Safety Assessment of Starch Phosphates as Used in Cosmetics

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ABBREVIATIONS

aq.	aqueous
ADP	adenosine diphosphate
ATP	adenosine triphosphate
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
CPSC	Consumer Product Safety Commission
Council	Personal Care Products Council
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FDRL	Food and Drug Research Laboratories
HRIPT	human repeated insult patch test
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	lethal dose, 50%
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
QSAR	quantitative structure-activity relationship
SIOPT	single insult occlusive patch test
SLS	sodium lauryl sulfate
SPF	specific-pathogen-free
US	United States
VCRP	Voluntary Cosmetic Registration Program
WHO	World Health Organization
wINCI	web-based *International Cosmetic Ingredient Dictionary and Handbook*

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 4 starch phosphates as used in cosmetic formulations. Distarch Phosphate is reported to function in cosmetics as an anticaking agent and binder. Distarch Phosphate Acetate, Hydroxypropyl Starch Phosphate, and Sodium Hydroxypropyl Starch Phosphate are all reported to function as viscosity increasing agents. The Panel considered the available data and concluded that these ingredients are safe in cosmetics in the present practices of use and concentrations described in this safety assessment.

INTRODUCTION

The safety of the following 4 starch phosphates as used in cosmetics is reviewed in this safety assessment.

Distarch Phosphate	Hydroxypropyl Starch Phosphate
Distarch Phosphate Acetate	Sodium Hydroxypropyl Starch Phosphate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Distarch Phosphate is reported to function in cosmetics as an anticaking agent and a binder (Table 1).[1] Distarch Phosphate Acetate, Hydroxypropyl Starch Phosphate, and Sodium Hydroxypropyl Starch Phosphate have several reported functions, but all 3 are reported to function as viscosity increasing agents.

All of the ingredients reviewed in this safety assessment may be consumed in food, and daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. Therefore, although oral studies are included in the document, the primary focus of the safety assessment is on the potential for local effects from topical exposure to these ingredients as used in cosmetics.

Some starch ingredients derived from a specific species (e.g., oryza sativa (rice) starch,[2] zea mays (corn) starch,[3] and triticum vulgare (wheat) starch[4]) have previously been reviewed by the Expert Panel for Cosmetic Ingredient Safety (Panel). These ingredients were found safe as used as described in the report.

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

Much of the data included in this safety assessment were found in reports by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA).[5-7] Similarly, data from a report by the European Food Safety Authority (EFSA) Panel on Food Additives and Nutrient Sources are also included.[8] Please note that these reports provide summaries of information from other sources, and it is those summary data that are included in this safety assessment when JECFA or EFSA are cited.

CHEMISTRY

Definition

According to the *Dictionary*, Distarch Phosphate (CAS No. 55963-33-2) is defined as the product resulting from the cross-linking of starch with sodium metaphosphate, and its acetate form, Distarch Phosphate Acetate (68130-14-3), is the product of Distarch Phosphate and acetic anhydride (Table 1).[1] Hydroxypropyl Starch Phosphate (CAS Nos. 113894-92-1, 39346-84-4, and 53124-00-8) is an ether, and Sodium Hydroxypropyl Starch Phosphate (CAS No. 221355-22-2) is the sodium salt of that ether.

Modified food starches are defined in the *Food Chemicals Codex* as products of the treatment of any of several grain- or root-based native starches (for example, corn, sorghum, wheat, potato, tapioca, and sago) with small amounts of certain chemical agents that modify the physical characteristics of the native starches to produce desirable properties.[9] Starch is composed of two kinds of polysaccharides, amylose and amylopectin,[10] and it is comprised of α-1,4 and α-1,6 linked glucose.[11] According to the *Food Chemicals Codex*, starch molecules are polymers of anhydroglucose and exist in both linear and branched form. The degree of polymerization and the molecular weight of the naturally-occurring starch molecules vary radically. Additionally, they vary in the ratio of branched-chain polymers (amylopectin) to linear-chain polymers (amylose), both within a given type of starch and from one type to another. These factors significantly affect the viscosity, texture, and stability of the starch sols.

Chemical Properties

Molecular weight data on starch phosphates were neither found in the available literature nor submitted as unpublished data. It is likely that these ingredients are similar to other modified polysaccharide gums,[4] varying primarily by phosphate

substitution and or/crosslinking. For example, carrageenan (a polysaccharide gum), has an average molecular weight > 100,000 Da and a molecular weight distribution of 196,000 - 257,000 Da. Properties data on some of the starch phosphates are presented in Table 2.

According to the *Food Chemicals Codex*, modified food starches usually occur as a white or nearly white powder or as intact granules that are insoluble in alcohol, in ether, and in chloroform, and when not pregelatinized, they are practically insoluble in cold water.[9] During heating in water (i.e., pregelatinization), the granules usually begin to swell at temperatures between 45°C and 80°C, depending on the botanical origin and the degree of modification. They gelatinize completely at higher temperatures. Pregelatinized starches hydrate in cold water, and occur as flakes, amorphous powders, or coarse particles.

Method of Manufacture

The following methods of manufacturing are general to the production of starch phosphates, and it is unknown whether they are used in the manufacture of these ingredients for use in cosmetics

Distarch Phosphate

Distarch Phosphate (a modified starch) is obtained by esterification of food starch with sodium trimetaphosphate or phosphorus oxychloride.[6] This treatment results in cross-linking, whereby a polyfunctional substituting agent, such as phosphorus oxychloride, connects two chains. Distarch Phosphate may also be subjected to acid, alkali, enzyme, or bleaching treatment. Additionally, Distarch Phosphate may be prepared by the combined use of sodium tripolyphosphate and sodium trimetaphosphate, which results in cross-linking and esterification of starch chains.[6] The overall extent of modification is small, with the residual phosphate being in the order of 0.4% phosphorus.

Distarch Phosphate Acetate

Distarch Phosphate Acetate (a modified starch) is obtained by esterification/cross-linking of food starch with sodium trimetaphosphate or phosphorus oxychloride, combined with esterification with acetic anhydride or vinyl acetate.[6] Acetylation results in substitution of hydroxyl groups with acetyl esters. Additionally, Distarch Phosphate Acetate may be subjected to acid, alkali, enzyme, or bleaching treatment.

Hydroxypropyl Starch Phosphate

Hydroxypropyl Starch Phosphate (a modified starch) is obtained by esterification of food starch with sodium trimetaphosphate or phosphorus oxychloride, combined with etherification by propylene oxide.[7] Hydroxypropylation results in the substitution of hydroxyl groups with 2-hydroxypropyl ether. Additionally, Hydroxypropyl Starch Phosphate may be subjected to acid, alkali, enzyme, or bleaching treatment.

Modified Food Starches

According to the *Food Chemicals Codex*, starch is chemically modified by mild degradation reactions or by reactions between the hydroxyl groups of the native starch and the reactant selected.[9] Either one or more of the following processes are used: mild oxidation (bleaching), moderate oxidation, acid and/or enzyme depolymerization, monofunctional esterification, polyfunctional esterification (cross-linking), monofunctional etherification, alkaline gelatinization, and certain combinations of these treatments.

Impurities

The JECFA purity specifications for Distarch Phosphate, Distarch Phosphate Acetate, and Hydroxypropyl Starch Phosphate for use as food additives are provided in Table 3.

Modified Food Starches

According to the *Food Chemicals Codex*, limitations on impurities in modified food starch are as follows: lead (not more than 1 mg/kg), sulfur dioxide (not more than 0.005%), crude fat (not more than 0.15%), cereal starch (nor more than 15%), potato starch (not more than 21%), sago starch (not more than 18%), tapioca starch (not more than 18%), pH (between 3.0 and 9.0) and protein (not more than 0.5%; except in modified high-amylose starches, not more than 1%).[9]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush

delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2022 FDA VCRP data, Hydroxypropyl Starch Phosphate is reported to have the greatest frequency of use; it is reported to be used in 261 cosmetic products, 193 of which are rinse-offs.[12] The results of a concentration of use survey, conducted by the Council in 2020 and provided to CIR in 2021, indicate that Distarch Phosphate has the highest maximum concentration of use; it is reported to be used at maximum use concentrations up to 7.5% in leave-on products. Further use data are presented in Table 4. According to VCRP and Council survey data, 1 of the starch phosphates (Distarch Phosphate Acetate) reviewed in this safety assessment is not currently in use in cosmetic products (Table 5).

Cosmetic products containing starch phosphates may incidentally come in contact with the eyes (e.g., Distarch Phosphate in eyeliners at concentrations up to 7.5%). Additionally, Distarch Phosphate is used in formulations that may be incidentally ingested (at up to 0.5% in lipstick) and some of these ingredients are used in products that come in contact with mucous membranes (e.g., Hydroxypropyl Starch Phosphate in bath soaps and detergents at up to 0.88%).[13]

Distarch Phosphate is used in cosmetic products that could possibly be inhaled; it is reported to be used in hair sprays (aerosols) at concentrations up to 5.3%, and in face powders (concentrations not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. 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.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The starch phosphates reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[14]

Non-Cosmetic

According to the US FDA, under 21 CFR 172.892, food starch-modified is a food additive permitted for direct addition to food for human consumption and may be safely used in food when it adheres to the modifications described in the CFR citation. The quantity of any substance employed to effect such modification shall not exceed the amount reasonably required to accomplish the intended physical or technical effect, nor exceed any limitation prescribed. To ensure safe use of the food starch-modified, the label of the food additive container shall bear the name of the additive "food starch-modified" in addition to other information required by the Act. Food starch may be modified by the treatments prescribed in the CFR citation.

TOXICOKINETIC STUDIES

Toxicokinetic studies on the starch phosphates reviewed in this safety assessment were neither found in the published literature, nor were these data submitted. A general overview of how starch is metabolized in the body is provided. The metabolism of starch begins via a maltodextrin glucosidase resulting in a water molecule and a sucrose. D-Fructose is phosphorylated through an adenosine triphosphate (ATP) driven fructokinase resulting in the release of an adenosine diphosphate (ADP), a hydrogen cation and a β-D-fructofuranose-6-phosphate.[15]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Distarch Phosphate

The acute oral toxicity of Distarch Phosphate was evaluated using various animal species in different experiments.[5] However, details relating to the protocol and number and strain of animals tested were not stated. Test results were as follows: female mice (LD_{50} > 24 g/kg), female mice (LD_{50} > 19 g/kg), female rats (LD_{50} > 20 g/kg), female rats (LD_{50} > 35 g/kg), guinea pigs (LD_{50} > 8.8 g/kg), guinea pigs (LD_{50} > 18 g/kg), rabbits (LD_{50} > 7 g/kg), rabbits (LD_{50} > 10 g/kg), cats (LD_{50} > 6 g/kg), and cats (LD_{50} > 9 g/kg).

Short-Term, Subchronic, and Chronic Toxicity Studies

Repeated dose oral toxicity studies are presented in Table 6. Each study is summarized below.

Distarch Phosphate

There are 9 repeated-dose oral studies of Distarch Phosphate on rats, pigs, and dogs. In the 4 short-term studies in rats, duration of 7 to 60 d and doses that varied between 0.9 g – 4 g or concentrations of 1% - 35%, and the 1 short-term study in miniature pigs, duration of 25 d and test concentration of 5.6% in diet, there were no significant differences between modified and unmodified starches when hematology, serum chemistry, uranalysis, body weight, and organ weights were compared.[5,16] In the 60-d rat study, male rats exhibited lower liver weights and both sexes exhibited lower kidney weights, but no histopathological changes were noted. [5] In the 3 subchronic (90-d) studies, 2 in rats with test concentrations up to 45% in the diet and 1 in dogs with up to 1250 mg/kg bw in gelatin capsules, there were no significant differences in body weight, hematology, serum chemistry, urinalysis, organ weights, and histopathology when compared to controls.[5,8] In the single chronic study in rats that lasted 104 wk and concentration varied between 0 - 30% (equivalent to 0 – 15,000 mg/kg bw/d), there were no significant differences in hematology, serum chemistry, and urinalysis when compared to control.[5,17] At the highest concentration of 30%, male rats showed a slight decrease in spleen weight while female rats showed an increase in spleen weight. Female rats also exhibited an increase in kidney weight at the highest concentration. Male rats at the highest concentration also exhibited in focal hyperplasia in the renal papillary as well as displayed some calcifications in the renal pelvic epithelium.[5]

Distarch Phosphate Acetate

There are 7 repeated-dose oral studies of Distarch Phosphate Acetate on rats, pigs, and hamsters.[8,17,18] In the 2 short-term studies in rats, durations of 7 d and 8 wk and test concentration up to 50%, and the one 30-d study in hamsters at up to 30% in the diet, rats exhibited reduced body weights at higher concentration. Fecal dry matter also increased in rats at higher concentrations, but histological studies showed no differences when compared to control.[8] In the 2 subchronic studies performed on pigs, durations of 14 – 14.5 wk at up to 70%, there were no significant differences in body weight, hematology, serum chemistry, urinalysis, organ weight, or histology. One pig developed neurological symptoms but recovered, and neuro histopathological studies performed showed no changes. In the 2 chronic studies performed on rats, durations of 9 mo to 2 yr and concentrations up to 30%, there were no significant differences in hematology and serum chemistry.[8,17,18] In the study that lasted 2 yr, at higher concentrations, body weight was ~10% lower in males compared to males given lower concentrations. Cecal weight increased in both sexes at higher concentration, but enlargement was attributed to fermentation as histopathology showed no changes. There were significant changes in the kidney as there was increased urinary calcium excretion, specifically in the rats that received diet fortified with 1% calcium, and histopathology studies showed pelvic nephrocalcinosis and increased calcium deposits in the kidney. At high doses, male kidneys showed suburothelial deposits of calcium with focal hyperplasia of renal pelvis epithelium. Females exhibited dose-related increase in adrenal weight at high doses. Other organs such as liver, uterus, parathyroid, and liver showed no treatment-related changes.[8,17]

Hydroxypropyl Starch Phosphate

There are 4 repeated-dose oral studies of Hydroxypropyl Starch Phosphate on rats and mice.[8,19] In the 1 short-term study, duration of 28 d at concentrations up to 100%, rats exhibited reduced body weights at higher concentrations. Liver weight was slightly increased at higher dose groups but no histological abnormalities were observed.[8] In 2 subchronic (90-d) studies performed on rats with up to 25% Hydroxypropyl Starch Phosphate in the diet, there were no significant differences in body weight, hematology, serum chemistry, urinalysis, or histology. In the study in which Hydroxypropyl Starch Phosphate was modified with 10% propylene oxide, full cecum weights showed treatment related increase (not specified) and empty cecum showed increase in weight only in males on 25% diet. In the study it was modified with 0.1% oxychloride and 5% propylene oxide, cecum weight, both full and empty, increased only in the 25% dietary groups in both male and females. The study with 0.1% phosphorus oxychloride and 5% propylene oxide noted slight decreases in weight of male testes at high doses. Mineralization of the renal pelvis was exhibited dose-dependently. No other organ weights showed variation when compared to control. In the chronic study (89 wk) performed on mice at 55% the diet, no significant differences were noted in serum chemistry. In the experiment group, loose stool and diarrhea was noted along with higher water intake. Males showed a decrease in body weight early in the study between weeks 16 – 48, while females showed decrease in body weight after week 40. High mortality was noted in male mice between weeks 39 – 65. Hematocrit reduced in both sexes at week 40, but not at week 78. Urinalysis showed males exhibited protein sediments in urine and produced more turbid urine along with intratubular mineralization in the kidneys of both test male and female mice. Both male and female test mice exhibited increased cecum and colon weight.[8,19]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Distarch Phosphate

A three-generation study on Distarch Phosphate (maize starch 'white milo,' cross-linked with sodium trimetaphosphate up to 0.04% introduced phosphorus and esterified with sodium tripolyphosphate up to a total content of 0.35% bound phosphorus) was performed using groups of 10 male and 20 female rats (Wistar-derived) of the parental (P), F_1 and F_2 generations, to produce 2 successive litters in each generation by mating at weeks 12 and 20 after weaning.[5,17] A total of 10

males and 10 females of the F_{1b} generation were maintained for 3 wk after weaning, and then killed for histopathological studies. The P, F_{1b}, and F_{2b} parents were used for determination of implantation sites. The F_{3b} generation was maintained for 3 wk after weaning and then killed for histopathological evaluation. The test substance was fed at 10% in the diet (equal to 5000 mg/kg bw/d). The control group was fed unmodified potato starch. No adverse effects were noted regarding appearance, behavior, body weight, fertility, litter size, resorption quotient, weights of pups, and mortality. Cecal weights were not increased, except for the filled cecum weight of F_1 male parents. The spleen weight of F_{3b} females was increased significantly ($p < 0.01$). Gross and macroscopic examination did not reveal histopathological changes that were attributable to ingestion of the starch.

Distarch Phosphate Acetate

A three-generation study on Distarch Phosphate Acetate (potato starch cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%) was performed using groups of 10 male and 20 female rats (Wistar-derived) of the P, F_1 and F_2 generations, to produce 2 successive litters in each generation by mating at weeks 12 and 20 after weaning.[8,17] The study was performed according to the procedure in the study immediately above. The test substance was fed at 10% of the diet (equivalent to 5000 mg/kg bw/d). No adverse effects were noted with respect to health, behavior, mortality, growth, fertility, litter size, resorption quotient, weaning weight or mortality of the young. Cecal weight of parental rats fed the modified starch was not increased. Macroscopic examination did not reveal treatment-related effects in F_{3b} rats. Relative thyroid weight in males was decreased ($p < 0.05$), and a slightly increased cecum weight in females ($p < 0.05$) was observed. Histopathologic examination did not reveal any treatment-related changes.

GENOTOXICITY STUDIES

In Silico

Distarch Phosphate, Distarch Phosphate Acetate, and Hydroxypropyl Starch Phosphate

According to EFSA, in the absence of genotoxicity data on modified starches, an evaluation of genotoxicity was performed in silico.[8] On this basis, the identification of structural alerts for genotoxicity for the following starch phosphates was performed using the Organisation for Economic Co-operation and Development (OECD) quantitative structure-activity relationship (QSAR) Toolbox (version 3.3.5.17): Distarch Phosphate, Distarch Phosphate Acetate, and Hydroxypropyl Distarch Phosphate. No relevant structural alerts for genotoxicity were highlighted for any of the 3 ingredients.

In Vitro

Hydroxypropyl Starch Phosphate

The mutagenicity of Hydroxypropyl Starch Phosphate was examined by incubating 0, 100, 333, 1000,3 330 or 5000 µg/plate in deionized water with *Salmonella typhimurium* (TA98, TA100, TA135, or TA137) or *Escherichia coli* (WP2uvrA) with or without metabolic activation.[20] The assay was performed in triplicate. The vehicle and positive controls produced appropriate responses. The test article did not cause a positive increase in the number of revertants per plate of any of the tester strains either in the presence or absence of metabolic activation. Under the conditions of the assay, Hydroxypropyl Starch Phosphate was not mutagenic.

CARCINOGENICITY STUDIES

Oral carcinogenicity data are presented in Table 7 and summarized below.

Distarch Phosphate, Distarch Phosphate Acetate, and Hydroxypropyl Starch Phosphate were not carcinogenic in oral feeding studies. In one study, groups of 30 male and 30 female Wistar rats were fed Distarch Phosphate (maize starch 'white milo,' cross-linked with sodium trimetaphosphate up to 0.04% introduced phosphorus and esterified with sodium tripolyphosphate up to a total content of 0.35% bound phosphorus) at dietary levels of 0, 5, 10, or 30% (equivalent to 0, 2500, 5000, and 15,000 mg/kg bw/d, respectively) for 104 wk.[8,17] A similar 104-wk dietary feeding experiment on Distarch Phosphate Acetate (potato starch cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%) was performed using groups of rats (same strain and numbers of animals).[8,17] No treatment-related effect was observed on the pattern of neoplasm development. In a third study, groups of 75 male and 75 female Swiss albino SPF mice were fed a diet containing 55% Hydroxypropyl Starch Phosphate (equivalent to 27,500 mg/kg bw/d) or a control diet containing 55% pregelatinized potato starch for 89 wk.[8,19] Other results relating to chronic oral toxicity from these studies are included in that section of this report.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The skin irritation and sensitization studies summarized below are presented in Table 8.

A 1-in² patch containing 0.5 g of Hydroxypropyl Starch Phosphate powder applied to intact and abraded skin of New Zealand white male rabbits for 24 hours was considered to be a mild irritant.[20] A conditioner containing 2% Hydroxypropyl

Starch Phosphate, tested as a 25% aqueous solution of the formulation (Hydroxypropyl Starch Phosphate effective concentration = 0.5%), was not an irritant in a 24-h single occlusive insult patch test (SIOPT; 15 subjects).[21]

In a Buehler study with 20 guinea pigs treated with 0.2 g of Hydroxypropyl Starch Phosphate powder moistened with polyethylene glycol 400, sensitization was not observed.[20] An eyeliner containing 7.181% Distarch Phosphate was not a sensitizer in a maximization test with sodium lauryl sulfate (SLS) pretreatment (applied neat; 25 subjects).[22] A conditioner containing 2% Hydroxypropyl Starch Phosphate, tested as a 25% aqueous solution of the formulation (Hydroxypropyl Starch Phosphate effective concentration=0.5%), was not considered a sensitizer in a human repeated insult patch test (HRIPT; 104 subjects).[23]

OCULAR IRRITATION STUDIES

Hydroxypropyl Starch Phosphate

One-tenth (0.1) ml (0.05 g) of Hydroxypropyl Starch Phosphate powder was placed in the conjunctival sac of the right eye of 6 (2 male and 4 female) New Zealand White rabbits.[20] Iritis, which was observed in 5/6 test eyes at 1 h, resolved completely in all affected test eyes by 24 h. Conjunctivitis was noted in 6/6 test eyes at 1 h, and resolved completely by 72 h. Under the conditions of the study, Hydroxypropyl Starch Phosphate is considered to be a mild ocular irritant.

CLINICAL STUDIES

Other Clinical Reports

Distarch Phosphate

On each of 4 successive days, 12 volunteers consumed 60 g of Distarch Phosphate (maize starch 'white milo,' cross-linked with sodium trimetaphosphate up to 0.04% introduced phosphorus and esterified with sodium tripolyphosphate up to a total content of 0.35% bound phosphorus).[8] No abnormalities were observed. (No other details were provided.)

Distarch Phosphate Acetate

Twelve volunteers consumed (on each of 4 successive days) 60 g of Distarch Phosphate Acetate (potato starch cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%).[8] No abnormalities were observed with regard to frequency and amount of feces, as well as fecal water and lactic acid content. No other adverse effects were noted. (No other details were provided.)

SUMMARY

The safety of 4 starch phosphates (all modified starches) as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, Distarch Phosphate functions as an anticaking agent and binder. Viscosity increasing agent is a common cosmetic function of Distarch Phosphate Acetate, Hydroxypropyl Starch Phosphate, and Sodium Hydroxypropyl Starch Phosphate. Modified food starches are defined in the *Food Chemicals Codex* as products of the treatment of any of several grain- or root-based native starches (for example, corn, sorghum, wheat, potato, tapioca, and sago) with small amounts of certain chemical agents that modify the physical characteristics of the native starches to produce desirable properties.

Distarch Phosphate, Distarch Phosphate Acetate, and Hydroxypropyl Starch Phosphate are obtained by esterification of food starch.

According to 2022 FDA VCRP data, Hydroxypropyl Starch Phosphate is reported to be used in 261 cosmetic products. Of the 4 starch phosphates reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey, conducted by the Council in 2020 and provided in 2021, indicate that Distarch Phosphate has the highest concentration of use; it is reported to be used at maximum use concentrations up to 7.5% in leave-on products. According to VCRP and Council survey data, Distarch Phosphate Acetate is not currently in use in cosmetic formulations.

The acute oral toxicity of Distarch Phosphate was evaluated using various animal species in different experiments. However, details relating to the protocol and number and strain of animals tested were not stated. The following acute oral LD_{50} values have been reported for Distarch Phosphate: female mice (LD_{50} > 24 g/kg), female mice (LD_{50} > 19 g/kg), female rats (LD_{50} > 20 g/kg), female rats (LD_{50} > 35 g/kg), guinea pigs (LD_{50} > 8.8 g/kg), guinea pigs (LD_{50} > 18 g/kg), rabbits (LD_{50} > 7 g/kg), rabbits (LD_{50} > 10 g/kg), cats (LD_{50} > 6 g/kg), and cats (LD_{50} > 9 g/kg).

There are 9 repeated-dose oral studies of Distarch Phosphate on rats, pigs, and dogs. In the 4 short-term studies in rats, duration of 7 to 60 d and doses that varied between 0.9 g – 4 g and one with concentrations of 1% - 35%, and the 1 short-term study in miniature pigs, duration of 25 d and test concentration of 5.6% in diet, there were no significant differences between modified and unmodified starches when hematology, serum chemistry, urine analysis, body weight, and organ weights were compared. In the 60 d rat study, male rats exhibited lower liver weights and both sexes exhibited lower kidney weights, but no histopathological changes were noted. In the 3 subchronic (90 d) studies, 2 in rats with test concentrations up to 45% in the diet and 1 in dogs with up to 1250 mg/kg bw in gelatin capsules, there were no significant differences in body weight,

hematology, serum chemistry, urinalysis, organ weights, and histopathology when compared to controls. In the single chronic study in rats that lasted 104 wk and concentration varied between 0 - 30% (equivalent to 0 – 15,000 mg/kg bw/d), there were no significant differences in hematology, serum chemistry, and urinalysis when compared to control. At the highest concentration of 30%, male rats showed a slight decrease in spleen weight while female rats showed an increase in spleen weight. Female rats also exhibited an increase in kidney weight at the highest concentration. Male rats at the highest concentration also exhibited in focal hyperplasia in the renal papillary as well as displayed some calcifications in the renal pelvic epithelium.

There are 7 repeated-dose oral studies of Distarch Phosphate Acetate on rats, pigs, and hamsters. In the 2 short-term studies in rats, durations of 7 d and 8 wk and test concentration up to 50%, and the one 30-d study in hamsters at up to 30% in the diet, rats exhibited reduced body weights at higher concentration. Fecal dry matter also increased in rats at higher concentrations, but histological studies showed no differences. In the 2 subchronic studies performed on pigs, durations of 14 – 14.5 wk at up to 70%, there were no significant differences in body weight, hematology, serum chemistry, urinalysis, organ weight, or histology. One pig developed neurological symptoms but recovered, and neuro histopathological studies performed showed no changes. In the 2 chronic studies performed on rats, durations of 9 mo to 2 yr and concentrations up to 30%, there were no significant differences in hematology and serum chemistry. In the study that lasted 2 yr, at higher concentrations, body weight was ~10% lower in males. Cecal weight increased in both sexes at higher concentration, but enlargement was attributed to fermentation as histopathology showed no changes. There was significant changes in the kidney as there was increased urinary calcium excretion, specifically in the rats that received diet fortified with 1% calcium, and histopathology studies showed pelvic nephrocalcinosis and increased calcium deposits in the kidney. At high doses, male kidneys showed suburothelial deposits of calcium with focal hyperplasia of renal pelvis epithelium. Females exhibited dose-related increase in adrenal weight at high doses. Other organs such as liver, uterus, parathyroid, and liver showed no treatment-related changes.

There are 4 repeated-dose oral studies of Hydroxypropyl Starch Phosphate on rats and mice. In the 1 short-term study, duration of 28 d at concentrations up to 100%, rats exhibited reduced body weights at higher concentrations. Liver weight was slightly increased at higher dose groups but no histological abnormalities were observed 8. In 2 subchronic (90 d) studies performed on rats with up to 25% in the diet, there were no significant differences in body weight, hematology, serum chemistry, urinalysis, or histology. Cecum weight increased in the high-dose males, and one study noted slight decrease in weight of male testes at high doses. Mineralization of the renal pelvis was exhibited dose-dependently. No other organ weights showed variation when compared to control. In the chronic study (89 wk) performed on mice at 55% cin the diet, no significant differences were noted in serum chemistry. In the experiment group, loose stool and diarrhea was noted along with higher water intake. Males showed a decrease in body weight early in the study between weeks 16 – 48, while females showed decrease in body weight after week 40. High mortality was noted in male mice between weeks 39 – 65. Hematocrit reduced in both sexes at week 40, but not at week 78. Urinalysis showed males exhibited protein sediments in urine and produced more turbid urine along with intratubular mineralization in the kidneys of both test male and female mice. Both male and female test mice exhibited increased cecum and colon weight.

A three-generation study was performed using groups of 10 male and 20 female rats (Wistar-derived) of the P, F_1 and F_2 generations to produce two successive litters in each generation by mating at wk 12 and 20 after weaning. Distarch Phosphate was fed at a concentration of 10% in the diet (equivalent to 5000 mg/kg bw/d). No adverse effects on fertility, litter size, resorption quotient, or weights of pups were observed. A study on Distarch Phosphate Acetate (same dietary concentration and protocol) yielded the same results.

A genotoxicity evaluation of modified starches was performed in silico. The identification of structural alerts for genotoxicity of the following starch phosphates was evaluated using the OECD QSAR Toolbox: Distarch Phosphate, Distarch Phosphate Acetate, and Hydroxypropyl Distarch Phosphate. No relevant structural alerts for genotoxicity were highlighted for any of the 3 ingredients. In an Ames test of Hydroxypropyl Starch at up to 5000 µg/plate in deionized water with *S. typhimurium* (TA98, TA100, TA135, or TA137) or *E. coli* (WP2uvrA), with or without metabolic activation, Hydroxypropyl Starch Phosphate was not mutagenic in the tested bacteria strains.

Groups of 30 male and 30 female rats (Wistar-derived) were fed Distarch Phosphate at dietary levels of 5, 10, and 30% (equivalent to 2500, 5000 and 15,000 mg/kg bw/d, respectively) for 104 wk. There was no indication of carcinogenicity. In a similar study on Distarch Phosphate Acetate (same dietary concentration and protocol), no treatment-related effect was observed on the pattern of neoplasm development. There was no evidence of carcinogenicity in a study in which groups of 75 male and 75 female Swiss albino SPF mice were fed a diet containing 55% Hydroxypropyl Starch Phosphate (equivalent to 27,500 mg/kg bw/d) for 89 wk.

A 1-in² patch containing 0.5 g of Hydroxypropyl Starch Phosphate powder applied to intact and abraded skin of New Zealand white male rabbits for 24 hours was considered to be a mild irritant. A conditioner containing 2% Hydroxypropyl Starch Phosphate, tested as a 25% aqueous solution of the formulation (Hydroxypropyl Starch Phosphate effective concentration = 0.5%), was not an irritant in a 24h single occlusive insult patch test (SIOPT; 15 subjects).

In a Buehler study with 20 guinea pigs treated with 0.2 g of Hydroxypropyl Starch Phosphate powder moistened with polyethylene glycol 400, sensitization was not observed. An eyeliner containing 7.181% Distarch Phosphate was not a

sensitizer in a maximization test with sodium lauryl sulfate (SLS) pretreatment (applied neat; 25 subjects). A conditioner containing 2% Hydroxypropyl Starch Phosphate, tested as a 25% aqueous solution of the formulation (Hydroxypropyl Starch Phosphate effective concentration = 0.5%), was not considered a sensitizer in a human repeated insult patch test (HRIPT; 104 subjects).

Hydroxypropyl Starch Phosphate was considered to be a mild ocular irritant when 0.1 ml (0.05 g) of Hydroxypropyl Starch Phosphate powder was placed in the conjunctival sac of the right eye of 6 (2 males and 4 females) New Zealand White rabbits.

No abnormalities were observed after 12 volunteers consumed, on each of 4 successive days, 60 g Distarch Phosphate. Similarly, no adverse effects were observed when 12 volunteers consumed 60 g Distarch Phosphate Acetate according to the same procedure.

DISCUSSION

This assessment reviews the safety of 4 starch phosphates as used in cosmetic formulations. The Panel reviewed the available data and concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The Panel noted the complete and favorable data profile for the ingredients in this report and determined that these data were sufficient to support the safety of all 4 starch phosphates. Safety was further supported by the fact that food starch-modified may be used as a food additive permitted for direct addition to food for human consumption. (All 4 ingredients are modified starches.) Additionally, the Panel noted the available irritation and sensitization data, particularly the negative human maximization test of an eyeliner containing 7.181% Distarch Phosphate.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., Distarch Phosphate is reported to be used in hair sprays at concentrations up to 5.3% and in face powders (concentrations not reported)). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (*see link above*) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 4 starch phosphates are safe in cosmetics in the present practices of use and concentrations described in this safety assessment:

Distarch Phosphate	Hydroxypropyl Starch Phosphate
Distarch Phosphate Acetate*	Sodium Hydroxypropyl Starch Phosphate

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

TABLES

Table 1. Definitions and reported functions of the ingredients in this safety assessment.[1]

Ingredient/CAS No.	Definition	Function(s)
Distarch Phosphate 55963-33-2	Distarch Phosphate is the product formed by the cross-linking of starch with sodium metaphosphate.	anticaking agents; binders
Distarch Phosphate Acetate 68130-14-3	Distarch Phosphate Acetate is the product obtained by the reaction of Distarch Phosphate with acetic anhydride.	emulsion stabilizers; viscosity increasing agents - aqueous
Hydroxypropyl Starch Phosphate 113894-92-1 39346-84-4 53124-00-8	Hydroxypropyl Starch Phosphate is the hydroxypropyl ether of Distarch Phosphate	bulking agents; viscosity increasing agents - aqueous
Sodium Hydroxypropyl Starch Phosphate 221355-22-2	Sodium Hydroxypropyl Starch Phosphate is the sodium salt of a 2-hydroxy-propyl ether of Distarch Phosphate	abrasives; bulking agents; viscosity increasing agents - aqueous

Table 2. Chemical properties

Property	Value/Results	Reference
Distarch Phosphate		
Form	White or nearly white powder or granules or (if pregelatinized) flakes, or amorphous powder or coarse particles.	6
Solubility	Insoluble in cold water (if not pre-gelatinized); forming typical colloidal solutions with viscous properties in hot water; insoluble in ethanol	6
Distarch Phosphate Acetate		
Form	White or nearly white powder or granules or (if pregelatinized) flakes, or amorphous powder or coarse particles	6
Solubility	Insoluble in cold water (if not pre-gelatinized); forming typical colloidal solutions with viscous properties in hot water; insoluble in ethanol	6
Hydroxypropyl Starch Phosphate		
Form	White or nearly white powder or granules or (if pregelatinized) flakes, or amorphous powder or coarse particles	7
Solubility	Insoluble in cold water (if not pre-gelatinized); forming typical colloidal solutions with viscous properties in hot water; insoluble in ethanol	7

Table 3. JECFA specifications for purity[6]

	Distarch Phosphate	Distarch Phosphate Acetate	Hydroxypropyl Starch Phosphate
loss on drying (120°C, 4 h, vacuum not exceeding 100 mm Hg)	cereal starch: not more than 15.0% potato starch: not more than 21.0% other starches: not more than 18.0%	cereal starch: not more than 15.0% potato starch: not more than 21.0% other starches: not more than 18.0%	cereal starch: not more than 15.0% potato starch: not more than 21.0% other starches: not more than 18.0%
acetyl groups	NA	*not more than 2.5%	NA
hydroxypropyl groups	NA	NA	*not more than 7.0%
propylene chlorohydrin	NA	NA	Not more than 1 mg/kg
phosphate (calculated as phosphorus)	*potato or wheat starch: not more than 0.5% *other starches: not more than 0.4%	*potato and wheat starch: not more than 0.14% *other starches: 0.04%	*potato or wheat starch: not more than 0.14% *other starches: 0.04%
vinyl acetate	NA	Not more than 0.1 mg/kg	NA
sulfur dioxide	*cereal starches: not more than 50 mg/kg *other modified starches: not more than 10 mg/kg	*modified cereal starches: not more than 50 mg/kg *other modified starches: not more than 10 mg/kg	*modified cereal starches: not more than 50 mg/kg *other modified starches: not more than 10 mg. kg
lead	*not more than 2 mg/kg	*not more than 2 mg/kg	*not more than 2 mg/kg
manganese	*not more than 50 mg/kg	*not more than 50 mg/kg	*not more than 50 mg/kg
carboxyl groups	*not more than 0.1%	*not more than 0.1%	*not more than 0.1%

NA – not applicable
*on a dried basis

Table 4. Frequency (2022) and concentration (2021) of use according to duration and type of exposure.[12,13]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Distarch Phosphate		Hydroxypropyl Starch Phosphate		Sodium Hydroxypropyl Starch Phosphate	
Totals*/Conc. Range	**81**	**0.5 – 7.5**	**261**	**0.0034 – 6.2**	**17**	**2.5 – 4.5**
Duration of Use						
Leave-On	*76*	*0.5 – 7.5*	*68*	*0.3 - 3.3*	*2*	*2.5*
Rinse off	*5*	*NR*	*193*	*0.0034 - 6.2*	15	*4.5*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	4	3.7 – 7.5	1	1.9	NR	NR
Incidental Ingestion	5	0.5	NR	NR	NR	NR
Incidental Inhalation- Sprays	20[a];31[b]	5.3	34[a];18[b]	0.3 -1.4[a]	1[a];1[b]	NR
Incidental Inhalation- Powders	15;31[b]	NR	18[b]	3.3[c]	1[b]	2.5[c]
Dermal Contact	76	3.7 – 7.5	185	0.0034 - 3.3	16	2.5 – 4.5
Deodorant (underarm)	NR	NR	NR	0.88	NR	NR
Hair - Non-Coloring	NR	5.3	47	0.3-6.2	1	NR
Hair-Coloring	NR	NR	29	2 – 2.7	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	5	0.5	113	0.88	NR	NR
Baby Products	NR	NR	2	NR	NR	NR

NR = Not Reported

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

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

[b] Not specified these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories

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

Table 5. No reported uses.[12,13]

Distarch Phosphate Acetate

Table 6. Repeated dose oral toxicity studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Short-Term Toxicity Studies						
Distarch Phosphate (starch modified using trimetaphosphate)	10 rats (strain not stated)	7 d	basal diet (4 g)	0.9 g or 3.6 g (modified or unmodified starch). After feeding period, body weight gain and weights of following organs recorded: liver, kidney, heart, and spleen. Additional protocol details not included	No significant differences between modified and unmodified starches, when body and organ weights were compared.	[5]
Distarch Phosphate (same as above)	10 male rats (strain not stated)	10 d	basal diet (5 g)	1 g, 2 g, or 4 g (unmodified or modified starch). Additional protocol details not included	Weight gains identical when the 3 doses were compared. No unusual behavioral reactions observed	[5]
Distarch Phosphate (same as above)	male and female weanling rats (Wistar-Purdue strain; number/ group not stated)	21 d	diet (5 g)	diet supplemented with 1 g or 2 g (modified or unmodified starch)	Weight gains comparable for modified and unmodified starches tested. Necropsy results normal. The organs examined microscopically were not stated.	[5,16]
Distarch Phosphate (same as above)	10 male and 10 female rats (strain not stated)	60 d	diet	10%, and increasing to concentration of 35%. Additional details relating to test protocol not included	Consistent, reduced rate of weight gain throughout study observed in female rats. All animals behaved normally. Four test and 2 control (treatment details not provided) rats died during study; findings considered unrelated to test substance administration. Hematological examination and urinalysis were normal and comparable in various groups. In male rats, liver weights were lower when compared to controls. Kidney weights were lower in both sexes. Authors noted that findings relating to liver and kidney weights were not associated with any gross or histopathological changes	[5]
Distarch Phosphate	8 miniature pigs (Pitman-Moore strain)	25 d	Formula diet	Formula diet containing 5.6% Distarch Phosphate or 5.4% unmodified starch	Growth described as normal during study. At end of study, hemoglobin and the following serum chemistry values in test and control animals were similar: cholesterol, triglyceride, calcium, phosphorus, alkaline phosphatase, urea nitrogen, total protein, albumin, and globulin. Also, values for relative organ weight, carcass composition (water, fat, calcium, phosphate, sodium, and magnesium) and liver composition (water, fat, protein, and ash) in test animals were similar to those in control animals. The organs examined microscopically were not stated.	[5]
Distarch Phosphate Acetate (cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%)	10 male and 10 female rats (CIVO colony, Wistar-derived)	7 d	diet	25% and 50% (equal to 30,000 and 60,000 mg/kg bw/d, respectively). Thereafter, 4% cellulose added in diet for additional 3 d	Body weights slightly reduced (at 50% concentration) in both sexes after 7 d. Fecal dry matter increased in all test groups. Moderate diarrhea (at 50% concentration) in both sexes, and was unaffected by feeding of additional cellulose in diet. No loss of hair noted	[8]
Distarch Phosphate Acetate (cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%)	10 male and 10 female rats (CIVO colony, Wistar derived)	8 wk	diet	25% and 50% (equal to 22,500 and 45,000 mg/kg bw/d, respectively). Control group received diet only	Differences in body weights not statistically significant. At 50% concentration, body weights of males slightly lower when compared to control and dosing with 25% concentration. Water content of feces higher in males, but not in females. Feces dry matter increased in both sexes at 50% concentration, and slight increase at 25% concentration. Incidence of diarrhea insignificant. Dose-related increase in cecal weight in both sexes. Histological examination of the cecum showed no abnormalities, when compared to control.	[8]

Table 6. Repeated dose oral toxicity studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Distarch Phosphate Acetate	10 male and 10 female Syrian golden hamsters	30 d	diet	30% Distarch Phosphate Acetate or 30% untreated starch	Hamsters fed 30% Distarch Phosphate Acetate showed slightly lower daily intake (statistics not reported); daily body weight gain comparable or slightly higher when compared to control. No effects observed at hematological examination, clinical chemistry examination, or urinalysis. Histopathological evaluation of liver and kidney revealed no treatment-related effects. No additional details provided.	[8]
Hydroxypropyl Starch Phosphate	10 male rats (strain not stated)	28 d	diet	25%, 50%, 75% and 100% (equivalent to 30,000, 60,000, 90,000 and 120,000 mg/kg bw/d, respectively)	At highest doses tested, growth and body weights were reduced, compared to controls. At same doses, relative liver weights slightly increased, compared to controls fed food grade, unmodified starch. Relative organ weights of empty ceca increased at all doses tested. No histological abnormalities observed in heart, liver, spleen, kidney and cecum.	[8]
Subchronic Toxicity Studies						
Distarch Phosphate (starch modified using trimetaphosphate)	25 male and 25 female rats (strain not stated)	90 d	diet	diets containing t Distarch Phosphate or unmodified starch at concentrations of 0.2%, 1%, and 5%	Animal deaths included 11 controls (treatment details not provided) and 3 test animals, all with intercurrent disease. Organ weights and hematological examination (at days 45 and 90) classified as normal in test and control groups. Pooled urinalysis comparable for all groups. No obvious gross or histopathological changes attributable to feeding with any concentration. The organs examined microscopically were not stated.	[5]
Distarch Phosphate (0.085% esterified and 0.128% esterified phosphate)	10 male and 10 female rats (strain not stated)	90 d	diet	0%, 5%, 15%, and 45%	When compared to controls, no treatment-related abnormal changes in the following: general appearance, behavior, mortality, food consumption, hematology, serum chemistry and urinalysis. Test substance-related abnormalities not observed at gross or histopathologic examination. No diarrhea or increased cecal weight was exhibited. No other organs examined were stated.	[5]
Distarch Phosphate	3 male and 3 female Beagle dogs	90 d	gelatin capsule	50, 250 and 1250 mg/kg bw	No significant differences in body weight among the groups. Food consumption was comparable for all groups. No untoward behavioral reactions noted during entire testing period. Results of hematology, clinical blood chemistry, urine analyses, and liver function tests negative for significant abnormalities. Gross or histopathological findings showed no adverse effects. Organ weight data and organ-body weight ratios calculated did not reveal any significant inter-group differences. The organs examined microscopically were not stated.	[8]
Distarch Phosphate Acetate	8 pigs (strain not stated)	14 wk	diet	0%, 5%, 15% and 25% (equivalent to 0, 1250, 2500 and 6250 mg/kg bw/d)	No effect on growth, food consumption, hematology or biochemistry. One pig (treatment group not specified) died of unknown causes. No significant abnormalities found post-mortem, but histological examination was not performed, except for the animal that died	[8]
Distarch Phosphate Acetate	4 male and 4 female pigs (strain not stated)	14.5 wk	diet	0%, 35% or 70% Distarch Phosphate Acetate (equivalent to 0, 8750 and 17,500 mg/kg bw/d, respectively)	Growth rate and food consumption satisfactory. Hematology, blood chemistry, and urinalysis revealed no treatment-related abnormalities. Ophthalmoscopy showed no test substance-related abnormalities. Organ weights and gross and histopathological examinations revealed no abnormalities in test or control groups. Three pigs in higher dose group died suddenly at various intervals during study, without any evidence relating to cause of death. In one of the 3 pigs, evidence of neurological disorders observed before death. Neurological disorders also observed in 1 animal of 35% concentration group, although animal recovered. No histopathological evidence of nervous system involvement noted in any animal.	[8]

Table 6. Repeated dose oral toxicity studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Hydroxypropyl Starch Phosphate (modified with 10% propylene oxide)	15 male and 15 female weanling rats FDRL_Wistar strain)	90 d	diet	5%, 10% or 25% (equivalent to 4500, 9000 and 22,500 mg/kg bw/d, respectively), or 25% unmodified starch	Four rats died during test period, but deaths were not treatment-related. At the highest dose, feces were soft and bulky during first 7 wk, but normal for remainder of study. Growth, food intake, and food efficiency of all groups were normal, except for a slight decrease in feed efficiency in males of 25% modified starch group. Hematological, biochemical, and urine analyses within normal limits. At necropsy, absolute and relative organ weights of the test and control animals were comparable, except for cecum. Full cecum weights showed treatment-related response; however, in case of empty ceca, significant increase in weight observed only in males on 25% diet. Histopathological examination of the kidneys showed that several rats in test groups had mineralization of renal pelvis (5% group: 18/30; 10% group: 20/30; and 25% group: 22/30). No other test substance-related changes observed, with exception of slight thinning of ceca, which was not accompanied by histopathological changes	[8]
Hydroxypropyl Starch Phosphate (prepared by treating cornstarch with 0.1% phosphorus oxychloride and 5% propylene oxide)	15 male and 15 female rats (strain not stated)	90 d	diet	0%, 5%, 10% and 25% (equivalent to 4500, 9000 and 22,500 mg/kg bw/d, respectively)	The following unaffected by feeding at any dietary level: general condition, growth, food intake and efficiency, hematology, serum chemistry and urinalysis. No diarrhea, but water content of feces and amount of feces dry matter per 100 g of food consumed increased after feeding at dietary concentrations of 10% and 25%. Cecal weights, both filled and empty, increased only in 25% dietary group (males and females). Males of this group also showed slightly decreased relative weights of testes. Macroscopically, no test substance-related differences among the various groups. No microscopic or histopathological examination was mentioned in this study.	[8]
Chronic Toxicity Studies						
Distarch Phosphate (maize starch cross-linked with sodium trimetaphosphate up to 0.04% introduced phosphorus and esterified with sodium tripolyphosphate up to a total content of 0.35% bound phosphorus)	30 male and 30 female rats (Wistar-derived)	104 wk	diet	0%, 5%, 10% and 30% (equivalent to 0, 2500, 5000 and 15,000 mg/kg bw/d, respectively)	No treatment-related effects noted on general appearance, behavior or mortality. Food intake, growth rate, and food efficiency in treated animals were comparable to controls. Hematology, clinical chemistry, and urinalysis revealed no consistent or dose-related differences between test and control groups. Major organs were weighed in all rats and the organ tissue (heart, kidney, liver, spleen, brain, testes, ovaries, adrenals, thyroid, and cecum were examined microscopically. Histological examination of the kidneys, urinary bladder, prostate and cecum were performed. Relative organ weights comparable to those of controls, except for significantly decreased spleen weight in males and significantly increased spleen and kidney weights in females fed at 30% in diet. These changes not associated with any gross pathological findings. Cecal weights were not increased. When compared to controls, males fed 30% in diet showed slightly increased degree and incidence of focal hyperplasia of renal papillary and pelvic epithelium, accompanied by calcified patches in underlying tissue. Hyperplastic and calcified tissues often protruded into renal pelvis and were localized in papilla near junction of papillary and pelvic epithelium. This lesion was observed to a slight or moderate degree in males and females at most dietary levels, including controls, but was more pronounced and of higher occurrence in males at the highest dietary level. Histological examination did not reveal distinct test substance-related changes.	[5,17]

Table 6. Repeated dose oral toxicity studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Distarch Phosphate Acetate	25 female Sprague-Dawley rats	1-yr in weanling rats (experiment 1) and separate 9-mo study utilizing 9-mo-old rats (experiment 2)	diet	30% Distarch Phosphate Acetate (equivalent to 15,000 mg/kg bw/d) or 30% unmodified starch, used as a control. Concentrations of calcium, phosphorus, and magnesium in the diet were 1%, 0.8% and 0.15%, respectively.	Study focused on kidney lesions associated with dietary modified starches. In both experiments, no differences between treated and control animals with respect to the following: body weight, food consumption, urine volume, urine pH and crystal content, or fecal mineral content. At necropsy, cecal weight was significantly increased, but no other treatment-related effects on relative organ weights observed. No treatment-related histopathological effects observed in uterus or lower urinary tract, liver, parathyroid, cecum or ovaries in either experiment. Histopathological examination of kidney sections demonstrated presence of treatment-related pelvic nephrocalcinosis. Apparent correlation observed between increased incidence of pelvic nephrocalcinosis, increased accumulation of calcium in kidney, and increased urinary excretion of calcium. Residues of calcium in kidney tissue significantly higher in test animals than in control animals.	[8,18]
Distarch Phosphate Acetate (potato starch cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%)	30 male and 30 female rats (Wistar-derived)	104 wk	diet	0%, 5%, 10% and 30% (equal to 0, 2500, 5000 and 15,000 mg/kg bw/d, respectively)	No treatment-related effects on general appearance, behavior or mortality. Food intake, growth rate, and food efficiency in treated animals comparable to controls. Final body weight slightly reduced (~10% lower; significant, at least in males at 30% in diet). Hematology, clinical chemistry and urinalysis revealed no consistent or dose-related differences between test and control groups. Females had dose-related increase in relative adrenal weight (significant at 30% in diet). Dose-related increase in cecal weight in both sexes at 30% in diet, but only in males at 10% in diet. Cecal enlargement attributed to adaptive response (fermentation) to presence of indigestible material, rather than to a pathological response. All other organ weights showed no treatment-related changes, but specific organs weighed were not stated. Only treatment-related effect observed histologically was kidney lesion, which occurred at higher incidence in high-dose males. Lesion consisted of suburothelial deposits of calcium, accompanied by focal hyperplasia of renal pelvis epithelium.	[8,17]
Hydroxypropyl Starch Phosphate	75 male and 75 female Swiss albino SPF mice	89 wk	diet	55% Hydroxypropyl Starch Phosphate (equivalent to 27,500 mg/kg bw/d) or control diet containing 55% pregelatinized potato starch	In wk 80, 10 mice/sex per group killed and necropsied. After 89 wk, all survivors killed and subjected to necropsy. Loose stools and slight diarrhea observed in 12% of males and 5% of females. In control group, these results slightly lower (males: 4; females: 3%). Loss of body weight prior to death observed in ~ 25% of male control animals; in other groups, at most 10% of males lost weight. Such differences between groups not observed in females. Death rate in groups quite normal for strain of mice used, except for fairly high mortality in males of control group between wk 39 and wk 65. Compared to controls, body weights in test group significantly decreased in males from wk 16 to 48, and in females from wk 40 onward. Water intake increased in males and females of test group (up to ~ 100% in wk 86). Organ weights and microscopic pathology were examined with special attention to the kidney and bladder. No other organs were mentioned. Hematocrit reduced in both sexes at wk 40, but not at wk 78. Clinical chemistry unaffected. In male mice, higher incidence of amorphous material in urine, and rate of turbid urine was higher. Urine sediment consisted of nearly 100% protein. Cecum weight of test animals, with or without contents, was statistically higher when compared to control group. Similar differences found for colon. Histopathological evaluation revealed increase in incidence of intratubular mineralization in the kidneys of test male and female mice.	[8,19]

Table 7. Oral carcinogenicity studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
Distarch Phosphate (maize starch 'white milo,' cross-linked with sodium trimeta-phosphate up to 0.04% introduced phosphorus and esterified with sodium tripolyphosphate up to a total content of 0.35% bound phosphorus)	30 male and 30 female rats (Wistar-derived)	104 wk	diet	0%, 5%, 10% and 30% (equivalent to 0, 2500, 5000 and 15,000 mg/kg bw/d, respectively)	No indication of carcinogenicity in the following tissues/organs examined: lung, adrenals, thyroid, pituitary, mammary glands, skin/subcutis, abdomen, brain, thymus, forestomach, liver, pancreas, testes, ovaries, and uterus	[8,17]
Distarch Phosphate Acetate (potato starch cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%)	30 male and 30 female rats (Wistar-derived)	104 wk	diet	0%, 5%, 10% and 30% (equivalent to 0, 2500, 5000 and 15,000 mg/kg bw/d, respectively)	No treatment-related effect observed on pattern of neoplasm development in the following tissues/organs: lung, adrenals, thyroid, pituitary, mammary glands, skin/subcutis, abdomen, brain, thymus, forestomach, liver, pancreas, testes, ovaries, and uterus	[8,17]
Hydroxypropyl Starch Phosphate	75 male and 75 female Swiss albino SPF mice	89 wk	diet	55% (equivalent to 27,500 mg/kg bw/d). Control diet containing 55% pregelatinized potato starch	After 89 wk, all survivors killed and subjected to necropsy. No evidence of carcinogenicity in the following tissues/organs: lung, adrenals, thyroid, pituitary, mammary glands, skin/subcutis, abdomen, brain, thymus, liver, pancreas, ovaries, uterus, blood, mesenteric lymph nodes, axillary lymph nodes, subparotic lymph nodes, spleen, intestines, ear shell, kidneys, parathyroid, uterus/cervix, and seminal vesicles	[8,19]

Table 8. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION					
ANIMAL					
Hydroxypropyl Starch Phosphate powder	0.5 g moistened with distilled water	6 New Zealand white male rabbits	A 1-in^2 patch was applied to both intact and abraded skin for 24 h. The skin was observed at pre-determined scoring intervals.	Both the intact and abraded skin sites produced very slight to well-defined erythema in all test animals at the 1-hour scoring interval. The dermal irritation resolved completely by study day 7 (intact) and 72 hours (abraded).	[20]
HUMAN					
Conditioner containing 2% Hydroxypropyl Starch Phosphate	tested as a 25% aqueous (aq.) solution (Hydroxypropyl Starch Phosphate effective concentration = 0.5%)	15 subjects (test article) 14 subjects (controls)	Single insult occlusive patch test (SIOPT). Patches were applied for 24 h. A different conditioner formulation served as reference control. Reactions were scored after patch removal, and a primary irritation index (PII) was calculated.	A PII of 0 was reported for the test article, and 0.03 for the reference control. It was concluded that there were no significant differences in irritation between the test material and the control.	[21]
SENSITIZATION					
ANIMAL					
Hydroxypropyl Starch Phosphate powder	0.2 g moistened with polyethylene glycol 400	guinea pigs 20 test animals 10 control	Buehler test. Induction consisted of a 6-h topical application 3 times a week for 3 wk with evaluations 24 and 48 h after application. After a 2-wk non-treatment period, both control and treated animals were challenged with a 6-h topical application, and the site was scored 48 and 72 h after application. The positive control (hexylcinnamaldehyde) was performed concurrently with 10 test and 5 control animals. .	Not an irritant or sensitizer After induction, no erythema or edema was observed. One test animal displayed slight patchy erythema 48 h after challenge application. The positive control produced the expected results.	[20]
HUMAN					
Eyeliner containing 7.181% Distarch Phosphate	applied neat	25 subjects	Maximization test evaluating sensitization potential. During induction, ~ 0.05 ml of aq. SLS (0.25%) applied for 24 h, under 15 mm occlusive patch to upper outer arm, volar forearm or the back. After 24 h, SLS patch removed and the test product (0.05 ml) was applied for 48 h to same site. (Induction patches remained in place for 72 h when placed over weekend.) This sequence repeated for a total of 5 induction exposures. After a 10-d non-treatment period, a previously untreated site was pre-treated with 5% aq. SLS for 1 h, after which an occlusive challenge patch was applied for 48 h. Reactions scored 15-30 min to 1 h after removal, and 24 h later.	There was no evidence of contact allergy in any of the subjects tested. It was concluded that the eyeliner did not possess a detectable contact-sensitizing potential, and thus, is not likely to cause contact sensitizing reactions under normal use conditions.	[22]
Conditioner containing 2% Hydroxypropyl Starch Phosphate	0.2 ml tested as a 25% aq. solution (Hydroxypropyl Starch Phosphate effective concentration = 0.5%)	104 subjects	HRIPT evaluating sensitization potential. During induction, diluted product (0.2 ml) placed on an occlusive patch (2 cm x 2 cm), was applied to the infrascapular area of the back (either to right or left of midline), or to the upper arm. Induction phase consisted of nine 24-h applications (made on Mondays, Wednesdays, and Fridays) made over 3 consecutive weeks. After a 10-15 d non-treatment period, challenge patches were applied for 24 h to previously untreated sites Reactions scored at 48 h and 72 h after patch removal.	During induction, definite erythema (readings 3 and 4) and a minimal doubtful response (readings 5-9) was reported for one subject. No other reactions were reported during induction, and none were observed for any of the subjects at challenge. Under the conditions employed in this study, there was no evidence of sensitization to the diluted product.	[23]

Abbreviations: HRIPT – human repeated insult patch test; SIOPT – single insult occlusive patch test; SLS – sodium lauryl sulfate

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