Safety Assessment of Starch Phosphates as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: February 11, 2022
Panel Meeting Date: March 7-8, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, former Senior Scientific Analyst/Writer, and Regina Tucker, Scientific Analyst/Writer, CIR.

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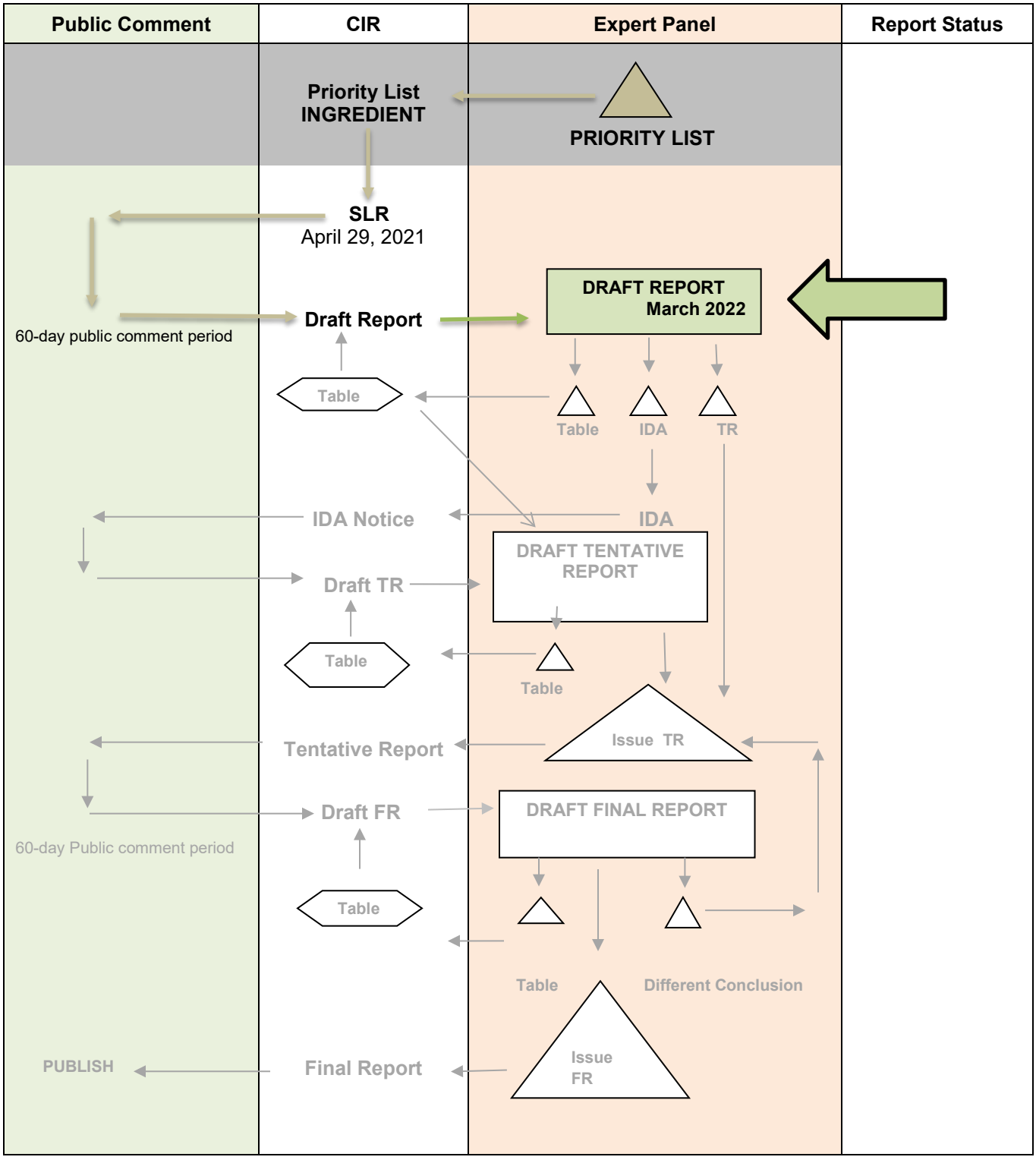
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Starch Phosphates

MEETING March 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Regina Tucker.
Scientific Analyst/Writer, CIR

Date: February 11, 2022

Subject: Safety Assessment of Starch Phosphates as Used in Cosmetics

Enclosed is a Draft Report of the Safety Assessment of Starch Phosphates as Used in Cosmetics (*report_StarchPhosphates_032022*). A Scientific Literature Review (SLR) on these 5 starch phosphates as used in cosmetic ingredients was issued on April 29, 2021. Comments on the SLR (*PCPCcomments_StarchPhosphates_032022*) and the following unpublished data, all received from the Council, have been added to the draft report that is included for the Panel's review:

- Use concentration data (*data1_StarchPhosphates_032022*)
- Anonymous. (2004) An evaluation of the contact-sensitizing potential of an eyeliner containing 7.181% Distarch Phosphate in human skin by means of the maximization assay. (*data2_StarchPhosphates_032022*)
- Anonymous. (2018) Clinical evaluation report: Human patch test of a conditioner containing 2% Hydroxypropyl Starch Phosphate. (*data2_StarchPhosphates_032022*)
- Anonymous. (2019) Repeated insult patch test of a conditioner containing 2% Hydroxypropyl Starch Phosphate. (*data2_StarchPhosphates_032022*)

Also included in this package for your review are the report history (*history_StarchPhosphates_032022*), flow chart (*flow_StarchPhosphates_032022*), literature search strategy (*search_StarchPhosphates_032022*), ingredient data profile (*dataprofile_StarchPhosphates_032022*), and 2022 FDA VCRP data (*VCRP_StarchPhosphates_032022*).

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

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

DATE: June 1, 2021

SUBJECT: Scientific Literature Review: Safety Assessment of Starch Phosphates as Used in Cosmetics (release date April 29, 2021)

The Personal Care Products Council has no suppliers listed for Sodium Dimaltodextrin Phosphate.

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Starch Phosphates as Used in Cosmetics.

Introduction – In the Introduction, it would be helpful to state that some starch ingredients have been reviewed by CIR as part of reviews of ingredients derived from a specific species, e.g., corn-derived ingredients. The Introduction should also note that Maltodextrin has been reviewed by CIR (safe as used conclusion).

Chemistry – It would be helpful to describe the general composition of starch.

Cosmetic Use – In the text, please state the 2 ingredients with no reported uses rather than putting them in a table.

Toxicokinetics – Some information on how starch is metabolized might be useful for this section.

Short-Term – Please revise: “rats (strain not stated) rats”

Other Clinical Reports – Please indicate what endpoints were assessed. It is not clear what is meant by “No abnormalities were observed.” or “No other adverse effects were noted.” without a statement about what was examined.

Table 6 – In Table 6, please state the organs that were examined in the carcinogenicity study.

Draft Report Comment Responses

Starch Phosphates – March 2022 – Wilbur Johnson/Regina Tucker	
Comment Submitter: Personal Care Products Council **Date of Submission: June 1, 2021**	
Comment	**Response/Action**
(1) Introduction – In the Introduction, it would be helpful to state that some starch ingredients have been reviewed by CIR as part of reviews of ingredients derived from a specific species, e.g., corn-derived ingredients. The Introduction should also note that Maltodextrin has been reviewed by CIR (safe as used conclusion).	Changed introduction by adding starch ingredients and noting review of Maltodextrin
(2) Chemistry- It would be helpful to describe the general composition of starch.	General composition of starch added.
(3) Cosmetic Use-In the text, please state the 2 ingredients with no reported uses rather than putting them in a table.	Added; Also, in Table 4 in accordance with our report format.
(4) Toxicokinetic-Some information on how starch is metabolized might be useful for this section.	A brief overview has been added to this section.
(5) Short-Term-Please revise: “rats (strain not stated) rats”.	Addressed
(6) Other Clinical Reports – Please indicate what endpoints were assessed. It is not clear what is meant by “No abnormalities were observed.” or “No other adverse effects were noted.” without a statement about what was examined.	Details relating to exactly what was examined are not included in the source document.
(7) Table 6 – In Table 6, please state the organs that were examined in the carcinogenicity study.	Tissues/organs added

CIR History of:

Starch Phosphates

April 2021

A Scientific Literature Review (SLR) on Starch Phosphates was issued on April 29, 2021.

May 2021
Unpublished data received from the Personal Care Products Council

June 2021

Comments on the scientific literature review, Safety Assessment of Starch Phosphates as Used in Cosmetics received.

January 2022

Updated (2022) VCRP data were received and incorporated.

Draft Report, Teams/Panel: March 07-08, 2022

Comments on the SLR and the following unpublished data, all received from the Council, have been added to the draft report that is included for the Panel's review:

- Use concentration data
- Human skin irritation study on 1 conditioner, containing 2% Hydroxypropyl Starch Phosphate (25% aqueous solution tested; Hydroxypropyl Starch Phosphate actual concentration = 0.5%)
- Skin sensitization study (HRIPT) on a conditioner containing 2% Hydroxypropyl Starch Phosphate (25% w/v aqueous solution tested; Hydroxypropyl Starch Phosphate actual concentration = 0.5%)
- Human maximization test on an eyeliner containing 7.181% Distarch Phosphate

					Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Impurities	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Silico	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Other Clinical Reports
Distarch Phosphate	**81**		X	X				X			X			X	X			X											X
Distarch Phosphate Acetate	**0**		X	X							X			X	X			X						X					X
Hydroxypropyl Starch Phosphate	**261**		X	X							X				X			X			X			X					
Sodium Dimaltodextrin Phosphate	**0**																												
Sodium Hydroxypropyl Starch Phosphate	**17**																												

* "X" indicates that data were available in a category for the ingredient

Starch Phosphates

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Hydroxypropyl Starch Phosphate	113894-92-1 39346-84-4 53124-00-8	Yes		8 (4)		Yes	No	No	No	No	No	No	No	No	No	Yes	No	Yes*
Sodium Hydroxypropyl Starch Phosphate	221355-22-2			0		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Distarch Phosphate	55963-33-2			35 (7)		Yes	No	No	No	No	No	No	No	No	No	Yes	No	Yes**
Distarch Phosphate Acetate	68130-14-3			0		No	No	No	No	No	No	No	No	No	No	No	No	Yes**
Sodium Dimaltodextrin Phosphate				0		No	No	No	No	No	No	No	No	No	No	No	No	Yes***

- *MW data on 3rd CAS No. (PubChem)
- ** MW data (PubChem)
- ***Definition at Good Scents Company

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus (Substances added to Food);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1

IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=39346-84-4

NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

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ABBREVIATIONS

aq.	aqueous
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
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*

INTRODUCTION

The safety of the following 5 starch phosphates as used in cosmetics is reviewed in this safety assessment.

Distarch Phosphate
Distarch Phosphate Acetate
Hydroxypropyl Starch Phosphate
Sodium Dimaltodextrin Phosphate
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 binder, and Sodium Dimaltodextrin Phosphate functions as a dispersing agent (Table 1).[1] Viscosity increasing agent is a common cosmetic ingredient function of Distarch Phosphate Acetate, Hydroxypropyl Starch Phosphate, and Sodium Hydroxypropyl Starch Phosphate.

Some 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 of these ingredients as used in cosmetics is on the potential for local effects from topical exposure. 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) and found safe as used as described in the report. Additionally, the Panel has reviewed ingredients that comprise some of the starch phosphates. In 2015, the Panel issued a final report with the conclusion that maltodextrin is safe in the present practices of use and concentration in cosmetics described in that assessment.[4]

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 used and the sources that sources provided 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.

A significant amount of the data included in this report is 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]

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 Dimaltodextrin Phosphate and Sodium Hydroxypropyl Starch Phosphate (CAS No. 221355-22-2) are sodium salts.

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] Modified food starch usually occurs as white or nearly white powder or as intact granules. Starch is composed of two kinds of polysaccharides, amylose and amylopectin;[10] it is comprised of α1,4 and α1,6 linked glucose[11]. If pregelatinized (that is, subjected to heat treatment in the presence of water), it occurs as flakes, amorphous powders, or coarse particles. In addition to the definitions of 5 starch phosphates (all modified starches) included in Table 1, the following relevant information on starch is included in 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 are insoluble in alcohol, in ether, and in chloroform.[9] When not pregelatinized, modified food starches are practically insoluble in cold water. During heating in water, 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.

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

Distarch Phosphate

According to the JECFA, some of the specifications for impurities in Distarch Phosphate are: sulfur dioxide (not more than 50 mg/kg on the dried basis for modified cereal starches; not more than 10 mg/kg on the dried basis for other modified starches), lead (not more than 2 mg/kg on the dried basis), and manganese (not more than 50 mg/kg on the dried basis).[6]

Distarch Phosphate Acetate

The JECFA specifications for impurities in Distarch Phosphate Acetate include: vinyl acetate (not more than 0.1 mg/kg), sulfur dioxide (not more than 50 mg/kg on the dried basis for modified cereal starches; not more than 10 mg/kg on the dried basis for other modified starches), lead (not more than 2 mg/kg on the dried basis), and manganese (not more than 50 mg/kg on the dried basis).[6]

Hydroxypropyl Starch Phosphate

According to the JECFA, some of the specifications for impurities in Hydroxypropyl Starch Phosphate are: propylene chlorohydrin (not more than 1 mg/kg), sulfur dioxide (not more than 50 mg/kg on the dried basis for modified cereal starches; not more than 10 mg/kg on the dried basis for other modified starches), lead (not more than 2 mg/kg on the dried basis), and manganese (not more than 0.1% on the dried basis).[6,7]

Modified Food Starches

According to the *Food Chemicals Codex*, limitations on impurities in modified food starch include: 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%), and protein (not more than 0.5%; except in modified high-amylose starches, not more than 1%).[9]

USE

Cosmetic

The safety of starch phosphates is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in

cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

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 concentration of use; it is reported to be used at maximum use concentrations up to 7.5% in leave-on products (eyeliners). Further use data are presented in Table 3.

According to VCRP and Council survey data, 2 of the starch phosphates (Distarch Phosphate Acetate and Sodium Dimaltodextrin Phosphate) reviewed in this safety assessment are not currently in use in cosmetic products. These ingredients are listed in Table 4.

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 (at up to 0.5% in lipstick) and Hydroxypropyl Starch Phosphate (at up to 0.88% in bath soaps and detergents) are used in products that come in contact with mucous membranes.[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, 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. Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[14,15] 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.[16-18]

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.[19]

Non-Cosmetic

According to the US FDA, under 21 CFR 172.892, food starch-modified may be safely used in food. The quantity added to effect such modification shall not exceed the amount reasonably required to accomplish the intended physical or technical effect, nor exceed any limitation prescribed. Food starch may be modified by various treatments.

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.[20]

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 5 and summarized below.

Distarch Phosphate

In a short-term study, groups of 10 rats were fed a basal diet with 0.9 or 3.6 g of Distarch Phosphate for 7 d; no significant differences in body weight gain or organ weights were noted between animals fed modified or unmodified starch in the diet.[5] In another study, groups of 10 male rats were fed a basal diet supplemented with 1, 2, or 4 g unmodified starch or Distarch Phosphate for 10 d. Weight gains were identical at all 3 levels of supplementation, and no unusual behavioral reactions were observed. Necropsy results were normal in groups of male and female weanling Wistar-Purdue rats (number not stated) fed a diet

supplemented with 1 or 2 g Distarch Phosphate over a 21-d period.[5,21] Groups of 10 male and 10 female rats were fed a diet initially containing 10% Distarch Phosphate, and increasing to a concentration of 35%, for a total of 60 d; no test substance-related deaths or gross or histopathological changes were observed.[5] In a subchronic study in which groups of 25 male and 25 female rats were fed diets containing 0.2, 1%, or 5% Distarch Phosphate (trimetaphosphate- modified starch) or unmodified starch for 90 d, there were no obvious gross or histopathological changes that were attributable to test substance administration. Two types of Distarch Phosphate (0.085% esterified and 0.128% esterified phosphate) were administered in the diet at concentrations of 5%, 15%, and 45% to groups of 10 male and 10 female rats for 90 d; test substance-related abnormalities were not observed at gross or histopathologic examination. In a chronic toxicity 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, or15,000 mg/kg bw/d, respectively) for 104 wk.[5,22] Relative organ weights were comparable to those of the controls, except for significantly decreased spleen weight in males and significantly increased spleen and kidney weights in females fed at 30%. When compared to controls, the males fed the 30% concentration had a slightly increased degree and incidence of focal hyperplasia of the renal papillary and pelvic epithelium. (Results relating to carcinogenicity are included in that section of this report.)

Groups of 8 miniature pigs (Pitman-Moore strain) were fed formula diets containing 5.4% unmodified starch or 5.6% Distarch Phosphate for 25 d.[5] At the end of the study, serum chemistry values and relative organ weights in test and control animals were similar. Groups of 3 male and 3 female Beagle dogs were given gelatin capsules containing 50, 250, or 1250 mg/kg bw/d Distarch Phosphate for 90 d; no adverse gross or microscopic effects were reported.[8]

Distarch Phosphate Acetate

A short-term study was conducted in groups of 10 male and 10 female rats given 25% or 50% Distarch Phosphate Acetate (cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%) in the diet (equivalent to 30,000 and 60,000 mg/kg bw/d, respectively) for 7 d; moderate diarrhea was observed in both sexes of the 50% group.[8] In an 8-wk study with the same test article, groups of 10 male and 10 female rats were fed 0%, 25%, or 50% of Distarch Phosphate Acetate in their diet (equivalent to 0, 22,500, and 45,000 mg/kg bw/d, respectively); histological examination indicated no abnormalities when compared to the control. In a chronic toxicity study, groups of 25 female Sprague-Dawley rats were fed Distarch Phosphate Acetate (equivalent to 15,000 mg/kg bw/d) or 30% unmodified starch (used as a control); this comprised a 1-yr study in weanling rats (experiment 1) and a separate 9-month study utilizing 9-mo-old rats (experiment 2).[8,23] No treatment-related histopathological effects were observed in the uterus or lower urinary tract, liver, parathyroid, cecum, or ovaries in either experiment. Histopathological examination of kidney sections demonstrated the presence of treatment-related pelvic nephrocalcinosis. In a 2-yr study, groups of 30 male and 30 female Wistar-derived rats were fed Distarch Phosphate Acetate (potato starch cross-linked with 0.02% phosphorus oxychloride and acetylated with 8% acetic anhydride; acetyl content of 2.33%) at dietary levels of 0%, 5%, 10%, or 30% (equivalent to 0, 2500, 5000, or 15,000 mg/kg bw/d, respectively); the only treatment-related effect that was observed histologically was a kidney lesion, which occurred at a higher incidence in high-dose males.[8,22] (Results relating to carcinogenicity are included in that section of this report.)

Histopathological evaluation of the liver and kidney showed no treatment-related effects in groups of 10 male and 10 female Syrian golden hamsters fed a diet containing 30% Distarch Phosphate Acetate for 30 d.[8] No significant abnormalities were found in pigs (8/group) fed 0%, 5%, 15%, or 25% Distarch Phosphate Acetate (equivalent to 0, 1250, 2500 and 6250 mg/kg bw/d, respectively) in the diet for 14 wk; histological examination was not performed on animals that survived until study termination. Additionally, gross and histopathological examination revealed no abnormalities in pigs (4 males and 4 females/group) fed 0%, 35%, or 70% Distarch Phosphate Acetate (equivalent to 0, 8750, or 17,500 mg/kg bw/d, respectively) in the diet over a 14.5-wk period.

Hydroxypropyl Starch Phosphate

Groups of 10 male rats were fed diets containing 25%, 50%, 75%, or 100% Hydroxypropyl Starch Phosphate (equivalent to 30,000, 60,000, 90,000, or 120,000 mg/kg bw/d, respectively) in a short-term (28-d) study.[8] No histological abnormalities were observed in the heart, liver, spleen, kidney and cecum. Groups of 15 male and 15 female weanling FDRL_Wistar rats were fed diets containing 5%, 10%, or 25% Hydroxypropyl Starch Phosphate (starch modified with 10% propylene oxide; equivalent to 4500, 9000, or 22,500 mg/kg bw/d, respectively) in a subchronic (90-d) study. Histopathological examination indicated that more than half that rats in each test groups had mineralization of the renal pelvis. Except for a slight thinning of the ceca (without histopathological changes), no other test substance-related changes were observed. In another 90-d study, groups of 15 male and 15 female rats were fed diets containing 0%, 5%, 10%, or 25% of a Hydroxypropyl Starch Phosphate (prepared by treating cornstarch with 0.1% phosphorus oxychloride and 5% propylene oxide; equivalent to 4500, 9000, and 22,500 mg/kg bw/d). Males of the highest dose group had slightly decreased relative weights of the testes; no macroscopic test substance-related differences were observed among the various groups. In a chronic toxicity 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.[8,24] Histopathological evaluation revealed an increase in the incidence of intratubular

mineralization in the kidneys of treated male and female mice. (Results relating to carcinogenicity are included in that section of this report.)

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.[5,22] 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.[8,22] 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.

CARCINOGENICITY STUDIES

Oral carcinogenicity data are presented in Table 6 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.[8,22] 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).[8,22] 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.[8,24] 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 7.

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).[25] 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)[26]or a sensitizer in a human repeated insult patch test (HRIPT; 104 subjects).[27]

OCULAR IRRITATION STUDIES

Data on the ocular irritation potential of the starch phosphates reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

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 5 starch phosphates (all modified starches) as used in cosmetics is reviewed in this safety assessment. 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. According to the *Dictionary*, Distarch Phosphate functions as an anticaking agent and binder, and Sodium Dimaltodextrin Phosphate functions as a dispersing agent. Viscosity increasing agent is a common cosmetic ingredient function of Distarch Phosphate Acetate, Hydroxypropyl Starch Phosphate, and Sodium Hydroxypropyl Starch Phosphate.

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 5 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 (eyeliners). According to VCRP and Council survey data, Distarch Phosphate Acetate and Sodium Dimaltodextrin Phosphate are not currently in use in cosmetic products.

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).

In a short-term feeding studies involving groups of 10 rats (strains not stated) fed Distarch Phosphate (doses up to 4 g in diet) for 7 or 10 d, there were no significant differences in body or organ weights when compared to rats fed a basal diet. Necropsy results were normal in groups of weanling rats (Wistar-Purdue strain, number not stated) fed Distarch Phosphate (up to 2 g) in the diet for 21 d. Similarly, no gross/histopathological changes were observed in groups of 20 rats (strains not stated) fed 10% to 35% Distarch Phosphate in the diet for 60 d. Groups of 8 miniature pigs (Pitman-Moore strain) were fed formula diets containing 5.6% Distarch Phosphate for 25 d. Serum chemistry values and relative organ weights in test and control animals were similar. Groups of 20 rats (CIVO colony, Wistar-derived) were given 25% and 50% Distarch Phosphate Acetate in the diet (equal to 30,000 and 60,000 mg/kg bw/d, respectively) for 7 d. Moderate diarrhea occurred at the higher concentration, and there was no evidence of hair loss. When the same test substance was fed (22,500 and 45,000 mg/kg bw/d) to groups of 20 rats of the same strain for 30 d, no abnormalities were observed at histopathological evaluation. Histopathological evaluation of the liver and kidney showed no treatment-related effects in groups of 10 male and 10 female Syrian golden hamsters fed a diet containing 30% Distarch Phosphate Acetate for 30 d. Histological abnormalities also were not observed in a study in which groups of 10 male rats (strain not stated) were fed up to 100% Hydroxypropyl Starch Phosphate (120,000 mg/kg bw/d) in the diet for 28 d.

In a subchronic feeding study, groups of 25 male and 25 female rats (strain not stated) were fed diets containing Distarch Phosphate at concentrations up to 5% for 90 d. There were no test substance-related gross or histopathological changes. Similarly, neither gross nor histopathologic changes were observed when Distarch Phosphate was administered to groups of 20 rats (strain not stated) at dietary concentrations up to 45% for 90 d. In another study, groups of 6 Beagle dogs were given Distarch Phosphate (in gelatin capsules, doses up to 1250 mg/kg bw/day) for 90 d. No adverse effects were noted at gross or histopathologic examination. When groups of 8 pigs (strain not stated) were fed Distarch Phosphate Acetate at dietary concentrations up to 25% (up to 6250 mg/kg bw/d) for 14 wk, no significant abnormalities were observed at post-mortem examination. Similarly, results from gross and histopathological examinations were negative in groups of 8 pigs (strain not stated) fed Distarch Phosphate Acetate at concentrations up to 70% (up to 17,500 mg/kg bw/d) for 14.5 wk. Groups of 30 weanling rats (FDRL Wistar) were fed diets containing 5%, 10%, or 25% of Hydroxypropyl Starch Phosphate (equivalent to 4500, 9000, and 22,500 mg/kg bw/d) for a period of 90 d. Histopathological examination revealed mineralization of the renal pelvis in each of the 3 dietary groups. In another study (same duration and dietary concentrations), no macroscopic test substance-related changes were observed among the 3 dietary groups (groups of 30 rats; strain not stated).

Groups of 25 female Sprague-Dawley rats were fed 30% Distarch Phosphate Acetate (equivalent to 15,000 mg/kg bw/d) in the diet in a 1-yr study involving weanling rats and in a separate 9-mo study involving 9-mo-old rats. Histopathological examination of kidney sections revealed treatment-related pelvic nephrocalcinosis; no other histopathological effects were observed. In another chronic study, groups of 60 rats (Wistar-derived) were fed Distarch Phosphate at dietary levels up to 30% (equivalent to 15,000 mg/kg bw/d) for 104 wk. When compared to controls, male rats in this highest dietary concentration group had a slightly increased degree and incidence of focal hyperplasia of the renal papillary and pelvic epithelium. Significantly decreased spleen weight in males and significantly increased spleen and kidney weights in females were also noted in this dietary group. Groups of 60 rats (Wistar-derived) were fed Distarch Phosphate Acetate at dietary levels of 0%, 5%, 10% and 30% (equal to 0, 2500, 5000 and 15,000 mg/kg bw/d, respectively) for 104 wk. The only treatment-related effect observed histologically was a kidney lesion, which occurred at a higher incidence in high-dose males. 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. An increased incidence of intratubular mineralization in the kidneys was observed at histopathological examination.

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.

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.[8,22] 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.

The skin irritation potential of 2 conditioners, each containing 2% Hydroxypropyl Starch Phosphate, was evaluated. Each product was tested on a group of 15 subjects (different group per product). A 25% aqueous solution of each product (Hydroxypropyl Starch Phosphate effective concentration = 0.5%) was applied, under an occlusive patch, for 24 h. A PII of 0 was reported for 1 product, and testing of the other product yielded a PII of 0.03. There were no significant differences in irritation between either conditioner and the reference control(s).

An eyeliner containing 7.181% Distarch Phosphate was not a sensitizer in a maximization test with 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 an irritant in a 24-h SIOPT (15 subjects) or a sensitizer in a HRPT (104 subjects).

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

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions and 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 Dimaltodextrin Phosphate	Sodium Dimaltodextrin Phosphate is the sodium salt of a complex mixture of diesters of maltodextrin and phosphoric acid.	dispersing agents – non-surfactant
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. 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 4. Starch phosphate ingredients with no reported uses.[12,13]

Distarch Phosphate Acetate
Sodium Dimaltodextrin Phosphate

Table 5. 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	[5,21]
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.	[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 showed no abnormalities, when compared to control.	[8]
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	[8]

Table 5. Repeated dose oral toxicity studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
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	[5]
Distarch Phosphate (0.085% esterified and 0.128% esterified phosphate)	10 male and 10 female rats (strain not stated)	90 d	diet	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	[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	[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 5. 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 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.	[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. 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.	[5,22]

Table 5. 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.	[8,23]
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. 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.	[8,22]
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). 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	[8,24]

Table 6. 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	[8,22]
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	[8,22]
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	[8,24]

Table 7. Irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
HUMAN					
Irritation					
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.	[26]
Sensitization					
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.	[25]
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.	[27]

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

REFERENCES

1. Nikitakis J, Kowcz A, (eds) *International Cosmetic Ingredient Dictionary and Handbook*, Online Version (wINCI). http://webdictionary.personalcarecouncil.org/jsp/Home.jsp.2020. Accessed. March 11, 2020.

2. Andersen FA (ed). Amended Final Report on the Safety Assessment of Oryza Sativa (Rice) Bran Oil, Oryza Sativa (Rice) Germ Oil, Rice Bran Acid, Oryza Sativa (Rice) Bran Wax, Hydrogenated Rice Bran Wax, Oryza Sativa (Rice) Bran Extract, Oryza Sativa (Rice) Extract, Oryza Sativa (Rice) Germ Powder, Oryza Sativa (Rice) Starch, Oryza Sativa (Rice) Bran, Hydrolyzed Rice Bran Extract Hydrolyzed Rice Bran Protein, Hydrolyzed Rice Extract, and Hydrolyzed Rice Protein. *Int J Toxicol* 2006;25(S2):91-120.

3. Andersen FA, Bergfeld WF, Belsito DV, et al. Final report of the safety assessment of cosmetic ingredients derived from Zea mays (corn). *Int J Toxicol.* 2011;30(S1):17S-39S.

4. Johnson W Jr, Heldreth B, Bergfeld WF, et al. 2015. Final report of the safety assessment of polysaccharide gums as used in cosmetic. Washington, DC. Available on the CIR website. (https://www.cir-safety.org/ingredients)

5. World Health Organization (WHO), Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. WHO Food Additives Series No. 5. http://www.inchem.org/documents/jecfa/jecmono/v05je75.htm.1974. Accessed. 2/3/2021.

6. World Health Organization (WHO). Joint FAO/WHO Expert Committee on Food Additives, 82nd meeting. Compendium of Food Additive Specifications. http://www.fao.org/3/a-i6413e.pdf#page=39%22%3E.2016. Accessed. 2/2/2021.

7. World Health Organization (WHO), Joint FAO/WHO Expert Committee on Food Additives. Residue monograph; Hydroxypropyl Distarch Phosphate (Tentative). http://www.fao.org/3/a-bt056e.pdf.2016. Accessed. 2/2/2021.

8. Mortensen A, Aguilar F, Crebelli R, et al. Re-evaluation of oxidised starch (E 1404), monostarch phosphate (E 1410), distarch phosphate (E 1412), phosphated distarch phosphate (E 1413), acetylated distarch phosphate (E 1414), acetylated starch (E 1420), acetylated distarch adipate (E 1422), hydroxypropyl starch (E 1440), hydroxypropyl distarch phosphate (E 1442), starch sodium octenyl succinate (E 1450), acetylated oxidised starch (E 1451) and starch aluminium octenyl succinate (E 1452) as food additives. *EFSA J.* 2017;15(10):e04911.

9. United States Pharmacopeial Convention. *Food Chemicals Codex.* 10th ed. Rockville, MD2016.

10. National Library of Medicine (NLM), ChemIDplus. Starch (RN 9005-25-8). https://chem.nlm.nih.gov/chemidplus/name/starch.2022. Accessed. 1/18/2022.

11. Arnal G, Cockburn DW, Brumer H, Koropatkin NM. Structural basis for the flexible recognition of α-glucan substrates by Bacteroides thetaiotaomicron SusG. *Protein Sci.* 2018 27(6):1093-1101.

12. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). 2022. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2022; received January 11, 2022

13. Personal Care Products Council (Council). 2021. Concentration of use by FDA product category: Starch Phosphates. Unpublished data submitted by the Personal Care Products Council on January 6, 2021

14. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: principles on inhalation risk assessment. *Toxicol Lett.* 2011;205(2):97-104.

15. Bremmer HJ, Prud'homme de Lodder LCH, van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. Bilthoven, Netherlands2006. RIVM 320104001/2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Accessed 8/24/2011. Pages 1-77.

16. Aylott RI, Byrne GA, Middleton J, Roberts ME. Normal use levels of respirable cosmetic talc: preliminary study. *Int J Cosmet Sci.* 1979;1(3):177-186.

17. Russell R, Merz R, Sherman W, Sivertson J. The determination of respirable plarticles in talcum powder. *Food Cosmet Toxicol.* 1979;17(2):117-122.

18. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 2015. Cosmetic powder exposure. Unpublished data submitted by the Personal Care Products Council on November 3, 2015

19. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated: 2020. Accessed: 2/1/2021.

20. National Library of Medicine, PubChem. Starch and Sucrose Metabolism (Pathway). https://pubchem.ncbi.nlm.nih.gov/pathway/PathBank:SMP0000058.2022. Accessed. 1/18/2022.

21. Whistler RL, Belfort AM. Nutritional value of chemically modified corn starches. *Science.* 1961;133(3464):1599-1600.

22. de Groot AP, Til HP, Ferron VJ, Van der Meullen HCD, Williams MI. Two-year feeding and multigeneration studies in rats on five chemically modified starches. *Food Cosmet Toxicol.* 1974;12(5-6):651-663.

23. Hodgkinson A, Davis D, Fourman J, Robertson WG, Roe FJ. A comparison of the effects of lactose and of two chemically modified waxy maize starches on mineral metabolism in the rat. *Food Chem Toxicol.* 1982;20(4):371-382.

24. Til HP, Feron VJ, Immel HR, Vogel WF. Chronic (89-week) feeding study with hydroxypropyl distarch phosphate, starch acetate, lactose and sodium alginate in mice. *Food Chem Toxicol.* 1986;24(8):825-834.

25. Anonymous. 2004. An evaluation of the contact-sensitizing potential of a topical coded product in human skin by means of the maximization assay (eyeliner containing 7.181% Distarch Phosphate. Unpublished data submitted by the Personal Care Products Council on May 10, 2021

26. Anonymous. 2018. Clinical evaluation report: Human patch test (conditioner contains 2% Hydroxypropyl Starch Phosphate). Unpublished data submitted by the Personal Care Products Council on May 10, 2021

27. Anonymous. 2019. Repeated insult patch test (conditioner contains 2% Hydroxypropyl Starch Phosphate). Unpublished data submitted by the Personal Care Products Council on May 10, 2021

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: January 25, 2021

SUBJECT: Concentration of Use by FDA Product Category: Starch Phosphates

Concentration of Use by FDA Product Category – Starch Phosphates*

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

Ingredient	Product Category	Maximum Concentration of Use
Distarch Phosphate	Eyebrow pencils (3A)	3.7%
Distarch Phosphate	Eyeliners (3B)	7.5%
Distarch Phosphate	Other eye makeup preparations (3G)	3.7%
Distarch Phosphate	Hair sprays (5B) Aerosols	5.3%
Distarch Phosphate	Lipstick (7E)	0.5%
Hydroxypropyl Starch Phosphate	Other eye makeup preparations (3G)	1.9%
Hydroxypropyl Starch Phosphate	Hair conditioners (5A)	1.8-6.2%
Hydroxypropyl Starch Phosphate	Shampoos (noncoloring) (5F)	2.2%
Hydroxypropyl Starch Phosphate	Tonics, dressings, and other hair grooming aids (5G)	0.3-1.4%
Hydroxypropyl Starch Phosphate	Hair dyes and colors (6A)	2-2.7%
Hydroxypropyl Starch Phosphate	Hair rinses (coloring) (6C)	2%
Hydroxypropyl Starch Phosphate	Other hair coloring preparations (6H)	2%
Hydroxypropyl Starch Phosphate	Bath soaps and detergents (10A)	0.88%
Hydroxypropyl Starch Phosphate	Deodorants (10B) Not spray	0.88%
Hydroxypropyl Starch Phosphate	Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (12A)	0.4-3%
Hydroxypropyl Starch Phosphate	Body and hand products (12D) Not spray	3.3%
Hydroxypropyl Starch Phosphate	Paste masks and mud packs (12H)	0.0034%
Hydroxypropyl Starch Phosphate	Skin fresheners (12I)	1%
Sodium Hydroxypropyl Starch Phosphate	Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (12A)	4.5%
Sodium Hydroxypropyl Starch Phosphate	Body and hand products (12D) Not spray	2.5%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2020
Table prepared: January 25, 2021

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 10, 2021

SUBJECT: Distarch Phosphate and Hydroxypropyl Starch Phosphate

Anonymous. 2004. An evaluation of the contact-sensitizing potential of a topical coded product in human skin by means of the maximization assay (eyeliner containing 7.181% Distarch Phosphate.

Anonymous. 2018. Clinical evaluation report: Human patch test (conditioner contains 2% Hydroxypropyl Starch Phosphate).

Anonymous. 2019. Repeated insult patch test (conditioner contains 2% Hydroxypropyl Starch Phosphate).

[redacted]

FINAL REPORT May 4, 2004

[redacted] Protocol: #5560

Sample: Eyeliner coded [redacted]

[redacted]

[redacted]

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

contains 7.181% Distarch Phosphate

Sponsor: [redacted]

Principal Investigator: [redacted] (Board Certified Dermatologist)

Testing Facility: [redacted]

Protocol: [redacted] Protocol #**5560**

Final Report Date: **May 4, 2004**

[redacted]

May 4, 2004
Date

Principal Investigator

[redacted]

F I N A L R E P O R T

[redacted] PROTOCOL:

[redacted] Protocol #**5560**

SPONSOR:

[redacted]

[redacted]

SPONSOR STUDY:

Authorization Letter Dated: March 22, 2004

STUDY TITLE:

Evaluation of the contact-sensitizing potential of a coded topically-applied test agent.

STUDY OBJECTIVE:

The objective of this study is to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

TEST MATERIAL:

The test sample, supplied by the sponsor, was a product labeled Eyeliner coded [redacted] and tested as supplied.

TEST PRODUCT ACCOUNTABILITY:

All test samples and materials were received in good condition by our Quality Assurance Department. The test materials and quantities were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). All test materials were stored under ambient conditions in an inaccessible location under the supervision of the investigator.

PRINCIPAL INVESTIGATOR:

[redacted], M.D. (Board Certified Dermatologist)

Medical Director, [redacted].

[redacted]

[redacted]

[redacted] **ADMINISTRATIVE STRUCTURE:**

[redacted] (Screening, Patch Applications/Removals, Recognize AE's)

[redacted] (Expert Grader)

[redacted] (Recruitment, Initial Screening and Medical Records Database)

TESTING FACILITY:

[redacted]

[redacted]

[redacted]

CONDUCTION DATES:

This study was conducted from March 29, 2004 through April 30, 2004

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics. The criteria for exclusion were:

1 - History of sun hypersensitivity and photosensitive dermatoses

2 - History of drug hypersensitivity or recurrent dermatological diseases

3 - Pregnancy or mothers who are breastfeeding

4 - Scars, moles or other blemishes over the test site which can interfere with the study

5 - Recent sunburn

6 - Subjects receiving systemic or topical drugs or medications, including potential sensitizers within the previous 4 weeks

7 - Other medical conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

INFORMED CONSENT:

After the protocol, reasons for the study, possible associated risks and potential benefits or risks of the treatment had been completely explained, signed, informed subject consent was obtained from each volunteer prior to the start of the study. Copies of all consent forms are on file at [redacted]

METHOD:

Patches were applied to the upper outer arm, volar forearm or the back of each subject. The entire test was composed of two distinct phases: (1) an Induction phase and (2) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material coded [redacted] (Eyeliner) was applied to the same site before the site was again covered with occlusive tape [Blenderm, 3M] (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Challenge Phase**:

After a ten day rest period which follows the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded 15-30 minutes hour later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	**GRADES:**	**CLASSIFICATION**:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

RESULTS:

A total of twenty-five (25) healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 13 females and 12 males. Their ages ranged from 19 to 57 years. All 25 subjects completed this investigation as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Eyeliner and coded [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	MJN	51	M	B
02	AJH	43	M	B
03	CYJ	45	F	B
04	PJR	50	M	C
05	RHT	50	M	C
06	BDR	47	F	B
07	SDJ	32	F	B
08	SMH	26	M	B
09	TNR	21	F	B
10	DBK	46	M	C
11	J-M	48	F	B
12	A-D	39	M	C
13	RWT	57	M	B
14	PAS	44	F	C
15	CAD	56	M	C
16	MEL	34	F	C
17	MTO	46	M	C
18	G-M	47	F	B
19	TAA	54	F	B
20	ZSP	21	F	B
21	LAD	44	M	B
22	MJM	54	F	C
23	MLC	27	M	C
24	CAV	19	F	C
25	AYS	48	F	B

B = Black
C = Caucasian

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Eyeliner coded [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0

Challenge Readings:

48-Hour Reading – April 28, 2004
72-Hour Reading – April 29, 2004

[redacted] [redacted]

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1 **TO:** [redacted]

PRODUCT PROFILE NO: [redacted] REPORT DATE: November 19, 2018 LAB REF.: [redacted]-3105-18

TEST DATES: November 14 ,2018 to November 16 ,2018

1. TEST MATERIAL: Alfaparf Post Treatment Conditioner [redacted]

2. CONTROL MATERIAL: AT Ultimate Volume Conditioner [redacted]

3. TEST PROCEDURE:

Single-Insult (24hr.) X Occlusive Patch X Semi-Occlusive Patch .

4. CONCENTRATION:

Full-Strength_____ Aqueous X (25%) Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

_____Volatiles were allowed to evaporate ~15 minutes prior to occlusion on the patch
_____Patch was hydrated just prior to application to skin.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	+	1	1+	2	2+	3	3+	4	PII
Alfaparf Post Treatment Conditioner [redacted]	15	15	0	0	0	0	0	0	0	0	0.00
AT Ultimate Volume Conditioner [redacted]	15	14	1	0	0	0	0	0	0	0	0.03

___ Skin staining noted. Erythematous response was read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). X .

B. _____.
_____.
_____.
_____.

Study Conducted By: [redacted]

Written By: [redacted]

* SCORE
0 = No evidence of any effect.
+ (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

CC:

REPEATED INSULT PATCH STUDY

[redacted]

CONDUCTED FOR:

[redacted]

DATE OF ISSUE:

February 1, 2019

[redacted] [redacted]

TABLE OF CONTENTS

APPENDICES

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and [redacted]s Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

[redacted]

[redacted], MD
Dermatologist
Principal Investigator

February 1, 2019
Date

[redacted]

[redacted]
Director, Dermatologic Safety Operations

February 1, 2019
Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIAL

F# [redacted], Conditioner

DATE STUDY INITIATED

December 5, 2018

DATE STUDY COMPLETED

January 12, 2019

DATE OF ISSUE

February 1, 2019

INVESTIGATIVE PERSONNEL

[redacted], MD - Dermatologist
Principal Investigator

[redacted]
Director, Dermatologic Safety Operations

CLINICAL SITE

[redacted]

SUMMARY

One (1) product, F# [redacted], was evaluated as a 25.0% w/v aqueous solution to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. One hundred four (104) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to product, F# [redacted].

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of [redacted]. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 100 completed subjects. In the absence of any sensitization reactions in this sample size (100 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 3.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 years of age or older, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. Patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2] Following the 9th evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last Induction Visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading). Subjects who missed the 9th evaluation (N9G) but have had 9 patch applications were considered to have completed the Induction Phase.

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Following a negative Induction, a 48/72-hour sequence of "-/+," "?/+," or "+/+" resulted in an additional reading being performed at the 96-hour interval. Rechallenge was performed whenever there was evidence of possible sensitization.

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY ACTIVITIES

1[3] Staff obtained informed consent, reviewed completed medical screening form, applied patches

2 Subject removed patches

3 Staff graded sites, applied patches

4 Subject removed patches

5 Staff graded sites, applied patches

6 Subject removed patches

WEEK 2

1 Staff graded sites, applied patches

2-6 Same as Week 1

WEEK 3

1-6 Same as Week 2

WEEK 4

1 Staff graded sites; applied make-up (MU) induction patches, if required

2 Subject removed MU induction patches

3 Staff graded MU induction sites at MU visit

2-7 Rest Period

WEEK 5

1-7 Rest Period

WEEK 6

1 Staff applied patches

2 Subject removed patches

3 Staff graded sites

4 Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

[3] Study flow starting with Week 1, Day 1, will be altered when enrollment occurs other than on Monday. Study flow could be altered when a holiday occurs during the study.

- = No reaction

? = Minimal or doubtful response, slightly different from surrounding normal skin

+ = Definite erythema, no edema

++ = Definite erythema, definite edema

+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema

S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)

p = Papular response > 50%

pv = Papulovesicular response > 50%

D = Damage to epidermis: oozing, crusting and/or superficial erosions

I = Itching

X = Subject absent

PD = Patch dislodged

NA = Not applied

NP = Not patched (due to reaction achieved)

N9G = No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting [redacted] strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : F# 1[redacted], Conditioner
Amount Applied : 0.2 mL
Special Instructions : The study material was prepared fresh daily as a 25.0% w/v aqueous solution. The study material was mixed well until dissolved and prior to patch preparation.

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm. Unless otherwise directed by the Sponsor, the study material was discarded upon completion of the study.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. [redacted] preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a [redacted] facility in a secured room accessible only to [redacted] employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of [redacted].

7.0 RESULTS AND DISCUSSION

One hundred twenty-one (121) subjects between the ages of 18 and 70 were enrolled and 104 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition:

Number enrolled:		121
Number discontinued:		17
Lost to follow-up:	15	
Voluntary withdrawal:	2	
Number completed:		104

Source: Table 1, Appendix I

There were no adverse events (AEs) reported during the study.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to product, F# [redacted].

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

Draize JH, Woodward G, Calvary HO. Methods for the study of irritation and toxicology of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 82: 377-390.

Lanman BM, Elvers WB, Howard CS. The role of human patch testing in a product development program. Joint Conf Cosmet Sci Toilet Goods Assoc 1968; 135-145.

Marzulli FN, Maibach HI. Contact allergy: predictive testing in man. Contact Dermatitis 1976; 2:1.

Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

APPENDIX I

SUMMARY TABLES

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	121
Subjects completed induction phase	109 (90.1)
Subjects completed all phases	104 (86.0)
Total subjects discontinued	17 (14.0)
Lost to follow-up	15 (12.4)
Voluntary withdrawal	2 (1.7)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	36 (29.8)
N (%) 45 to 65	74 (61.2)
N (%) 66 and up	11 (9.1)
Mean (SD)	51.2 (12.9)
Median	53.8
Range	18.2 to 70.4
Sex	
N (%) Male	48 (39.7)
N (%) Female	73 (60.3)
Race	
Amer Ind	1 (0.8)
Asian	2 (1.7)
Black	68 (56.2)
Caucasian	50 (41.3)
Ethnicity	
Hispanic/Latino	40 (33.1)
Not Hispanic/Not Latino	81 (66.9)

See data listing 2 for further detail.

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Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = F# [redacted]

	Induction Reading										Challenge Phase		
Response	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Make Up**	**48hr**	**72hr**	**96hr(*)**
-	111	112	106	110	109	105	102	68	97	68	104	104	
?	0	0	0	0	1	1	1	1	1	0	0	0	
+	0	0	1	1	0	0	0	0	0	0	0	0	
Total evaluable	111	112	107	111	110	106	103	69	98	68	104	104	
Number absent	5	4	9	2	3	5	7	40	11		0	0	
Number discontinued	5	5	5	8	8	10	11	12	12		17	17	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=109)

Response	**n(%) Subjects**
-	108 (99.1%)
+	1 (0.9%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

APPENDIX II

DATA LISTINGS

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
002	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
003	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
004	12/05/18	12/05/18	--	12/17/18	I3	L	13
005	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
006	12/05/18	12/05/18	--	12/10/18	I0	L	6
007	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
008	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
009	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
010	12/05/18	12/05/18	--	12/10/18	I0	L	6
011	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
012	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
013	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
014	12/05/18	12/05/18	--	12/17/18	I3	L	13
015	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
016	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
017	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
018	12/05/18	12/05/18	01/09/19	01/12/19	C	C	39
019	12/05/18	12/05/18	01/09/19	01/10/19	I9	L	37
020	12/05/18	12/05/18	--	12/26/18	I7	S	22
021	12/05/18	12/05/18	--	12/10/18	I0	L	6
022	12/05/18	12/05/18	--	01/09/19	I9	L	36
023	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
024	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
025	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
026	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
027	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
028	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
029	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
030	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
031	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
033	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
034	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
035	12/07/18	12/07/18	--	12/19/18	I3	L	13
036	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
037	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
038	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
039	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
040	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
041	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
042	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
043	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
044	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
045	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
046	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
047	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
048	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
049	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
050	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
051	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
052	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
053	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
054	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
055	12/07/18	12/07/18	--	12/26/18	I6	S	20
056	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
057	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
058	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
059	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
060	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
061	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
062	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
064	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
065	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
066	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
067	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
068	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
069	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
070	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
071	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
072	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
073	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
074	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
075	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
076	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
077	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
078	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
079	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
080	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
081	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
082	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
083	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
084	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
085	12/07/18	12/07/18	--	12/21/18	I5	L	15
086	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
087	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
088	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
089	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
090	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
091	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
092	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
093	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
095	12/07/18	12/07/18	--	01/09/19	I9	L	34
096	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
097	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
098	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
099	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
100	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
101	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
102	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
103	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
104	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
105	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
106	12/07/18	12/07/18	--	01/09/19	I9	L	34
107	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
108	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
109	12/07/18	12/07/18	--	01/09/19	I9	L	34
110	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
111	12/07/18	12/07/18	--	12/12/18	I0	L	6
112	12/07/18	12/07/18	--	12/21/18	I5	L	15
113	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
114	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
115	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
116	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
117	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
118	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
119	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37
120	12/07/18	12/07/18	--	12/12/18	I0	L	6
121	12/07/18	12/07/18	01/09/19	01/12/19	C	C	37

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
001	64.3	Male	Not Hispanic/Not Latino	Caucasian
002	48.5	Male	Not Hispanic/Not Latino	Black
003	63.9	Male	Not Hispanic/Not Latino	Black
004	57.9	Female	Not Hispanic/Not Latino	Asian
005	58.1	Female	Not Hispanic/Not Latino	Black
006	18.2	Female	Hispanic/Latino	Caucasian
007	49.3	Female	Hispanic/Latino	Caucasian
008	70.1	Male	Not Hispanic/Not Latino	Black
009	43.1	Female	Hispanic/Latino	Caucasian
010	31.7	Male	Not Hispanic/Not Latino	Black
011	56.8	Female	Not Hispanic/Not Latino	Caucasian
012	58.1	Female	Not Hispanic/Not Latino	Black
013	63.3	Female	Not Hispanic/Not Latino	Caucasian
014	37.6	Male	Not Hispanic/Not Latino	Black
015	64.0	Female	Not Hispanic/Not Latino	Black
016	59.1	Female	Not Hispanic/Not Latino	Black
017	54.4	Female	Hispanic/Latino	Caucasian
018	58.7	Female	Not Hispanic/Not Latino	Caucasian
019	50.0	Female	Not Hispanic/Not Latino	Black
020	52.2	Male	Not Hispanic/Not Latino	Black
021	22.1	Male	Not Hispanic/Not Latino	Black
022	63.8	Male	Not Hispanic/Not Latino	Black
023	62.1	Male	Hispanic/Latino	Caucasian
024	68.6	Female	Hispanic/Latino	Caucasian
025	38.5	Male	Hispanic/Latino	Caucasian
026	58.0	Female	Not Hispanic/Not Latino	Black
027	63.4	Female	Not Hispanic/Not Latino	Caucasian
028	32.7	Male	Hispanic/Latino	Caucasian
029	36.7	Female	Hispanic/Latino	Caucasian
030	40.3	Male	Not Hispanic/Not Latino	Black
031	51.6	Male	Not Hispanic/Not Latino	Black
032	70.4	Female	Not Hispanic/Not Latino	Black
033	37.4	Male	Not Hispanic/Not Latino	Black
034	53.8	Male	Not Hispanic/Not Latino	Black
035	39.2	Male	Hispanic/Latino	Caucasian
036	63.7	Female	Not Hispanic/Not Latino	Black
037	65.6	Male	Not Hispanic/Not Latino	Black

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[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
038	43.1	Male	Not Hispanic/Not Latino	Black
039	60.5	Male	Not Hispanic/Not Latino	Black
040	69.4	Male	Not Hispanic/Not Latino	Black
041	51.6	Female	Not Hispanic/Not Latino	Caucasian
042	59.2	Female	Not Hispanic/Not Latino	Black
043	54.0	Male	Not Hispanic/Not Latino	Black
044	58.8	Male	Not Hispanic/Not Latino	Black
045	53.2	Female	Hispanic/Latino	Caucasian
046	48.4	Female	Not Hispanic/Not Latino	Caucasian
047	59.7	Female	Hispanic/Latino	Black
048	58.4	Male	Hispanic/Latino	Caucasian
049	31.4	Female	Hispanic/Latino	Black
050	48.1	Female	Hispanic/Latino	Black
051	43.1	Male	Not Hispanic/Not Latino	Black
052	36.0	Female	Not Hispanic/Not Latino	Black
053	19.9	Female	Not Hispanic/Not Latino	Black
054	67.6	Male	Hispanic/Latino	Caucasian
055	34.7	Female	Hispanic/Latino	Caucasian
056	35.9	Female	Not Hispanic/Not Latino	Black
057	52.1	Female	Not Hispanic/Not Latino	Black
058	67.0	Male	Not Hispanic/Not Latino	Black
059	48.2	Male	Not Hispanic/Not Latino	Black
060	53.6	Male	Not Hispanic/Not Latino	Black
061	65.2	Female	Not Hispanic/Not Latino	Black
062	55.1	Male	Hispanic/Latino	Caucasian
063	47.2	Female	Not Hispanic/Not Latino	Black
064	50.0	Female	Not Hispanic/Not Latino	Caucasian
065	52.7	Female	Not Hispanic/Not Latino	Caucasian
066	64.3	Female	Not Hispanic/Not Latino	Black
067	43.8	Female	Not Hispanic/Not Latino	Black
068	34.3	Female	Hispanic/Latino	Caucasian
069	64.0	Female	Hispanic/Latino	Caucasian
070	64.8	Male	Not Hispanic/Not Latino	Black
071	56.3	Female	Not Hispanic/Not Latino	Black
072	57.2	Female	Not Hispanic/Not Latino	Black
073	63.5	Female	Not Hispanic/Not Latino	Caucasian
074	60.0	Female	Not Hispanic/Not Latino	Black

[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
075	67.7	Male	Not Hispanic/Not Latino	Caucasian
076	67.7	Female	Hispanic/Latino	Amer Ind
077	62.2	Male	Not Hispanic/Not Latino	Caucasian
078	44.7	Female	Not Hispanic/Not Latino	Black
079	41.2	Female	Not Hispanic/Not Latino	Black
080	65.9	Female	Not Hispanic/Not Latino	Black
081	62.2	Female	Not Hispanic/Not Latino	Black
082	50.2	Female	Hispanic/Latino	Caucasian
083	35.0	Female	Hispanic/Latino	Black
084	47.1	Male	Not Hispanic/Not Latino	Black
085	36.9	Male	Not Hispanic/Not Latino	Black
086	61.6	Male	Not Hispanic/Not Latino	Caucasian
087	62.9	Female	Not Hispanic/Not Latino	Caucasian
088	44.5	Female	Hispanic/Latino	Caucasian
089	60.4	Male	Hispanic/Latino	Caucasian
090	23.9	Female	Hispanic/Latino	Caucasian
091	36.7	Male	Hispanic/Latino	Black
092	69.7	Female	Hispanic/Latino	Caucasian
093	58.2	Male	Hispanic/Latino	Caucasian
094	68.5	Female	Hispanic/Latino	Caucasian
095	18.3	Female	Not Hispanic/Not Latino	Black
096	56.0	Female	Not Hispanic/Not Latino	Black
097	53.5	Female	Not Hispanic/Not Latino	Caucasian
098	37.0	Female	Hispanic/Latino	Caucasian
099	56.6	Female	Not Hispanic/Not Latino	Black
100	56.1	Female	Hispanic/Latino	Black
101	24.7	Male	Hispanic/Latino	Asian
102	54.6	Female	Not Hispanic/Not Latino	Black
103	42.2	Female	Not Hispanic/Not Latino	Black
104	64.3	Male	Not Hispanic/Not Latino	Caucasian
105	49.5	Female	Not Hispanic/Not Latino	Caucasian
106	51.2	Female	Hispanic/Latino	Caucasian
107	54.9	Male	Not Hispanic/Not Latino	Caucasian
108	40.1	Male	Not Hispanic/Not Latino	Black
109	31.7	Female	Hispanic/Latino	Caucasian
110	45.3	Female	Hispanic/Latino	Caucasian
111	25.5	Female	Hispanic/Latino	Black
112	36.6	Female	Hispanic/Latino	Caucasian
113	55.4	Female	Not Hispanic/Not Latino	Caucasian
114	47.5	Male	Not Hispanic/Not Latino	Black
115	69.2	Male	Not Hispanic/Not Latino	Black
116	55.2	Male	Not Hispanic/Not Latino	Black
117	59.4	Male	Not Hispanic/Not Latino	Black
118	51.0	Male	Hispanic/Latino	Caucasian
119	57.4	Female	Hispanic/Latino	Caucasian
120	24.3	Female	Not Hispanic/Not Latino	Black
121	48.3	Female	Not Hispanic/Not Latino	Black

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	X	-	-	-	
002	-	-	-	-	-	-	-	-	-		-	-	
003	-	-	X	-	-	-	-	-	-	-	-	-	
004	-	-	-	X	X	X	X	X	X		X	X	
005	-	-	-	-	-	-	-	-	X	-	-	-	
006	X	X	X	X	X	X	X	X	X		X	X	
007	-	-	-	-	-	-	-	-	X	-	-	-	
008	-	-	-	-	-	-	-	-	X	-	-	-	
009	-	-	-	-	-	-	-	-	X	-	-	-	
010	X	X	X	X	X	X	X	X	X		X	X	
011	-	-	-	-	X	-	-	-	-	-	-	-	
012	-	-	+	+	?	?	?	?	?		-	-	
013	-	-	-	-	-	-	-	-	X	-	-	-	
014	-	-	-	X	X	X	X	X	X		X	X	
015	-	-	-	-	-	-	-	-	X	-	-	-	
016	-	-	-	-	-	-	-	-	X	-	-	-	
017	-	-	-	-	-	-	-	X	-	-	-	-	
018	X	-	-	-	-	-	-	-	-	-	-	-	
019	-	-	-	-	-	-	-	-	N9G		X	X	
020	-	X	-	-	-	-	-	X	X		X	X	
021	X	X	X	X	X	X	X	X	X		X	X	
022	-	-	-	-	-	-	-	-	X	-	X	X	
023	-	-	-	-	-	-	-	-	-		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required
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[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	-	-	-	-	-	-	X	-	-	-	-	
027	-	-	-	-	X	-	-	-	-	-	-	-	
028	X	-	-	-	-	-	-	-	-	-	-	-	
029	X	-	-	-	-	-	-	-	-	-	-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	-	-	-	X	-	-	-	-	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	-	X	X	X	X	X	X		X	X	
036	-	-	-	-	-	-	-	X	-	-	-	-	
037	-	-	-	-	-	-	-	X	-	-	-	-	
038	-	-	-	-	-	-	-	X	-	-	-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	X	-	-	-	-	
042	-	-	-	-	-	-	-	X	-	-	-	-	
043	-	-	-	-	-	-	-	X	-	-	-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 01/16/19: 9:54 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	-	-	-	-	-		-	-	
048	-	-	-	-	-	-	-	X	-	-	-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	X	-	-	-	-	
052	-	-	-	-	-	-	-	X	-	-	-	-	
053	-	-	X	-	-	-	-	-	-	-	-	-	
054	-	-	-	-	-	-	-	X	-	N9G	-	-	
055	-	X	-	-	-	-	X	X	X		X	X	
056	-	-	-	-	-	-	-	X	-	-	-	-	
057	-	-	-	-	-	-	-	X	-	-	-	-	
058	-	-	-	-	-	-	-	X	-	-	-	-	
059	-	-	-	-	-	-	-	-	-		-	-	
060	-	-	-	-	-	-	-	X	-	-	-	-	
061	-	-	-	-	-	-	-	-	-		-	-	
062	-	-	-	X	-	-	-	-	-	-	-	-	
063	-	-	-	-	-	X	-	-	-	-	-	-	
064	-	-	-	-	-	-	-	X	-	-	-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	-	-	X	-	-	-	N9G	-	-	
067	-	-	-	-	-	X	-	-	-	-	-	-	
068	-	-	-	-	-	X	-	-	-	-	-	-	
069	-	-	-	-	-	-	-	-	N9G		-	-	

(*) When required
Generated on 01/16/19: 9:54 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	-	-	-	-	X	-	-	-	-	
071	-	-	-	-	-	-	-	-	-		-	-	
072	-	-	-	-	-	-	-	-	-		-	-	
073	-	-	-	-	-	-	-	X	-	-	-	-	
074	-	-	-	-	-	-	-	X	-	N9G	-	-	
075	-	-	-	-	-	-	-	X	-	-	-	-	
076	-	-	-	-	-	-	-	X	-	-	-	-	
077	-	-	-	-	-	X	-	-	-	-	-	-	
078	-	-	-	-	-	-	X	-	-	N9G	-	-	
079	-	-	X	-	-	-	-	-	-	-	-	-	
080	-	-	X	-	-	-	-	-	-	N9G	-	-	
081	-	-	-	-	-	-	-	X	-	N9G	-	-	
082	-	-	-	-	-	-	X	-	-	-	-	-	
083	-	-	X	-	-	-	-	-	-	-	-	-	
084	-	-	-	-	-	-	X	-	-	-	-	-	
085	-	-	-	X	-	X	X	X	X		X	X	
086	-	-	X	-	-	-	-	-	-	-	-	-	
087	-	-	X	-	-	-	-	-	-	-	-	-	
088	-	-	-	-	X	-	-	-	-	N9G	-	-	
089	-	-	-	-	-	-	-	X	-	-	-	-	
090	-	X	-	-	-	-	-	-	-	-	-	-	
091	-	-	-	-	-	-	X	-	-	-	-	-	
092	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 01/16/19: 9:54 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	X	-	-	-	-	
094	-	-	-	-	-	-	-	X	-	-	-	-	
095	-	-	-	-	-	-	-	-	-		X	X	
096	-	X	-	-	-	-	-	-	-	-	-	-	
097	-	-	-	-	-	-	-	X	-	-	-	-	
098	-	-	X	-	-	-	-	-	-	N9G	-	-	
099	-	-	-	-	-	-	-	X	-	-	-	-	
100	-	-	-	-	-	-	-	X	-	-	-	-	
101	-	-	-	-	-	-	-	X	-	-	-	-	
102	-	-	-	-	-	-	-	X	-	-	-	-	
103	-	-	-	-	-	-	-	X	-	-	-	-	
104	-	-	-	-	-	-	-	X	-	-	-	-	
105	-	-	-	-	-	-	-	X	-	N9G	-	-	
106	-	-	-	-	-	-	X	-	-	-	X	X	
107	-	-	-	-	-	-	-	X	-	-	-	-	
108	-	-	-	-	-	-	X	-	-	N9G	-	-	
109	X	-	-	-	-	-	-	-	-	N9G	X	X	
110	-	-	-	-	-	-	-	-	-		-	-	
111	X	X	X	X	X	X	X	X	X		X	X	
112	-	-	X	-	-	X	X	X	X		X	X	
113	-	-	-	-	-	-	-	X	-	-	-	-	
114	X	-	-	-	-	-	-	-	-	-	-	-	
115	-	-	-	-	-	-	X	-	-	-	-	-	
116	-	-	-	-	-	-	-	X	-	-	-	-	
117	-	-	-	-	-	-	-	X	-	N9G	-	-	
118	-	-	-	-	-	-	-	-	-		-	-	
119	-	-	-	-	-	-	-	X	-	-	-	-	
120	X	X	X	X	X	X	X	X	X		X	X	
121	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 01/16/19: 9:54 by DETAIL.SAS/USES: RESPONSE, PRODLIST

APPENDIX III

INFORMED CONSENT DOCUMENT

INFORMED CONSENT

REPEATED INSULT PATCH STUDY

STUDY NO.: [redacted]

Study Doctor: [redacted]

Telephone Number: [redacted]

After Office Hours: [redacted]

AIRB Approved
Robert J. Staub, PhD
Date [redacted] 11/4/15

PURPOSE

You are invited to participate in this RIPT (Repeated Insult Patch Test) research study. The purpose of this research is to determine if the study materials being tested can be applied to human skin without causing an allergic reaction. The study will involve a minimum of 100 participants.

STUDY MATERIALS

The study materials being tested include or may be components of skin care products, shampoos, skin cleansers, fragrances, and/or any other materials which are intended for and/or may come into contact with human skin.

The cosmetic/inactive ingredients of the study materials are commonly used in industry for topical products and have history of safe use in our product portfolio.

STUDY DURATION

This study consists of 13 visits (14 visits, if required) over 6 weeks, most visits lasting approximately 10-30 minutes. You will receive a schedule of visit dates and instructions.

PROCEDURE

Before you can start the study, the study staff will speak about any questions you may have. You will be asked to read and sign this form stating that you understand the study procedures. The study staff will begin screening you to see if you meet all study entrance requirements. This study consists of three phases, which include Induction, Rest and Challenge which are explained below.

Each patch received during this study will contain one cosmetic study product. However, more than one patch will be applied with several different cosmetic study products. The dose of the study product will be about 0.2mL, covering a 2cm by 2cm area. You will wear the study product and 2cm x 2cm patch(s) on your back.

Induction: The first three weeks of the study are called the induction phase. During the induction phase you will report to [redacted] on Mondays, Wednesdays (or Thursday due to the holiday schedule) and Fridays. At each visit study staff will apply a set of patches to your back. Each patch will be removed 24 hours after application and new patch(s) will be applied at each visit. Your skin will be examined before any study product is applied. The patch(s) applied on Monday, Wednesday (or Thursday due to the holiday schedule) and Friday will remain on your back for 24 hours. At each of these induction visits, a clinical evaluator will examine your back to see if you are reacting to any of the products. If you have a strong reaction at the study site (where the study product is applied), the study product will not be applied to that site, but may be applied to another site. The induction period consists of 10 visits.

Rest: During week four of the study, you will begin a rest period during which study product will not be applied to your back and you will not have to report to [redacted] This rest period will last through weeks four and five.

Challenge: After the rest period is over and week six begins (the final week of the study), you will receive the same products applied on a new area of the back. The study products (with patches) will be put on the part of your back that

[redacted]

INFORMED CONSENT

REPEATED INSULT PATCH STUDY

STUDY N[redacted]

has not received study product before. During this phase of the study, you will have to return to [redacted] for three more visits. The first visit during the challenge phase you will have your back evaluated and identical patches re-applied. These patches will be removed by you 24 hours later. You will return t[redacted] 48 hours after initial challenge patch application for skin evaluation. Finally, you will return to [redacted] for your final visit, 72 hours after initial challenge patch application, for your final evaluation. If the study doctor/staff determines that it is necessary to make additional evaluations, due to reactions, you will be asked to come back for an additional visit.

If you are a female of childbearing potential (i.e., not surgically sterile or have not experienced menopause), you must agree to prevent pregnancy throughout this study by using at least one form of accepted birth control [e.g., oral/ injectable/transdermal contraceptive pill, IUD, condom/diaphragm with spermicide, abstinence (no sexual intercourse)].

If you are breastfeeding a child, you will not be permitted to participate in this study. Pregnancy and breastfeeding are prohibited to prevent any unforeseen risk to an unborn child or breast-feeding child.

SUBJECT REQUIREMENTS

You must agree to make all your scheduled visits to [redacted] You must not apply products such as creams, lotions and moisturizers on or near the test sites. You must avoid sun exposure or the use of tanning beds on your back (including the rest period). You must agree to refrain from swimming during the course of the study. You must agree to minimize water exposure on the patch area while showering or bathing by taking a low tub bath or frontal shower. You will receive written instructions for this study.

POTENTIAL RISKS

Some of the materials may be irritating under certain conditions but the degree of irritation is not expected to be greater than that described below. Individuals participating in this study may experience side effects such as redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. Reactions usually occur only where the study materials or patch materials (such as the patch tape adhesive) touch the skin. On rare occasions, the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist in an occasional individual. Reactions may be due to either skin irritation or allergy to either study materials or patch materials (e.g., patch tape adhesive). It may be necessary to do additional application (rechallenge) to determine if an allergic reaction has occurred. If you should prove to be allergic, you can expect to react to this material if you encounter it at a later date. Whenever possible, you will be informed as to the identity of the material in order that you may avoid contact with it in the future. Photographs of the test sites only, will be taken if reactions occur during the study. These photographs will be shared with study personnel and will be use for the investigator's review and assessment of the reactions.

COMPENSATION FOR INJURY

For any significant reactions that may occur as a direct result of your participation in this study, appropriate and reasonable medical treatment will be provided by [redacted] at no cost to you to resolve the immediate problem. Provision of such medical care is not an admission of legal liability or responsibility for the condition being treated. If such reactions occur, [redacted] personnel should be contacted immediately at [redacted] day and [redacted] at night or on weekends. Extended medical care will not be provided.

SIGNIFICANT NEW FINDINGS

You will be informed of any significant new findings that may affect your willingness to continue your participation.

AIRB Approved
Robert J. Staub, PhD
Date. 11 Sept

POTENTIAL BENEFITS

There is no personal benefit other than the satisfaction of participation in a clinical research study.

[redacted]

INFORMED CONSENT

REPEATED INSULT PATCH STUDY

STUDY NO.: [redacted]

ALTERNATIVE TREATMENT

Since this study is for research only, the only alternative is for you not to participate.

WITHDRAWAL FROM STUDY

Participation in the study is voluntary and you may refuse to participate or may withdraw at any time without penalty or loss of benefits, other than financial, to which you are otherwise entitled. Your participation may also be discontinued at any time without your consent by the study doctor, the Institutional Review Board (IRB) (a committee that reviews studies to help ensure that the rights and welfare of the participants are protected and that the study is carried out in an ethical manner), the Food and Drug Administration (FDA), or the study sponsor(s) (the company(ies) that makes the product(s) being evaluated). If you fail to comply with study procedures, your participation may be terminated.

AIRB Approved
Robert J. Staab, PhD
Date: 11/14/18

COST

Your participation in the study will not incur any cost to you.

FINANCIAL INCENTIVE

You will be paid a sum of $170.00 upon completion of this study. If in the judgment of the investigating personnel, it is best to discontinue your participation in this study due to an adverse experience or severe reaction you will be paid in full for your participation. If you drop out of your own accord for personal reasons beyond your control you will be paid proportionately ($6.50 per visit). If you are dismissed for refusal to obey rules or follow instructions you will not be paid.

CONFIDENTIALITY AND AUTHORIZATION

Reports prepared by [redacted] will utilize statistical information only and at no time will your name be used. A federal regulation called the "Health Insurance Portability and Accountability Act"(HIPAA), which went into effect on April 14, 2003, describes how your personal health information may be used, disclosed and made accessible to you. This privacy rule is designed to protect the confidentiality of your personal health information. The following information describes how the HIPAA rule applies to you and your rights.

This study can be performed only by collecting and using your personal health information. Your study records will be kept as confidential as possible under local, state and federal laws. Personnel from the following organizations may examine your study records: the sponsor, personnel associated with this study, regulatory agencies, such as the Food and Drug Administration (FDA) or Environmental Protection Agency (EPA), and the Allendale Institutional Review Board (IRB), a committee that has reviewed this study to help ensure that your rights and welfare as a research participant are protected and that the study is carried out in an ethical manner. Because of the number of individuals who may see your records, absolute confidentiality cannot be guaranteed.

Personal health information that may be used and disclosed includes that which is obtained to determine your eligibility to participate and that which is collected from the procedures that are carried out. It may identify you by name, address, telephone number, Social Security Number, study number, date of birth or other identifiers. Once the information is disclosed, it is possible that it may be re-disclosed, at which time it is no longer protected by federal regulations but may be by state laws.

If the final study data are prepared for publication and other reports, your identity will not be revealed. Under these federal privacy regulations, you have the right to see and copy any of the information gathered about you, until your study records are no longer kept by the study doctor. However, your records may not be available until the study has been completed. There is no expiration date for this authorization.

You may, by written notice to the study doctor, cancel your authorization to use or disclose your personal information at any time. If you withdraw your authorization, the information collected to that time may still be used to preserve the

[redacted]

INFORMED CONSENT

REPEATED INSULT PATCH STUDY

STUDY NO.: [redacted]

scientific integrity of the study.

By signing this consent form, you authorize these uses and disclosures of your personal information. If you do not authorize these uses and disclosures, you will not be able to participate in the study.

WHO TO CALL

Additional information regarding this research is available either before or during the course of this study. If you have any questions or research related side effect or injury, you may contact [redacted], Director Dermatologic Safety at [redacted]. You may contact the Allendale Institutional Review Board, Old Lyme, Connecticut, 860.434.5872, if you have a question about your rights as a research subject. Review of this research study by Allendale IRB is not an endorsement of the study or its outcome.

A signed copy of this consent form will be given to you.

.....

I have read the information and description of this research study given in this consent form. I have been informed of the risks and benefits, and all my questions have been answered to my satisfaction. I voluntarily consent to participate. By signing this form I have not given up any of my legal rights which I would otherwise have as a research subject.

Entry Number	Print Name	Signature	Date

Signature of Person Explaining the Consent Form	Date

AIRB Approved
Robert J. Staub, PhD
Date: 11/2019

APPENDIX IV

DERMATOLOGIST SIGNED LETTER

[redacted]

September 4, 2018

[redacted]

Dear Ms. [redacted]

All Dermatologic Safety Studies at [redacted]. are conducted under the supervision and coordination of a board-certified dermatologist. [redacted], MD is a board-certified dermatologist and site Medical Director who serves as the Principal Investigator for all Dermatologic Safety studies. As Principal Investigator, Dr. [redacted] follows NIH and Good Clinical Practices (GCP) in his responsibility for delegating authority to trained and qualified personnel, whose credentials are documented on their curriculum vitae (CV) on file with site standard operating procedures. All subject's grading is performed under the supervision of the dermatologist. The dermatologist is responsible for all Clinical Grading Assessments, and for reviewing and signing all laboratory reports.

[redacted]
Director, Dermatologic Safety

2022 FDA VCRP – Starch Phosphates

Distarch Phosphate Acetate and Sodium Dimaltodextrin Phosphate- 0 reported uses

DISTARCH PHOSPHATE	03A	Eyebrow Pencil	1
DISTARCH PHOSPHATE	03B	Eyeliner	2
DISTARCH PHOSPHATE	03D	Eye Lotion	1
DISTARCH PHOSPHATE	07B	Face Powders	15
DISTARCH PHOSPHATE	07C	Foundations	1
DISTARCH PHOSPHATE	07E	Lipstick	5
DISTARCH PHOSPHATE	12A	Cleansing	3
DISTARCH PHOSPHATE	12C	Face and Neck (exc shave)	11
DISTARCH PHOSPHATE	12D	Body and Hand (exc shave)	20
DISTARCH PHOSPHATE	12F	Moisturizing	19
DISTARCH PHOSPHATE	12G	Night	1
DISTARCH PHOSPHATE	12H	Paste Masks (mud packs)	2

Total 81

HYDROXYPROPYL STARCH PHOSPHATE	01C	Other Baby Products	2
HYDROXYPROPYL STARCH PHOSPHATE	03G	Other Eye Makeup Preparations	1
HYDROXYPROPYL STARCH PHOSPHATE	05A	Hair Conditioner	25
HYDROXYPROPYL STARCH PHOSPHATE	05E	Rinses (non-coloring)	1
HYDROXYPROPYL STARCH PHOSPHATE	05F	Shampoos (non-coloring)	3
HYDROXYPROPYL STARCH PHOSPHATE	05G	Tonics, Dressings, and Other Hair Grooming Aids	6
HYDROXYPROPYL STARCH PHOSPHATE	05I	Other Hair Preparations	12
HYDROXYPROPYL STARCH PHOSPHATE	06A	Hair Dyes and Colors (all types requiring caution statements and patch tests)	2
HYDROXYPROPYL STARCH PHOSPHATE	06C	Hair Rinses (coloring)	8
HYDROXYPROPYL STARCH PHOSPHATE	06F	Hair Lighteners with Color	1
HYDROXYPROPYL STARCH PHOSPHATE	06G	Hair Bleaches	2
HYDROXYPROPYL STARCH PHOSPHATE	06H	Other Hair Coloring Preparation	16
HYDROXYPROPYL STARCH PHOSPHATE	07I	Other Makeup Preparations	1
HYDROXYPROPYL STARCH PHOSPHATE	10A	Bath Soaps and Detergents	104
HYDROXYPROPYL STARCH PHOSPHATE	10E	Other Personal Cleanliness Products	9
HYDROXYPROPYL STARCH PHOSPHATE	12A	Cleansing	17
HYDROXYPROPYL STARCH PHOSPHATE	12C	Face and Neck (exc shave)	10
HYDROXYPROPYL STARCH PHOSPHATE	12D	Body and Hand (exc shave)	8
HYDROXYPROPYL STARCH PHOSPHATE	12F	Moisturizing	20
HYDROXYPROPYL STARCH PHOSPHATE	12G	Night	1
HYDROXYPROPYL STARCH PHOSPHATE	12H	Paste Masks (mud packs)	5

HYDROXYPROPYL STARCH PHOSPHATE	12J	Other Skin Care Preps	7

Total 261

SODIUM HYDROXYPROPYL STARCH PHOSPHATE	05C	Hair Straighteners	1
SODIUM HYDROXYPROPYL STARCH PHOSPHATE	12A	Cleansing	14
SODIUM HYDROXYPROPYL STARCH PHOSPHATE	12D	Body and Hand (exc shave)	1
SODIUM HYDROXYPROPYL STARCH PHOSPHATE	12G	Night	1
SODIUM HYDROXYPROPYL STARCH PHOSPHATE	12A	Cleansing	3

Total 17