg/d for 1 month (1 dog). 2 other dogs dosed similarly for 1 month, and dose had increased to 4 g/kg/d by end of 5-month period	3 dogs	Kidney tubule damage in dogs receiving higher doses. No treatment-related changes in dog dosed with 0.1 g/kg/d only.[8]
Sodium Polyphosphate/Sodium Hexametaphosphate	0%, 0.2%, 2%, or 10% in diet for 30 d	Rats	NOEL = 103 mg/kg/d*.[90]
Sodium Polyphosphate/Sodium Hexametaphosphate	0%, 0.1%, 1%, and 10% in diet (0, 45, 450, 4500 mg/kg/d*) for 104 wk	Rats	NOAEL = 450 mg/kg/d*.[90]
Sodium Polyphosphate/Sodium Hexametaphosphate	0%, 0.05%, 0.5%, or 5% in diet (0, 23, 225, 2250 mg/kg/d*) for 104 wk	Rats	NOAEL = 225 mg/kg/d*.[90]
Sodium Polyphosphate/Sodium Hexametaphosphate	0%, 0.93%, or 3.5% in diet (0, 419, 1575 mg/kg/d*) for 21 wk	Rats	NOAEL = 1575 mg/kg/d*.[48,107]
Sodium Polyphosphate/Sodium Hexametaphosphate	0 or 100 mg/kg/d for 30 d	Dogs	NOAEL = 100 mg/kg/d.[90]
Sodium Phosphate	0.4% or 0.6% in diet for 28 d	Juvenile female Wistar rats (RIV: TOX)	At 0.6% in diet, significant increase in kidney weight (25%) and in incidence of nephrocalcinosis.[30,109]
Sodium Phosphate	1%, 2.5%, or 5% in Sherman diet for 16 wk	Groups of 20 male and female rats	Increased kidney weight (females) and decreased kidney function (males) at $\geq$ 2.5% in diet. Kidney damage (calcification, degeneration, and necrosis) in greater % of rats in 1% dietary group, when compared to control group.[8]
Sodium Phosphate	1.8%, 3%, or 5% in modified Sherman diet (810, 1350, 2250 mg/kg/d*) for 6 mo	Groups of 34 to 36 young rats	Nephrocalcinosis in 3% and 5% dietary groups. At microscopic examination, kidney calcification in some of the animals (number not stated). Slight increase (statistically significant) in kidney weight in 1.8% dietary group.
Sodium Phosphate	8% in diet for 7 mo or until exitus	Weanling rats	Gradual bone decalcification, renal calcium deposition, and significant parathyroid hypertrophy and hyperplasia. Histological evidence of metastatic calcium deposits in renal tubules and long-bone periosteum and endosteum.[59]
Sodium Phosphate	1.1% in diet (495 mg/kg/d*) for 39 wk	Rats	Slight degree of kidney calcification.[8,103]
Sodium Phosphate	0, 43, 129, or 258 mg/kg/d for 70 d	Sheep	NOEL = 258 mg/kg/d.[99]

(continued)

Table 7. (continued)

Ingredient	Test Concentration/Dose	Animals (number stated, if available from source)	Results
Sodium Trimetaphosphate	0.2%, 2%, or 10% in diet for 1 month	Weanling male rats (5 per group)	Reduced body weight, increased relative kidney weights, and renal tubular necrosis at 10% in diet. Acute inflammation or pelvic lesions in some of the rats (number not stated) fed 2% in diet. Dietary no-effect-level of 0.2% in diet (equivalent to 103 mg/kg/d, assuming that 0.35 kg rat consumes 18 g of food/d).[30,90]
Sodium Trimetaphosphate	0.1%, 1%, or 10% in diet (45, 450, 4500 mg/kg/d*) for 2 yr	Rats	At 10% in diet, substantial growth retardation (males and females) and anemia (females).[110]
Sodium Trimetaphosphate	0.05%, 0.5%, or 5% in diet (23, 225, 2250 mg/kg/d*) for 2 yr	Rats	Substantial growth retardation in males of 5% dietary group, but females slightly affected. 65% of rats examined in 5% dietary group presented with intertubular calcification, as distinguished from the coexistent pyelonephritis present in old rats. NOAEL = 450 mg/kg/d (Extrapolated from level of chemical in diet, assuming 0.35 kg rat eats 18 g food/d.)[90,110]
Sodium Trimetaphosphate	0 and 100 mg/kg/d for 30 d	Dogs	NOAEL = 100 mg/kg/d.[90]
Tetrasodium Pyrophosphate	250, 500, or 1000 mg/kg/d by gavage for 90 d (5 d/week) (OECD Guideline 408)	Groups of 20 Sprague-Dawley rats (10 males and 10 females/group)	No treatment-related mortalities. Increased white blood cell count (males and females) and decreased red blood cell count (males) at 1000 mg/kg/d. Significantly increased liver weight in males and females of 500 and 1000 mg/kg/d groups. Kidney lesions in males and females of 1000 mg/kg/d group. NOEL = 250 mg/kg/d; NOAEL = 500 mg/kg/d.[31]
Tetrasodium Pyrophosphate	0%, 1.1%, 1.8%, 3%, or 5% in diet (0, 495, 810, 1350 mg/kg/d*) for 39 wk	Rats	LOEL = 495 mg/kg/d*.[48,103]
Trisodium Phosphate	8% in diet (3600 mg/kg/d*) for 7 mo or until animals died	Mature rats	Pathological effects in parathyroids, kidneys, and bones. LOEL < 3600 mg/kg/d*.[8,111,112]
		Sodium and Potassium Salts	
Diets high (1.5%) in P (as monophosphate or tripolyphosphate sodium or potassium salts)	Feeding for 13 d	Male rats	Nephrocalcinosis.[30,113]
Tetrasodium Pyrophosphate + Potassium Metaphosphate	0.5% commercial preparation containing 67% Tetrasodium Pyrophosphate and 33% Potassium Metaphosphate (effective concentration [Tetrasodium Pyrophosphate = 0.5% × 67% = 0.34%; effective concentration [Potassium Metaphosphate] = 0.5% × 33% = 0.17%])	Rats (10 males, 10 females). Feeding continued through second and third generations	Growth, average life span, and kidney weight normal.[8,58]
Tetrasodium Pyrophosphate + Potassium Metaphosphate	1% commercial preparation containing 67% Tetrasodium Pyrophosphate and 33% Potassium Metaphosphate (effective concentration [Tetrasodium Pyrophosphate = 1% × 67% = 0.67%; effective concentration [Potassium Metaphosphate] = 1% × 33% = 0.33%])	Rats (10 males, 10 females). Feeding continued through second and third generations	Growth and average life span normal. Nephrocalcinosis and slight increase (significant increase only in males) in kidney weight observed.[8,58]
Tetrasodium Pyrophosphate + Potassium Metaphosphate	2.5% commercial preparation containing 67% Tetrasodium Pyrophosphate and 33% Potassium Metaphosphate (effective		Growth and average life span normal. Nephrocalcinosis and increased kidney weight observed.[8,58]

(continued)

Table 7. (continued)

Ingredient	Test Concentration/Dose	Animals (number stated, if available from source)	Results
	concentration [Tetrasodium Pyrophosphate = 2.5% × 67% = 1.7%; effective concentration [Potassium Metaphosphate] =2.5% × 33% = 0.83%])	Rats (10 males, 10 females). Feeding continued through second and third generations	
Tetrasodium Pyrophosphate + Potassium Metaphosphate	5% commercial preparation containing 67% Tetrasodium Pyrophosphate and 33% Potassium Metaphosphate (effective concentration [Tetrasodium Pyrophosphate = 5% × 67% = 3.4%; effective concentration [Potassium Metaphosphate] = 5% × 33% = 1.7%])	Rats (10 males, 10 females). Feeding continued through second and third generations	Growth retardation, increased kidney weight, and nephrocalcinosis observed.[8,58]
		Potassium Salts	
Dipotassium Phosphate	10% in diet for 8 wk	Male Wistar rats	Nephrotoxicity at 10% in diet.[62]
Dipotassium Phosphate	0.87% and 5.1% in diet for 60 d and 150 d. 5.1% in diet equivalent to 2623 mg/kg/d*	Groups of 12 Wistar male rats	Kidney weight significantly increased after 150 d of feeding at 5.1% in diet; no histopathological lesions in kidney. No other treatment-related effects at gross or histopathological examination. NOAEL = 2623 mg/kg/d*.[17]
Dipotassium Phosphate	0.87% or 5.1% for 21 wk	Rats	NOAEL = 2295 mg/kg/d*.[48,107]
Dipotassium Phosphate	5% in diet (2250 mg/kg/d*) in medium-term bioassay	Male Wistar rats	Renal calcification and severe nephropathy.[62]
Dipotassium Phosphate	Oral doses (by gavage) of 1000 mg/kg/d for 42 d (males) and 42 to 54 d (females)	Rats (males and females)	Significant decreases in liver and heart weights-to-body weight ratio. No gross or histopathological alterations. LOEL = 1000 mg/kg/d.[114]
Dipotassium Phosphate	Oral doses (by gavage) of 1000 mg/kg/d for 42 d (males) and for 42 to 54 d (females)	Sprague-Dawley rats (16 males and 16 females/group)	No deaths or abnormal clinical changes. Statistically significant reductions in red blood cells in females but not in males. Significantly lower relative liver and heart weights observed not considered toxicological findings, due to absence of histopathological changes. LOEL = 1000 mg/kg/d.[17]
Dipotassium Phosphate	Diet providing 800 mg/kg/d for 14 and 38 wk	15 Beagle dogs	Renal damage consisted of disseminated tubular atrophy (usually of the proximal tubules), focal scar tissue, and nephrocalcinosis. Renal morphological changes in all dogs after 14 and 38 wk; renal damage greater after 38 wk. LOEL < 800 mg/kg/d.[17,48,115,116]
Tetrapotassium Pyrophosphate	0.6%, 1.25%, 2.5%, 5%, or 10% in diet (270, 563, 2250, 4500 mg/kg/d*; to estimate maximum tolerable dose for long-term carcinogenicity study)	Groups of 60 male and female F344 rats	3 rats (from 10% dietary group) died of renal failure. Histopathological examination results for 5% and 10% dietary groups: necrosis and calcification of renal tubules, ulceration and / or granuloma formation in tongue mucosa, and hypertrophy of salivary glands.[117]
		Calcium Salts	
Calcium Phosphate	0.8% calcium and 0.9% phosphorus in diet (duration not stated)	Guinea pigs	Calcium deposits in soft tissues. Reduction in deposits when phosphorus content reduced to 0.5%.[8,118]
Calcium Phosphate	0.56% calcium and 0.42% phosphorus in the diet for up to 150 d	12 rats	No adverse physiological effects at necropsy or microscopic examination.[8,107]
Calcium Phosphate	0.47% calcium and 0.43% phosphorus in the diet for up to 150 d	12 rats	No adverse physiological effects at necropsy or microscopic examination.[8,107]

(continued)

Table 7. (continued)

Ingredient	Test Concentration/Dose	Animals (number stated, if available from source)	Results
Calcium Phosphate	0.5% calcium and 1.30% phosphorus in the diet for up to 150 d	12 rats	No adverse physiological effects at necropsy or microscopic examination.[8,107]
Calcium Phosphate	High phosphorus containing diets (Ca: P ratios of up to 1:4) for 88 mo	Cinnamon ringtail monkeys (Cebus albifrons)	Minor bone changes observed microscopically.[8,119]
Calcium Pyrophosphate (in saline; β-)	Feeding 7 d/week (30 mg/kg/d) for 90 d.	Sprague-Dawley rats (10 males, 10 females)	No deaths or adverse toxic effects.[37]
Dicalcium Phosphate	Doses of 0, 250, 500, or 1000 mg/kg/d by gavage for 28 d	Rats (10 per sex in control and highest dose groups; 5 per sex in other groups)	No treatment-related clinical, hematological, or necropsy findings. Statistically significant increase in relative liver weight in males of the 250 mg/kg group, but no morphological findings in the liver. NOAEL = 1000 mg/kg/d.[86,120]
Dicalcium Phosphate	Doses of 0, 250, 500, or 1000 mg/kg/d for 28 d by gastric intubation	Sprague-Dawley rats (10/sex/dose)	No gross or microscopic effects. NOAEL > 1000 mg/kg/d.[67]
Tricalcium Phosphate	Doses of 0, 250, 500, or 1000 mg/kg/d by gavage. Males dosed from 2 wk before mating to end of mating. Females dosed from 2 wk before mating to d 4 of lactation (including the mating and gestation periods)	Rats (10 per sex in each group)	No deaths or toxicologically significant findings. NOAEL = 1000 mg/kg/d.[54,55]

LOEL = lowest-observed-effect level; NOEL = no-observed-effect level; NOAEL = no-observed-adverse-effect level; OECD = Organization for Economic Co-operation and Development.
*Extrapolated from level of chemical in diet, assuming 0.4 kg rat eats 18 g food/d.

Table 8. Reproductive and Developmental Toxicity Studies.

Ingredient	Test Protocol	Animals/Embryos	Results
		Acids	
Phosphoric Acid	0.4% and 0.75% in diet for 90 wk	Rats from 3 successive generations (number not stated)	No adverse effects on reproduction at either dietary concentration.[8,121]
Phosphoric Acid	Oral doses of 0, 125, 250, or 500 mg/kg/d, to male rats for 42 d (2 wk prior to mating to 2 wk after mating); to female rats for 40 to 52 d (2 wk prior to mating to d 4 postpartum)	Rats (13 males 13 females/group)	No reproductive effects or treatment-related changes in neonatal survival or external abnormalities.[65,68]
		Ammonium Salts	
Diammonium Phosphate	Oral doses of 0, 250, 750, or 1500 mg/kg/d (7 d/week) for 35 d	Rats (5 males and 10 females/group)	No reproductive or developmental effects at doses administered. NOAEL = 1500 mg/kg/d.[88,100]
		Sodium Salts	
Disodium Pyrophosphate	Doses (in water) up to 335 mg/kg/d on gestation d 6-15	19 to 22 CD-1 mice	No treatment-related effects (NOEL > 335 mg/kg).[122]
Disodium Pyrophosphate	Doses (in water) up to 169 mg/kg/d on gestation d 6-15	21 to 24 Wistar rats	No treatment-related effects (NOEL > 169 mg/kg).[122]
Disodium Pyrophosphate	Doses (in water) up to 166 mg/kg/d on gestation d 6-10	20 to 22 Golden hamsters	No treatment-related effects (NOEL > 166 mg/kg).[122]
Disodium Pyrophosphate	Doses (in water) up to 128 mg/kg/d on gestation d 6-18	9 to 12 Dutch-belted rabbits	No treatment-related effects (NOEL > 128 mg/kg).[122]
Pentasodium Triphosphate	Oral doses (in water) up to 238 mg/kg/d on gestation d 6-15	Groups of 21 to 24 pregnant albino, CD-1 outbred mice.	No clearly discernible treatment-related effect on nidation or on maternal or fetal survival. Number of abnormalities (in soft or skeletal tissues) in test animals did not differ from number occurring in sham-treated controls. NOEL > 238 mg/kg.[123,124]
Pentasodium Triphosphate	Oral doses (in water) up to 170 mg/kg/d on gestation d 6-15	Groups of 19 to 23 Wistar albino rats	No clearly discernible treatment-related effect on nidation or on maternal or fetal survival. Number of abnormalities (in soft or skeletal tissues) in test animals did not differ from number occurring in sham-treated controls. NOEL > 170 mg/kg.[123,124]
Pentasodium Triphosphate	Oral doses (in water) up to 141 mg/kg/d on gestation d 6-10	Groups of 20 to 21 pregnant female golden hamsters	No clearly discernible treatment-related effect on nidation or on maternal or fetal survival. Number of abnormalities (in soft or skeletal tissues) in test animals did not differ from number occurring in sham-treated controls. NOEL > 141 mg/kg.[123,124]
Pentasodium Triphosphate	Oral doses (in water) up to 250 mg/kg/d on gestation d 6-18	Groups of 13 to 16 pregnant female Dutch-belted rabbits	No clearly discernible treatment-related effect on nidation or on maternal or fetal survival. Number of abnormalities (in soft or skeletal tissues) in test animals did not differ from number occurring in sham-treated controls. NOEL > 250 mg/kg.[125,126]
	5% in diet for 2 yr		

(continued)

Table 8. (continued)

Ingredient	Test Protocol	Animals/Embryos	Results
Pentasodium Triphosphate		Groups of weanling rats (50 males and 50 females/group). Feeding through 3 generations (2 litters produced in each generation)	Normal reproduction and no adverse reproductive effects in offspring.[8]
Pentasodium Triphosphate	Injection (increasing doses of 0.7 to 10 mg, and dose of 30 mg) into air chamber of chick embryo after 24 h and 72 h of incubation	Chick embryos	No effects at any dose after 24 h or 72 h of incubation.[127]
Sodium Hexametaphosphate	5% in diet for 2 yr	Groups of weanling rats (50 males and 50 females/group). Feeding through 3 generations (2 litters produced in each generation)	Normal reproduction and no adverse reproductive effects in offspring.[8]
Sodium Hexametaphosphate	Doses (vehicle not stated) up to 370 mg/kg/d on gestation d 6-16	~24 albino CD-1 mice	No treatment-related effects (NOEL > 370 mg/kg).[8]
Sodium Hexametaphosphate	Doses (vehicle not stated) up to 138 mg/kg/d on gestation d 6-16	~24 Wistar albino rats	No treatment-related effects (NOEL > 138 mg/kg).[8]
Sodium Hexametaphosphate	Injection via the air cell/yolk. Doses up to 10 mg/egg (maximum volume injected = 100 µl). LD_{50} values determined and gross examination for developmental abnormalities performed	100 chick embryos per dose level	LD_{50} = 1.53 mg/egg (air cell injection). Cleft palate and other anomalies at all doses (0.5-10 mg/egg). Teratogenic.[128]
Sodium Metaphosphate	Injection (increasing doses of 0.7 to 10 mg, and dose of 30 mg) into air chamber of chick embryo after 24 h and 72 h of incubation	Chick embryos	No effects at any dose after 72 h of incubation. Doses of 10 to 15 mg had lethal effect after 24 h of incubation. Embryos of second and third brooding day had characteristic misshapes of the brain, heart primordium, and somites. Anomalies observed at microscopic examination.[127]
Sodium Phosphate	Injection via the air cell/yolk. Doses up to 10 mg/egg (maximum volume injected = 100 µL). LD_{50} values determined and gross examination for developmental abnormalities performed	100 chick embryos per dose level	LD_{50} = 2 mg/egg (air cell injection); LD_{50} = 0.53 mg/egg (yolk injection). Cleft palate and other anomalies at all doses (0.5 to 10 mg/egg). Teratogenic.[128]
Sodium Polyphosphate/ Sodium Hexametaphosphate	Doses (vehicle not stated) up to 141 mg/kg/d; day of gestation not stated	Rats and mice	No treatment-related effects (NOEL > 141 mg/kg).[112]
Sodium Phosphate	Doses (in water) up to 370 mg/kg/d on gestation d 6-15	19 to 22 CD-1 mice	No treatment-related effects (NOEL > 370 mg/kg).[129]
Sodium Phosphate	Doses (in water) up to 410 mg/kg/d on gestation d 6-15	20 Wistar rats	No treatment-related effects (NOEL > 410 mg/kg).[129]
Sodium Trimetaphosphate	0.1%, 1%, or 10% in diet for 2 yr	Weanling rats (number/strain not stated)	At up to 10% in diet, no effect on fertility or litter size through F_2 generation.[59]
Tetrasodium Pyrophosphate	Doses (in corn oil) up to 130 mg/kg/d on gestation d 6-15	18 to 21 CD-1 mice	No treatment-related effects (NOEL > 130 mg/kg).[130]
Tetrasodium Pyrophosphate	Doses (in corn oil) up to 138 mg/kg/d on gestation d 6-15	19 to 21 Wistar rats	No treatment-related effects (NOEL > 138 mg/kg).[130]
Tetrasodium Pyrophosphate	Injection via the air cell/yolk. Doses up to 5 mg/egg (maximum volume injected = 100 µl). LD_{50} values determined and gross examination for developmental abnormalities performed	100 chick embryos per dose level	LD_{50} values: 3.87 mg/egg (air cell injection at 0 h), 0.34 mg/egg (air cell injection at 96 h), and 0.12 mg/egg (yolk sac injection at 0 h). Serious terata reported, including 1 observation of ectopia cordis. Teratogenic.[128]

(continued)

Table 8. (continued)

Ingredient	Test Protocol	Animals/Embryos	Results
		Sodium and Potassium Salts	
Tetrasodium Pyrophosphate + Potassium Metaphosphate	0.5% commercial preparation (in Sherman diet) containing 67% Tetrasodium Pyrophosphate and 33% Potassium Metaphosphate (effective concentration [Tetrasodium Pyrophosphate = 0.5% × 67% = 0.34%; effective concentration [Potassium Metaphosphate] = 0.5% × 33% = 0.17%])	Rats (10 males, 10 females). Feeding continued through second and third generations	Growth and fertility were normal. No difference in incidence of abnormalities between treated and control animals.[8,58]
Tetrasodium Pyrophosphate + Potassium Metaphosphate	1% commercial preparation (in Sherman diet) containing 67% Tetrasodium Pyrophosphate and 33% Potassium Metaphosphate (effective concentration [Tetrasodium Pyrophosphate = 1% × 67% = 0.67%; effective concentration [Potassium Metaphosphate] = 1% × 33% = 0.33%])	Rats (10 males, 10 females). Feeding continued through second and third generations	Growth and fertility were normal. No difference in incidence of abnormalities between treated and control animals.[8,58]
Tetrasodium Pyrophosphate + Potassium Metaphosphate	5% commercial preparation (in Sherman diet) containing 67% Tetrasodium Pyrophosphate and 33% Potassium Metaphosphate (effective concentration [Tetrasodium Pyrophosphate =5% × 67% = 3.4%; effective concentration [Potassium Metaphosphate] = 5% × 33% = 1.7%])	Rats (10 males, 10 females). Feeding continued through second and third generations	Growth and fertility were normal. No difference in incidence of abnormalities between treated and control animals.[8,58]
		Potassium Salts	
Dipotassium Phosphate	Doses of 1000 mg/kg/d for 42 d (males) and 42 to 54 d (females)	Sprague-Dawley rats (males and females)	No reproductive or developmental toxic effects. NOAEL = 1000 mg/kg/d.[17]
Potassium Phosphate	Doses (in water) up to 320 mg/kg/d on gestation d 6-15	20 to 22 CD-1 mice	No treatment-related effects (NOEL > 320 mg/kg).[131]
Potassium Phosphate	Doses (in water) up to 282 mg/kg/d on gestation d 6-15	20 to 25 Wistar rats	No treatment-related effects (NOEL > 282 mg/kg).[131]
Potassium Phosphate	Injection (in water) via the air cell and via the air cell/yolk. Doses up to 10 mg/egg (maximum volume injected = 100 µL). LD_{50} values determined and gross examination for developmental abnormalities performed	100 chicken embryos per dose level	LD_{50} = 1.51 mg/egg. Nonteratogenic.[128]
		Calcium Salts	
Calcium Phosphate	Doses (in water) up to 465 mg/kg/d on gestation d 6-15	19 to 24 CD-1 mice	No treatment-related effects (NOEL > 465 mg/kg).[132]
Calcium Phosphate	Doses (in water) up to 410 mg/kg/d on gestation d 6-15	19 to 22 Wistar rats	No treatment-related effects (NOEL > 410 mg/kg).[132]
Calcium Phosphate	Doses (in water) up to 217 mg/kg/d on gestation d 6-18	9 to 17 Dutch-belted rabbits	No treatment-related effects (NOEL > 217 mg/kg).[132]
Calcium Phosphate	Injection (in 1 N HCl) via the air cell/yolk. Doses up to 2.5 mg/egg (maximum volume injected = 100 µL). LD_{50} values determined and gross examination for developmental abnormalities performed	100 chick embryos per dose level	LD_{50} = 0.37 mg/egg. Nonteratogenic.[128]
Dicalcium Phosphate	Doses of 0, 250, 500, or 1000 mg/kg/d. Males dosed once daily for 2 wk prior to, during, and postmating (42 d total). Females dosed once daily for wk prior to mating, throughout gestation, and 4 d after delivery	Rats (13/sex/dose)	No dose-related effects on mating, gestation, or external malformations. NOAEL of 1000 mg/kg/d (parents and pups).[86,120]

(continued)

Table 8. (continued)

Ingredient	Test Protocol	Animals/Embryos	Results
Tricalcium Phosphate	Doses of 0, 250, 500, or 1000 mg/kg/d by gavage. Males dosed from 2 wk before mating to end of mating. Females dosed from 2 wk before mating to d 4 of lactation (including the mating and gestation periods)	Rats (10/sex/dose)	No treatment-related adverse effects on reproductive parameters and no externally malformed neonates in any dose group. NOAEL for reproductive and developmental toxicity = 1000 mg/kg/d.[54,55]
Tricalcium Phosphate	Injection (in water) via the air cell and via the air cell/yolk. Doses up to 2.5 mg/egg (maximum volume injected = 100 µL)	100 chick embryos per dose level	LD_{50} = 0.85 mg/egg. Nonteratogenic.[128]

NOEL = no-observed-effect level.

Table 9. Genotoxicity Studies.

Ingredient/Similar Chemical	Strain/Cell type	Assay	Dose/Concentration	Results
		Acids		
Phosphoric Acid	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA	Ames test	Up to 5000 μg/plate	Negative in all strains (with and without metabolic activation).[65,68]
Phosphoric Acid (75%-85% solution)	*S typhimurium* strains TA97, TA98, TA100, TA102, and TA1535	Ames test	Concentrations not stated (pHs ranged from 4 to 9)	Negative in all strains (with and without metabolic activation).[68,133]
Phosphoric Acid (75%-85% solution)	*S typhimurium* strains TA97, TA98, TA100, and TA104	Ames test	Up to 2 μL/plate	Negative in all strains (with and without metabolic activation).[134]
Phosphoric Acid	Chinese hamster lung cells	Chromosome aberrations assay	Up to 450 μg/mL	Negative (with and without metabolic activation).[65,68]
		Ammonium Salts		
Diammonium Phosphate	*S typhimurium* strains TA98, TA100, TA1535, TA1537 and *E coli* strain WP2uvrA	Ames test	Up to 5000 μg/plate	Negative (with and without metabolic activation).[97]
Diammonium Phosphate	Chinese hamster ovary cells	Chromosome aberrations assay	Up to 1230 μg/mL	Negative (with and without metabolic activation).[97]
		Sodium Salts		
Disodium Phosphate	*S typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537	Ames test	Up to 100 mg/plate	Negative in all strains (with and without metabolic activation).[135]
Disodium Phosphate	*S typhimurium* strains TA98, TA100, TA1535, and TA1537	Ames test	Up to 10000 μg/plate	Negative in all strains (with and without metabolic activation).[136]
Disodium Phosphate	Chinese hamster fibroblasts (CHL cell line)	Chromosome aberrations assay	Up to 2 mg/mL	Negative.[135]
Disodium Pyrophosphate	*S typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537	Ames test	Up to 10 mg/plate	Negative in all strains (with and without metabolic activation).[135]
Disodium Pyrophosphate	*S typhimurium* strains TA97, TA98, TA100, TA102, and TA1535	Ames test	5% (w/v)	Negative in all strains (with and without metabolic activation).[112]
Disodium Pyrophosphate	*Saccharomyces cerevisiae*	*S cerevisiae* mutation assay	Not stated	Negative (with or without metabolic activation not stated).[112]
Disodium Pyrophosphate	*S typhimurium* strain TA1530 and *S cerevisiae* strain D3	Host mediated assay	Up to 1400 mg/kg	Negative in both strains.[112]
Disodium Pyrophosphate	Rats	Dominant lethal test	Up to 720 mg/kg	Negative.[112]
Disodium Pyrophosphate	Male mice	Mouse translocation test	Up to 1400 mg/kg	Negative.[112]
Disodium Pyrophosphate	Chinese hamster fibroblasts (CHL cell line)	Chromosome aberrations assay	Up to 0.5 mg/mL	Negative.[135]
Pentasodium Triphosphate	WI-38 human lung cells (without metabolic activation)	In vitro cytogenetics assay	Up to 10 μg/ml	Negative.[137]
Pentasodium Triphosphate	Rats (bone marrow cells)	In vivo cytogenetics assay	Up to 2500 mg/kg	Negative.[137]
Pentasodium Triphosphate	*S typhimurium* strains his G46 and TA1530, and *S cerevisiae* strain D3	Host mediated assay (cells inoculated into mice)	Up to 2500 mg/kg	Negative.[137]
Pentasodium Triphosphate	Rats	Dominant lethal test	Up to 2500 mg/kg	Negative.[137]
Sodium Hexametaphosphate	*S typhimurium* strains TA1535, TA1537, and TA1538	Ames test	Not stated	Negative in all strains (with and without metabolic activation).[8]
	S typhimurium strains TA1535, TA1537, and TA1538	Ames test	Up to 0.018 μg/plate	

(continued)

Table 9. (continued)

Ingredient/Similar Chemical	Strain/Cell type	Assay	Dose/Concentration	Results
Sodium Polyphosphate/ Sodium Hexametaphosphate				Negative in all strains (with and without metabolic activation).[112]
Sodium Polyphosphate/ Sodium Hexametaphosphate	*S cerevisiae* strain D4	*S cerevisiae* mutation assay	Up to 0.018 µg/plate	Negative (with and without metabolic activation).[112]
Sodium Phosphate	*S typhimurium* strains TA1535, TA1537, and TA1538	Ames test	Up to 1.25%	Negative in all strains (with and without metabolic activation).[138]
Sodium Phosphate	*S cerevisiae* strain D4	*S cerevisiae* mutation assay	Up to 5%	Negative (with and without metabolic activation).[138]
Sodium Phosphate	*E coli* strain WP2uvrA	SOS chromotest (without metabolic activation)	10 to 100000 nM/mL	Negative.[139,140]
Tetrasodium Pyrophosphate	*S typhimurium* strains TA1535, TA1537, and TA1538	Ames test	Up to 0.1% (w/v)	Negative in all strains (with and without metabolic activation).[137]
Tetrasodium Pyrophosphate	*S typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E coli* strain WP2uvrA	Ames test	Up to 4820 µg/plate	Negative in all strains (with and without metabolic activation).[141]
Tetrasodium Pyrophosphate	*S cerevisiae* strain D4	*S cerevisiae* mutation assay	Up to 2.25% (w/v)	Negative (with and without metabolic activation).[137]
		Potassium Salts		
Dipotassium Phosphate (liquid)	*S typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538; *S cerevisiae* strain D4	Ames test	Up to 5 µL/plate	Negative in all strains (with and without metabolic activation).[48]
Dipotassium Phosphate	*S typhimurium* strains TA97 and TA102	Ames test	Up to ∼10 mg/plate	Negative (with and without metabolic activation).[17]
Dipotassium Phosphate	Chinese hamster lung cells	Chromosome aberrations assay	Up to 5000 µg/mL	Negative (with and without metabolic activation).[17]
Potassium Phosphate	*S typhimurium* strains TA1535, TA1537, and TA1538; *S cerevisiae* strain D4	Ames test	Up to 5% (w/v)	Negative in all strains (with and without metabolic activation).[142]
Tetrapotassium Pyrophosphate	*S typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538; *S cerevisiae* strain D4	Ames test	Up to 5 µL/plate	Negative in all strains (with and without metabolic activation).[48]
		Calcium Salts		
Calcium Phosphate	*S typhimurium* strains TA1535, TA1537, and TA1538	Ames test	Up to 0.75%	Negative in all strains (with and without metabolic activation).[143]
Calcium Phosphate	*S cerevisiae* strain D4	*S cerevisiae* mutation assay	Up to 5% (w/v)	Negative.[143]
Dicalcium Phosphate	*S typhimurium* strains TA97 and TA102	Ames test	Not stated	Negative (with or without metabolic activation not stated).[48,144]
Dicalcium Phosphate	*S typhimurium* strains TA98, TA100, TA1535, and TA1537; *E coli* strain WP2uvrA	Ames test	Up to 2000 µg/plate	Negative (with or without metabolic activation).[86]
Dicalcium Phosphate	Chinese hamster lung fibroblasts (CHL cells)	Chromosome aberrations assay	Up to 500 µg/mL	Not clastogenic (with or without metabolic activation).[86]
Tricalcium Phosphate	*S typhimurium* strains TA98, TA100, TA1535, and TA1537; *E coli* strain WP2uvrA	Ames test	Up to 1250 µg/plate	Negative (with or without metabolic activation).[13,55]
Tricalcium Phosphate	Chinese hamster lung cells (CHL/IU)	Chromosome aberrations assay	Up to 200 µg/mL	Negative (with or without metabolic activation).[13]

Table 10. Skin Irritation/Sensitization Studies.

Ingredient (test concentration, if available)	Test Protocol	Non-humans/Humans (number stated, if available from source)	Results
		Acids	
Animal Studies			
Phosphoric Acid (5% and 30%)	Intracutaneous application (intact skin). 6-h observation period	Juvenile white mice	5% concentration moderately irritating; 30% concentration severely irritating.[68]
Phosphoric Acid (100%)	4-h application (under occlusion) to abraded and intact skin	Rabbits	Corrosive.[48]
Phosphoric Acid (85% solution)	24-h application (under occlusion) to abraded and intact skin	Rabbits	Moderately to severely irritating.[48]
Phosphoric Acid (85% solution)	24-h application	New Zealand white rabbits	Corrosive.[68]
Phosphoric Acid (75%-85%)	24-h application (0.5 mL under semiocclusive patch)	New Zealand albino rabbits	Corrosive.[145]
Phosphoric Acid (80%)	24-h application (0.5 mL under 1″ × 1″ occlusive patch) to abraded and intact skin	Rabbits (at least 6)	Highly irritating.[146]
Phosphoric Acid (75%, 80%, and 85%)	4-h application (0.5 mL under 1″ × 1″ occlusive patch) to abraded and intact skin	Albino rabbits (at least 6)	Noncorrosive (75% and 80%). Corrosive (85%).[147]
Phosphoric Acid (75%)	4-h application (no occlusion) to intact skin	Rabbits	Nonirritating.[48]
Phosphoric Acid (75%)	4-h application (semiocclusion) to intact skin	1 New Zealand white rabbit	Nonirritating.[68]
Phosphoric Acid (70%)	4-h application (under occlusion) to abraded and intact skin	Rabbits	Corrosive.[48]
Phosphoric Acid (52%)	Applied (under occlusion) to abraded and intact skin	Rabbits	Severely irritating and corrosive.[48]
Phosphoric Acid (30%)	Buchner method.[148]	Not stated	Highly irritating.[149]
Phosphoric Acid (19%)	Not stated	2 Rabbits	Nonirritating.[150]
Phosphoric Acid ($\geq$ 17.5% [pH 0.6 to 0.2])	Under occlusion for 4 h	Rabbits	Corrosive (formation of scar tissue).[65]
Phosphoric Acid (2.5%, pH 2.1)	Not stated	3 Rabbits	Severe erythema with mild to moderate swelling (1 rabbit) at 42 h to 72 h after exposure.[65]
Human Studies			
Phosphoric Acid (concentration not stated)	Not stated	Human subjects	Nonsensitizer.[48,66]
		Ammonium Salts	
Animal Studies			
Ammonium Phosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Mildly irritating.[48]
Ammonium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]
Diammonium Phosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Mildly irritating.[48]
Diammonium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Slightly irritating.[48]
Diammonium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]
		Sodium Salts	
Animal Studies			
Disodium Phosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Moderately irritating (abraded skin) and mildly irritating (intact skin).[48]
Disodium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]
Disodium Pyrophosphate	24-h application (under occlusion) to intact skin	Rabbits	Mildly irritating.[98]

(continued)

Table 10. (continued)

Ingredient (test concentration, if available)	Test Protocol	Non-humans/Humans (number stated, if available from source)	Results
Disodium Pyrophosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Slightly irritating.[48]
Disodium Pyrophosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]
Pentasodium Triphosphate	4-h application (no occlusion) to intact skin	Rabbits	Slightly irritating.[48]
Pentasodium Triphosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Slightly to moderately irritating.[48]
Pentasodium Triphosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Moderately irritating.[48]
Pentasodium Triphosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Slightly irritating.[48]
Sodium Polyphosphate/Sodium Hexametaphosphate	4-h application (no occlusion) to intact skin	Rabbits	Slightly irritating.[48]
Sodium Polyphosphate/Sodium Hexametaphosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]
Sodium Phosphate	4-h application (no occlusion) to intact skin	Rabbits	Nonirritating.[48]
Sodium Phosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
Sodium Phosphate	Local lymph node assay. Up to 10% in propylene glycol	Female mice of the CBA/Ca (CBA/CaOlaHsd) strain	Nonsensitizer.[67]
Sodium Trimetaphosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]
Tetrasodium Pyrophosphate (50% aqueous paste)	24-h application (under occlusion) to intact skin	Rabbits	Irritating.[48]
Tetrasodium Pyrophosphate (25% aqueous suspension)	24-h application (under occlusion) to abraded and intact skin	Rabbits	Irritating.[48]
Tetrasodium Pyrophosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
Tetrasodium Pyrophosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating[98]
Tetrasodium Pyrophosphate	4-h application (no occlusion) to intact skin	Rabbits	Nonirritating.[48]
Trisodium Phosphate (95% purity)	24-h application (under occlusion) to abraded and intact skin	Rabbits	Minimally irritating (abraded skin) and nonirritating (intact skin).[98]
Trisodium Phosphate (95% purity)	4-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[98]
Trisodium Phosphate (19% solution)	4-h or 24-h application (under occlusion) to abraded and intact skin	Rabbits	Slightly irritating at 4 h and nonirritating at 24 h
Trisodium Phosphate (15% solution)	4-h or 24-h application (under occlusion) to abraded and intact skin	Rabbits	Slightly irritating at 4 h and nonirritating at 24 h
Trisodium Phosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Irritating (abraded and intact skin).[48]
Trisodium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Slightly irritating.[48]
Human Studies			
Pentasodium Triphosphate (50% solution)	Not stated	6 subjects	Negligible irritation potential.[30]

(continued)

Table 10. (continued)

Ingredient (test concentration, if available)	Test Protocol	Non-humans/Humans (number stated, if available from source)	Results
Sodium Metaphosphate (1%)	Application to intact skin	20 subjects (with suspected or verified contact allergy to cosmetic products)	Mild skin irritation.[30]
		Potassium Salts	
Animal Studies			
Dipotassium Phosphate	4-h (under occlusion) or 24-h (no occlusion) application to intact skin	Rabbits	Slightly irritating,[48]
Dipotassium Phosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Mildly irritating.[48]
Dipotassium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Minimally irritating.[48]
Dipotassium Phosphate(liquid)	24-h application (under occlusion) to abraded and intact skin	Rabbits	Slightly irritating.[48]
Pentapotassium Triphosphate	4-h application (no occlusion) to intact skin	Rabbits	Nonirritating.[48]
Potassium Phosphate	4-h application (no occlusion) to intact skin	Rabbits	Nonirritating.[48]
Potassium Phosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
Potassium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Slightly irritating.[48]
Tetrapotassium Pyrophosphate	4-h application (no occlusion) to intact skin	Rabbits	Nonirritating.[48]
Tetrapotassium Pyrophosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
Tetrapotassium Pyrophosphate (aqueous solution)	24-h application (under occlusion) to intact skin	Rabbits	Slightly irritating.[48]
Tetrapotassium Pyrophosphate (aqueous solution)	24-h application (under occlusion) to intact skin	Rabbits	Mildly irritating.[48]
Tetrapotassium Pyrophosphate	24-h application (under occlusion) to intact skin	Rabbits	Slightly irritating.[48]
Tetrapotassium Pyrophosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]
		Calcium Salts	
Animal Studies			
Calcium Dihydrogen Phosphate	24 h application of 0.5 g (wrapped in rubber)	Rabbits (3 males and 3 females)	Nonirritating.[86]
Calcium Phosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Mildly irritating.[48]
Calcium Phosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
Calcium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[98]
Calcium Pyrophosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating[48]
Dicalcium Phosphate	24-h application (0.5 g, under occlusion) to abraded and intact skin	6 Rabbits	Nonirritating.[67]
Dicalcium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]

(continued)

Table 10. (continued)

Ingredient (test concentration, if available)	Test Protocol	Non-humans/Humans (number stated, if available from source)	Results
Tricalcium Phosphate	4-h application (no occlusion) to intact skin	Rabbits	Nonirritating.[48]
Tricalcium Phosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Slightly irritating.[48]
Tricalcium Phosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
		Magnesium Salts	
Animal Studies			
Magnesium Phosphate	4-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
Magnesium Phosphate	4-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]
Magnesium Phosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
Trimagnesium Phosphate	24-h application (under occlusion) to abraded and intact skin	Rabbits	Nonirritating.[48]
Trimagnesium Phosphate	24-h application (under occlusion) to intact skin	Rabbits	Nonirritating.[48]

Table 11. Ocular Irritation/Toxicity Studies.

Ingredient	Test Protocol	Animals (number stated, if available from source)	Results
	Acids		
Phosphoric Acid (119 mg)	Not stated	Rabbits	Irritating. Risk of serious damage to eyes.[151]
Phosphoric Acid (75%, 80%, and 85% solutions)	Draize test	3 rabbits	All corrosive.[68,69]
Phosphoric Acid (85%)	Draize test	Rabbits	Severe irritant.[48]
Phosphoric Acid (70% solution)	Draize test	Rabbits	Corrosive.[48]
Phosphoric Acid (10% and 17% in water)	OECD Guideline 405. Instilled (100 µL) into lower conjunctival sac	6 New Zealand white albino rabbits	Conjunctivitis observed (both concentrations), but classified as nonirritating.[65,68]
Phosphoric Acid	Irrigation with 0.16 M solution (buffered to pH 3.4)	Rabbits	Slight transient epithelial edema and conjunctival hyperemia.[3]
Metaphosphoric Acid	Injection into corneal stroma or application to cornea after removal of epithelium	Rabbits	Injury detected at $<$ pH 5.5.[3]
	Ammonium Salts		
Ammonium Phosphate	Draize test	Rabbits	At 24 h, slightly irritating.[48]
Ammonium Phosphate (solution, concentration not stated)	Draize test	Rabbits	At 24 h, mildly to moderately irritating.[48]
Diammonium Phosphate	Draize test	Rabbits	At 24 h, slightly irritating to moderately irritating.[97]
	Sodium Salts		
Disodium Phosphate	Draize test	Rabbits	At 24 h, practically nonirritating (rinsed eyes) and minimally irritating (unrinsed eyes).[48]
Disodium Phosphate	Instilled into eye	Rabbits	Minimal ocular irritation.[30]
Disodium Pyrophosphate	Draize test	Rabbits	At 24 h, mildly irritating (rinsed eyes) and extremely irritating (unrinsed eyes).[152]
Disodium Pyrophosphate	Instilled into eye (rinsed or unrinsed)	Rabbits	Marked ocular irritation in unrinsed eyes. Minimal-to-mild irritation after ocular rinsing.[30]
Pentasodium Triphosphate	Draize test	Rabbits	Nonirritating (rinsed eyes) and mildly irritating (unrinsed eyes).[48]
Pentasodium Triphosphate	Draize test	Rabbits	At 24 h, irritating.[48]
Sodium Metaphosphate	Not stated	Rabbits	Nonirritating.[30]
Sodium Polyphosphate/ Sodium Hexametaphosphate	Draize test	Rabbits	Nonirritating (rinsed eyes) and minimally irritating (unrinsed eyes)
Sodium Phosphate	Draize test	Rabbits	At 24 h, practically nonirritating (rinsed eyes) and minimally irritating (unrinsed eyes).[48]
Sodium Phosphate	Instilled into eye	Rabbits	Minimal ocular irritation.[30]
Sodium Trimetaphosphate	Draize test	Rabbits	At 24 h, slightly irritating.[48]
Tetrasodium Pyrophosphate	Draize test	Rabbits	Minimally irritating (rinsed eyes) and extremely irritating (unrinsed eyes).[152]
Tetrasodium Pyrophosphate (10% solution)	Draize test	Rabbits	At 24 h, irritating.[48]
Trisodium Phosphate	Draize test	Rabbits	Moderately irritating (rinsed eyes) and extremely irritating (unrinsed eyes).[152]
Trisodium Phosphate	Draize test	Rabbits	Slightly irritating (rinsed eyes) and corrosive (unrinsed eyes).[48]

(continued)

Table 11. (continued)

Ingredient	Test Protocol	Animals (number stated, if available from source)	Results
Trisodium Phosphate (15% aqueous solution)	Draize test	Rabbits	Mildly irritating.[30]
Trisodium Phosphate (10% solution)	Draize test	Rabbits	At 24 h, irritating.[48]
		Potassium Salts	
Dipotassium Phosphate	Draize test	6 rabbits	Dipotassium Phosphate (0.1 g solid or 0.1 mL liquid) practically nonirritating (rinsed eyes) and mildly irritating (unrinsed eyes).[48]
Pentapotassium Triphosphate	Draize test	Rabbits	Nonirritating (rinsed eyes) and mildly irritating (unrinsed eyes).[48]
Potassium Phosphate	Draize test	Rabbits	Nonirritating (rinsed and unrinsed eyes).[48]
Potassium Phosphate	Draize test	Rabbits	Slightly irritating.[48]
Tetrapotassium Pyrophosphate	Draize test	Rabbits	Mildly irritating (rinsed eyes) and moderately irritating (unrinsed eyes).[48]
	Calcium Salts		
Calcium Dihydrogen Phosphate	0.1 g in eye for 24 h	6 New Zealand albino rabbits	Transient, slight erythema. Nonirritating.[86]
Calcium Dihydrogen Phosphate	SkinEthic reconstituted human corneal model. Tissues treated with 30 mg for 10 minutes		Nonirritant.[86]
Calcium Phosphate	Draize test	Rabbits	Practically nonirritating (rinsed eyes) and moderately irritating (unrinsed eyes).[152]
Calcium Phosphate	Draize test	Rabbits	Extremely irritating (rinsed and unrinsed eyes).[48]
Calcium Pyrophosphate	Draize test	Rabbits	At 24 h, slightly irritating.[48]
Dicalcium Phosphate	Draize test	6 New Zealand rabbits	Slight erythema, fully reversible within 24 h. Nonirritating.[67]
Dicalcium Phosphate	Draize test	Rabbits	At 24 h, slightly irritating.[48]
Dicalcium Phosphate	Reconstructed human corneal model (human-derived keratinocytes, triplicate tissues) treated with 30 mg for 10 minutes		Relative mean viability of tissues was 102% after exposure. Test material unable to directly reduce MTT. Nonirritant.[67]
Dicalcium PhosphateDihydrate	0.1 g in eye for 24 h	3 albino rabbits (1 male and 2 females)	Transient, slight erythema. Low potential for ocular irritation.[86]
Tricalcium Phosphate	Draize test	Rabbits	Nonirritating (rinsed eyes).[48]
	Magnesium Salts		
Magnesium Phosphate	Draize test	Rabbits	Slightly irritating (unrinsed eyes).[48]
Trimagnesium Phosphate	Draize test	Rabbits	At 24 h, nonirritating.[48]

OECD = Organization for Economic Co-operation and Development.

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