Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	September 1, 2022
Panel Meeting Date:	September 26 - 27, 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.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi Raj, Senior Scientific Analyst/Writer, CIR.

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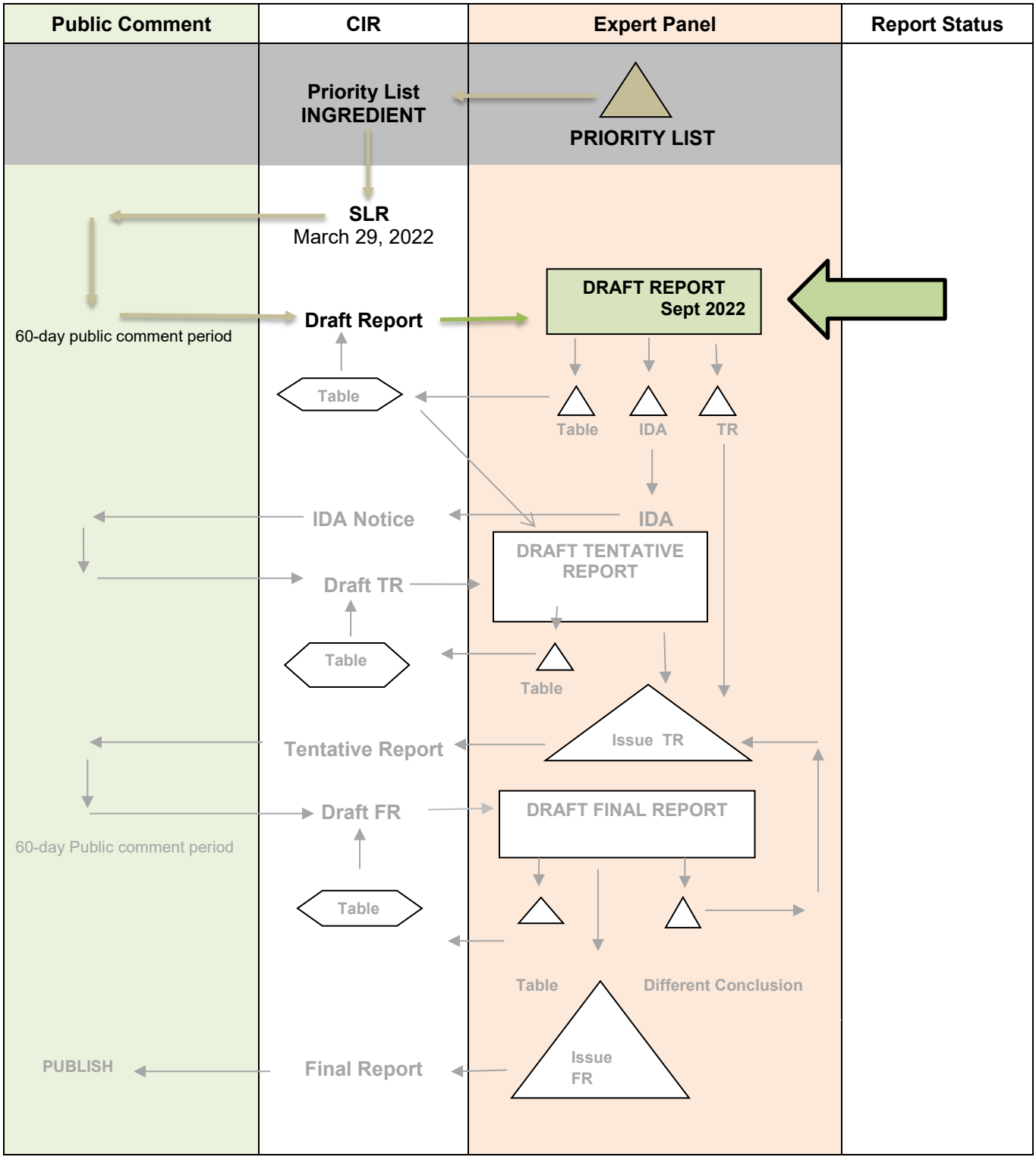
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Polyhydroxystearic Acid

MEETING September 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst, CIR
Date: September 1, 2022
Subject: Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics

Enclosed is the Draft Report of the Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics (identified as *report_PolyhydroxystearicAcid_092022* in the pdf). This is the first time the Panel is seeing a safety assessment of these 3 polymeric cosmetic ingredients. A Scientific Literature Review (SLR) was announced on March 29, 2022.

The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of the monomers of these ingredients, namely, hydroxystearic acid (original review published in 1999; conclusion reaffirmed in 2015) and lactic acid (originally report published in 1998; conclusion reaffirmed in 2017). The full reports on these ingredients are available on the CIR website (https://www.cir-safety.org/ingredients).

Following the announcement of the SLR, the following data were received:

data1_PolyhydroxystearicAcid_092022 (all for Polyhydroxystearic Acid)
- Chemistry and summary safety data; Phoenix Chemical, Inc. 2022
- Molecular weight information; Phoenix Chemical, Inc. 2021
- Repeated insult patch test; 50 subjects; 100% Polyhydroxystearic Acid; AMA Laboratories 2003

data2_PolyhydroxystearicAcid_092022
- Marzulli Maibach HRIPT; 104 subjects; product containing 4% Polylactic Acid; Anonymous 2014
- Modified Marzulli-Maibach; 107 subjects; product containing 3.45% Polyhydroxystearic Acid; Anonymous 2021

data3_PolyhydroxystearicAcid_092022
- 2022 concentration of use data

Polylactic Acid is listed as an ingredient in FDA-approved medical devices, such as surgical tape dressings and orthotic devices. Accordingly, a Freedom of Information Act (FOIA) request for related testing data for these uses, particularly pertaining to toxicity and irritation/sensitization, was submitted to the FDA on February 8, 2022; receipt of the request has been acknowledged, but to date no data have been received.

Comments on the SLR (*PCPCcomments_PolyhydroxystearicAcid_092022*) that were received from the Council have been addressed, and follow this memo. A comments response checklist is also included (*response-PCPCcomments_PolyhydroxystearicAcid_092022*).

The following is also included in the package, for your review: 2022 FDA VCRP data (*VCRP_PolyhydroxystearicAcid_092022*), a flow chart (*flow_PolyhydroxystearicAcid_092022*), literature search strategy (*search_PolyhydroxystearicAcid_092022*), data profile (*dataprofile_PolyhydroxystearicAcid_092022*), and ingredient history (*history_PolyhydroxystearicAcid_092022*).

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, unsafe, or split conclusion, and Discussion items should be identified. If the available data are deemed insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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: April 5, 2022

SUBJECT: Scientific Literature Review: Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid) and Polylactic Acid as Used in Cosmetics (release date: March 29, 2022)

The Personal Care Products Council has no suppliers listed for Poly(3-Hydroxoctanoic Acid).

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid) and Polylactic Acid as Used in Cosmetics.

Non-Cosmetic Use; Summary – Please revise the following sentence: "Additionally, the FDA issued a Recognized Consensus Standard (ASTM F2579-18) in 2019 which set specifications for amorphous Polylactic Acid used in surgical implants." ASTM International, not FDA issues ASTM standards. FDA recognizes ASTM standards. See https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=40178 for FDA recognition of the ASTM standard on Polylactic Acid. Please add ASTM to the abbreviations page (formerly called American Society for Testing and Materials, now called ASTM International).

Toxicokinetics; Summary – Please correct "C^{14}" to "^{14}C".

Polyhydroxystearic Acid - September 26-27, 2022 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: April 5, 2022 (comments received on SLR after March 29, 2022 posting)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Non-Cosmetic Use; Summary -Revise sentence to indicate that ASTM International issues ASTM standards (FDA recognizes, does not issue) -Add ASTM to Abbreviations	- Revised -Added	
2	Toxicokinetics; Summary Correct C^{14} to ^{14}C	-corrected	

CIR History of:

Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid

July 2021

-Concentration of use data submitted by Council

January 2022

-FDA frequency of use data obtained

March 2022; April 2022

- SLR posted on the CIR website; received SLR comments

Data received, by date:

April 11, 2022:
Polyhydroxystearic Acid
- Chemistry and molecular weight data
- 100% Polyhydroxystearic Acid; HRIPT in 50 subjects

April 15, 2022:
- Marzulli-Maibach HRIPT; product containing 4% Polylactic Acid (104 subjects)
- Modified Marzulli-Maibach HRIPT; product containing 3.45% Polyhydroxystearic Acid (107 subjects)

September 2022

-A Draft Report is being presented to the Panel.

Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid Data Profile* – September 26-27, 2022 – Writer, Preethi Raj																															
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Polyhydroxystearic Acid	X		X																		X			X						
Poly(3-Hydroxyoctanoic Acid)		X	X																											
Polylactic Acid	X	X	X			X									X	X				X	X			X		X				X

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

[Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid]

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Polyhydroxystearic Acid	27924-99-8 58128-22-6	NR	NR	NR	NR	✓*	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	✓*
Poly(3-Hydroxyoctanoic Acid)		✓*	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓*
Polylactic acid	9051-89-2 26917-25-9 26811-96-1	✓	✓*	NR	NR	✓	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	✓*

NR – not reported; ✓*- data available is not relevant to assessment

Search Strategy

[*total # of hits / # useful hits*]

PubMed (as of 08/03/2022):
((((((((((((((((((((((polyhydroxystearic acid) OR (Poly(3-Hydroxyoctanoic Acid))) OR (27924-99-8)) OR (58128-22-6)) OR (Dispersun DSP OL 100)) OR (Dispersun DSP OL 300)) OR (Octacare DSP OL100)) OR (Pelemel PHS-8)) OR (Salacos HS-6C)) OR (Polylactic acid)) OR (9051-89-2)) OR (26917-25-9)) OR (26811-96-1)) OR (polylactide)) OR (cyclic poly lactate)) OR (Ecoscrub 20 PC)) OR (Flo-Beads BF)) OR (FLO Beads-BL)) OR (Flo-Beads)) OR (BR)) OR (Lacea)) OR (PLLA-MS)) OR (Purasorb OL)) AND (toxicity) – 31, 765 hits/0 new or useful

General Search

Polyhydroxystearic Acid – 4/0
Poly(3-Hydroxyoctanoic Acid) – 29/2
Polyhydroxystearic acid cosmetic toxicity – 0/0
Polylactic acid cosmetic toxicity – 15/2
Polyhydroxystearic Acid toxicity – 0/0
Poly(3-Hydroxyoctanoic Acid) toxicity – 0/0
Polylactic Acid toxicity – 6787/3
polyhydroxystearic acid cosmetic toxicity - 20,100/2
poly(3-hydroxyoctanoic) acid method of manufacture – 114,000/1
polyhydroxystearic acid dermal toxicity – 23,500/0
polyhydroxystearic acid dermal irritation and sensitization – 16,800/0
poly(3-hydroxyoctanoic acid) dermal toxicity - 96,100/0
poly(3-hydroxyoctanoic acid) dermal irritation and sensitization – 17,600/0
polylactic acid dermal toxicity - 644,000/0
polylactic acid dermal irritation and sensitization – 70,900/1

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics

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ABBREVIATIONS

ASTM International	American Society for Testing Materials International
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DNFB	dinitrofluorobenzene
EFSA	European Food Safety Authority
FDA	Food and Drug Administration
HET-CAM	hen's egg-chorioallantoic membrane
HRIPT	human repeat insult patch test
MII	mean irritation index
MW	molecular weight
NR	none reported
Panel	Expert Panel for Cosmetic Ingredient Safety
PII	primary irritation index
RPMI	Roswell Park Memorial Institute
US	United States
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This assessment reviews the safety of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these 3 ingredients are reported to function in cosmetics as a non-surfactant dispersing agent, a skin-conditioning agent, and an abrasive, respectively (Table 1).[1]

These 3 ingredients each comprise a polymer synthesized from hydroxycarboxylic acid monomers. These monomers vary only in alkyl chain-length and position of the hydroxy substitution. The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of two of these monomers. In 1999, the Panel issued a final report on the safety of hydroxystearic acid; the Panel concluded that hydroxystearic acid is safe as a cosmetic ingredient in the present practices of use as described in the safety assessment.[2] When hydroxystearic acid was re-reviewed along with other fatty acids and fatty acid salts in 2019, the Panel reaffirmed the conclusion that hydroxystearic acid is safe in the cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be determined based on a quantitative risk assessment.[3] In 1998, the Panel published a final report with the conclusion that lactic acid is safe for use in cosmetic products at concentrations ≤ 10%, at final formulation pH ≥ 3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection, and that it is safe for use in salon products at concentrations ≤ 30%, at final formulation pH ≥ 3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection.[4] Upon re-review in 2017, the Panel reaffirmed the safety of lactic acid.[5] These reports are available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

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 listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment pertains to Polylactic Acid use in biomedical applications, and, hence, is not specific to cosmetic use. Data summaries pertaining to these Polylactic Acid uses are provided herein.

CHEMISTRY

Definition and Structure

Polyhydroxystearic Acid (CAS Nos. 27924-99-8; 58128-22-6), Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid (CAS Nos. 26811-96-1; 9051-89-2; 26917-25-9) are polymers synthesized from hydroxy carboxylic acids.[1,CIR Staff] For example, Polylactic Acid is a polymer prepared from lactic acid monomers (Figure 1). The definitions and structures of the ingredients included in this review are provided in Table 1.

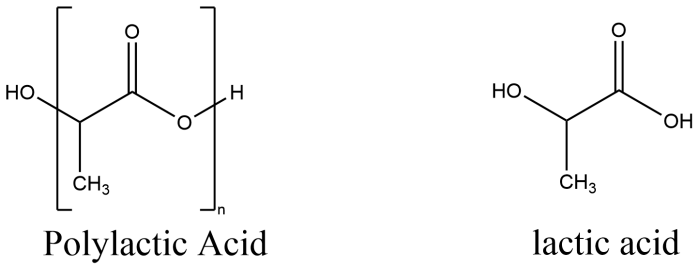


Figure 1. Polylactic Acid and lactic acid

Chemical Properties

The monomer of Polyhydroxystearic Acid, hydroxystearic acid, has a molecular weight (MW) of 300.5 g/mol;[6] however, the mean MW and distribution of weights/lengths is variable and based on reaction conditions. As described by a supplier, Polyhydroxystearic Acid has a number average MW of 1243 g/mol and a weight average MW of 8243 g/mol.[7] Polylactic Acid has a MW between 53,000 to 800,00 g/mol.[8] The MW of Poly(3-Hydroxyoctanoic Acid) was not found or submitted. Chemical properties for Polyhydroxystearic Acid and Polylactic Acid are further outlined in Table 2.

Polyhydroxystearic Acid is described by a supplier as a 100% active, fully vegetable-derived, polymeric ester with single terminal hydroxy and carboxy groups.[9] At ambient temperatures, Polyhydroxystearic Acid is a yellow, viscous liquid which has numerous nucleophilic sites, and is expected to complex water via hydrogen bonding on the skin. Polyhydroxystearic Acid

is soluble in castor oil, mineral oil, isododecane, isopropyl myristate, isononyl isononanoate, and pentaerythrityl tetraethylhexanoate, but is not soluble in water, ethanol, propylene glycol, cyclopentasiloxane, or dimethicone.

Polylactic Acid is a thermoplastic, stiff, glassy material, which has a density of 1.25 g/cm^3, and a glass transition temperature of 55 °C.[8] Additionally, Polylactic Acid is an aliphatic polyester, which is extremely hydrophobic and is soluble in organic solvents, such as benzene and chloroform, and is not soluble in water, methanol, or ethanol.[10,11] Made from L-, D-, or DL-stereoisomers of lactic acid, Polylactic Acid exists in different enantiomeric forms.[10] This variance in enantiomeric composition affects the crystallization, degradation rate, molecular weight, and glass-transition temperature of the resulting polymer, among other chemical properties; Poly-L-lactic Acid is semi-crystalline, Poly-D-lactic Acid is crystalline, and Poly-D,L-lactic Acid is amorphous.[10,12] In a study describing film-forming Polylactic Acid, exposure to ethanol and water resulted in concurrent hydrolytic degradation, producing changes in molecular weight and release of lactic acid monomer, and crystallization, characterized by swelling of the polymer matrix.[13]

Method of Manufacture

The methods described below are general to the processing of commercial forms of these ingredients. It is unknown if these apply to cosmetic ingredient manufacturing.

Poly(3-Hydroxyoctanoic Acid)

Large-scale synthesis of Poly(3-Hydroxyoctanoic Acid) using the bacterial strain *Pseudomonas putida* GPo1 in lyophilized cell material was evaluated.[14] Three batches of *P. putida* were cultivated, in mineral salts medium containing 20 mM sodium octanoate, as well as sodium hydroxide, ammonium hydroxide, or octanoic acid, at the 350-l or 400-l scale, in a 650-l capacity bioreactor for 48 h. Cells were harvested from the 400-l scale synthesis, were lyophilized, and extracted with acetone, resulting in 94% recovery of the Poly(3-Hydroxyoctanoic Acid) content in the cells. Subsequent use of a precipitation solvent of methanol and ethanol at a 1:1 ratio resulted in a highly purified Poly(3-Hydroxyoctanoic Acid), which once dried, yielded ~ 99 ± 0.2% (wt/wt) of the polymer.

Polylactic Acid

The main feedstock for Polylactic Acid includes renewable biomass, such as sugarcane, corn, wheat, rice.[11,15] Industrial production of lactic acid, the precursor of Polylactic Acid, is mostly achieved via microbial carbohydrate fermentation, which enables the mass production of optically pure lactic acid, an essential factor in determining the chemical properties of Polylactic Acid.[16]

Direct condensation, azeotropic dehydration condensation polymerization, and ring-opening polymerization methods are used to produce higher molecular weight Polylactic Acid, of which the last is the most efficient.[17,18] Ring-opening polymerization involves the polycondensation of lactic acid monomers to low-molecular weight Polylactic Acid, depolymerization of the Polylactic Acid into lactide, and catalyst-driven ring-opening polymerization of the lactide intermediate.

Impurities

Polyhydroxystearic Acid

According to a supplier, 20% of the MW of Polyhydroxystearic Acid is less than 1000 g/mol, which is attributable to oligomers.[7]

Poly(3-Hydroxyoctanoic Acid)

The purity of Poly(3-Hydroxyoctanoic Acid) precipitated from a salt, using various solvents, was evaluated.[14] Compared to purity resulting from the standard method of dissolving in chloroform and precipitating with ethanol (84 ± 1.5 % (wt/wt)), the highest purity of Poly(3-Hydroxyoctanoic Acid) was achieved from precipitation with ethanol-methanol (70%, v/v) mix, at 99 ± 0.2 %.

Polylactic Acid

Since Polylactic Acid is often produced via the polymerization of commercial lactic acid and lactide, impurities found in these stock solutions can often affect the purity and chemical properties of the resulting Polylactic Acid.[16] Commercial lactic acid solutions are typically 80 - 90% aqueous solutions of L-, D-, or D,L-lactic acid, reported to contain the following impurities: arsenic (< 1 ppm), iron (< 5 ppm), heavy metals (< 5 ppm), chloride (< 10 ppm), sulfates (< 10 ppm), sulfated ash (residue after pyrolysis), reducing sugars, methanol, and methyl ester. Commercial lactic acid used for the polymerization of Polylactic Acid often contains water, lactic acid dimers, trimers, as well as oligomers, and residual catalyst.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2022 VCRP survey data, Polyhydroxystearic Acid is reported to be used in 265 formulations, of which 116 uses are in lipsticks, and Polylactic Acid is reported to be used in 18 formulations (Table 3).[19] Results from a 2021 concentration of use survey, conducted by the Council, indicate Polyhydroxystearic Acid has the highest reported concentration of use; it is used at up to 14.2% in lipsticks.[20] Polylactic Acid is reported to be used at up to 5% in skin cleansing products. Poly(3-Hydroxyoctanoic Acid) is not reported to be in use according to the VCRP and industry survey (Table 4).

Polyhydroxystearic Acid and Polylactic Acid are reported to be used in products that may lead to incidental ingestion and exposure to mucous membranes; for example, as stated above, Polyhydroxystearic Acid is reported to be used in lipsticks at a maximum concentration of 14.2%. These ingredients have also been reported to be used in products that may come in contact with the eyes; for example, Polyhydroxystearic Acid is reported to be used at up to 8% in mascaras. Additionally, Polyhydroxystearic Acid is reported to be used at up to 0.9% in other baby products.

Furthermore, Polyhydroxystearic Acid is reported to be used in aerosol hair sprays at up to 0.5%, as well as in 5 face powder formulations (concentration of use not reported), and could possibly be inhaled. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

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

All 3 ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[21]

Non-Cosmetic

Polyhydroxystearic Acid is a polymer, exempt from the requirement of tolerance due to meeting criteria of a low-risk polymer, as an inert ingredient in pesticide chemical formulations, assuming good agricultural or manufacturing practices [40 CFR 180 § 960]. In 2010, the European Food Safety Authority (EFSA) issued the scientific opinion that Polyhydroxystearic Acid is safe for use in consumer food packaging, provided its migration does not exceed 5 mg/kg food.[22]

The EFSA also issued the scientific opinion in 2010 stating that Polylactic Acid is safe for indirect food contact.[23] Polylactic Acid has versatile use in various industries, such as food packaging, single use products, textiles, automobiles, agriculture, electronics, and construction,[15] and has been approved since 1970 by the FDA to be in contact with biological fluids.[10] Polylactic Acid is also approved by the FDA for use in surgical devices such as sutures, ligatures, and meshes, and is identified as an approved bone grafting material [21 CFR 872 § 3930]. Additionally, the FDA utilizes the Recognized Consensus Standard, ASTM F2579-18, issued by the American Society for Testing Materials International (ASTM International) in 2019, which set specifications for amorphous Polylactic Acid used in surgical implants.

Due to its biocompatible and resorbable characteristics, Polylactic Acid also has widespread use in biomedical applications such as drug delivery,[24] tissue engineering,[25] and tumor targeting.[26,27] It is common for Polylactic Acid to be combined with other polymers to form composite substances, notably, in uses such as surgical sutures,[28] bone regeneration,[29] and orthopedic fixtures and devices.[30] Polylactic Acid is also listed as an ingredient in FDA-approved medical devices (surgical tape dressings), as well as in two orthotic devices, a plate and a mesh, used in spinal intervertebral fusion.[31,32]

TOXICOKINETIC STUDIES

Animal

Subcutaneous

Polylactic Acid

In a 90-d study examining the in vivo degradation of Polylactic Acid in rats, an implant chamber containing 100 mg of Polylactic Acid was implanted on either side of the midline, subcutaneously, in 22 rats.[33] Radioactive, [^{14}C]Polylactic Acid was implanted in 15 rats, while the remaining 7 rats were implanted with non-radiolabeled Polylactic Acid to serve as controls. Seven rats (5 with the radiolabeled test article, and 2 controls) were placed in metabolic cages, and urine and feces were collected every 4 d for analysis of radioactivity. After 90 d, these 7 animals were killed and radioactivity was measured in the liver, kidney, lung, heart, brain, spleen, muscles, pouch around the chamber, and the contents of the implant chamber. The remaining 15 rats (10 with the radiolabeled test article and 5 controls) were placed in conventional cages and killed at 2 h, 7 d, 14 d, 1 mo, or 2 mo after implantation. Vital organs and implant chamber contents were analyzed for presence of the radioactive label. No significant radioactivity was recovered in the feces or urine of the animals during the 3-mo period, and no radioactivity was found in the vital organs of any of the animals. The authors surmised that these results evidenced the slow biodegradability of Polylactic Acid.

TOXICOLOGICAL STUDIES

Toxicological studies were not found in the published literature, and unpublished data were not submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies were not found in the published literature, and unpublished data were not submitted.

GENOTOXICITY STUDIES

Details for the genotoxicity studies summarized below can be found in Table 5.

Polylactic Acid film substrates (0.25 cm^2) were not genotoxic to Chinese hamster ovary cell lines in a Comet assay and an in vitro cytokinesis-blocked micronucleus assay.[34] Groups of 10 mice were injected with either saline (negative controls), cyclophosphamide (positive controls), or 0, 50, 100, or 200 ml/kg Polylactic Acid in an in vivo micronucleus test.[35] The incidences of micronucleated polychromatic erythrocytes in mice treated with the low, medium, and high concentrations of Polylactic Acid extracts were 2.0, 2.2, and 2.3%, respectively, which was similar to the incidence in the saline-treated group. Positive controls produced expected results. Groups of 5 male rats had a 2-mm thick, 4-mm diameter disc of 95% Polylactic Acid inserted in the calvarium for either 90 or 120 d in a micronucleus test (no test material inserted for controls).[36] Upon staining of bone marrow extracts, no significant decreases in the frequency of polychromatic erythrocytes or increases in micronucleated polychromatic erythrocytes were observed in the test animals, compared to controls. The authors deemed the test material as non-genotoxic.

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details for the dermal irritation and sensitization studies summarized below can be found in Table 6.

Groups of 2 New Zealand white rabbits had 0.2 g of Polylactic Acid film extracts applied to shaved back skin, via saturated gauze, for 24 h in a skin irritation test.[35] Both rabbits treated with the Polylactic Acid film extracts had a primary irritation score of 0 and primary irritation index (PII) of 0; the authors deemed the test article as non-irritating. Polyhydroxystearic Acid was not irritating or sensitizing when tested neat in an occlusive human repeated insult patch test (HRIPT) of 51 subjects.[37] A product containing 3.45% Polyhydroxystearic Acid was not irritating or sensitizing, when tested neat in a modified Marzulli-Maibach HRIPT using 107 subjects; the mean irritation index (MII) calculated for all subjects during induction was 0.[38] Similarly, in a Marzulli-Maibach HRIPT of a product containing 4% Polylactic Acid, using 104 subjects, the authors deemed the test article as a non-irritant and non-sensitizer.[39]

OCULAR IRRITATION STUDIES

According to a supplier, Polyhydroxystearic Acid was determined to have no ocular irritation potential in an in vitro hen's egg-chorioallantoic membrane test (HET-CAM).[9] Additional details were not provided. Further data on the ocular irritation potential of the ingredients reviewed in this safety assessment were not found in the published literature or submitted.

CLINICAL STUDIES

Case Reports

Polylactic Acid

A 30-yr-old woman, a 54-yr-old man, and a 62-yr-old woman, all healthy and with no prior history of cosmetic augmentation, each received repeated treatments with injectable Polylactic Acid (reconstituted with water) to address facial drooping and nasolabial wrinkles due to facial lipoatrophy.[40] No adverse effects were reported in any of the 3 subjects at the 15 mo post-treatment follow-up.

SUMMARY

This report addresses the safety of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid, as used in cosmetic formulations. All 3 of these ingredients are polymers synthesized from hydroxycarboxylic acids. According to the *Dictionary*, these ingredients are reported to function as a non-surfactant dispersing agent, a skin-conditioning agent, and an abrasive, respectively. According to 2022 VCRP data, Polyhydroxystearic Acid and Polylactic Acid are reported to be used in 265 cosmetic formulations and in 18 cosmetic formulations, respectively. The highest concentration of use reported in 2021 for Polyhydroxystearic Acid was 14.2% in lipsticks, and for Polylactic Acid, 5% in skin cleansing products.

Polylactic Acid is approved by the FDA for use in surgical devices such as sutures, ligatures, and meshes and as a food contact substance. The FDA utilizes the Recognized Consensus Standard (ASTM F2579-18), issued by ASTM International in 2019, which set specifications for amorphous Polylactic Acid used in surgical implants.

In a 90-d study, the in vivo degradation of 100 g of [^{14}C]Polylactic Acid implanted in rats was examined. No significant radioactivity was recovered in the feces or urine of the animals during the study period and no significant radioactivity was found in the liver, kidney, lung, heart, brain, spleen, muscles, pouch around the chamber, and contents of implant chamber upon necropsy.

Polylactic Acid film substrates (0.25 cm^2) were not mutagenic to Chinese hamster ovary cell lines in a comet assay or in an in vitro cytokinesis-blocked micronucleus assay, when compared to 0.25 µM doxorubicin or untreated controls. In an in vivo micronucleus test, the incidence of micronucleated polychromatic erythrocytes in mice injected twice, with 50, 100, or 200 ml/kg Polylactic Acid film extracts, were comparable to saline-injected controls; the test article was not considered genotoxic. The genotoxic potential of 95 % Polylactic Acid discs was evaluated in groups of 5 male rats in a micronucleus test following insertion in the calvarium for up to 120 d. No significant decreases in the frequency of polychromatic erythrocytes or increases in micronucleated polychromatic erythrocytes were observed in test animals, compared to untreated controls; the test article was considered non-genotoxic.

In a 24-h occlusive patch test, 0.2 g of a Polylactic Acid extract was not irritating to New Zealand white rabbit skin, when compared to saline controls, or DNFB positive controls. Both rabbits treated with the Polylactic Acid extracts had a primary irritation score of 0 and PII of 0; the test article was deemed non-irritating. Polyhydroxystearic Acid was not irritating or sensitizing when tested neat in an occlusive HRIPT of 51 subjects. A product containing 3.45% Polyhydroxystearic Acid was not irritating or sensitizing when tested neat in a modified Marzulli Maibach HRIPT of 107 subjects. The MII calculated for all subjects during induction was 0. Similarly, a product containing 4% Polylactic Acid was deemed a non-irritant and a non-sensitizer when tested neat in a Marzulli-Maibach HRIPT using 104 subjects. Polyhydroxystearic Acid was determined to have no ocular irritation potential in an in vitro HET-CAM test.

No adverse effects were observed over a 15-mo post-treatment period in a healthy 30-yr-old woman, 54-yr-old man, and a 62-yr-old woman who each received repeated treatments of injectable Polylactic Acid to address facial lipoatrophy.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions, structures, and reported functions of the ingredients in this assessment[1, CIR Staff]

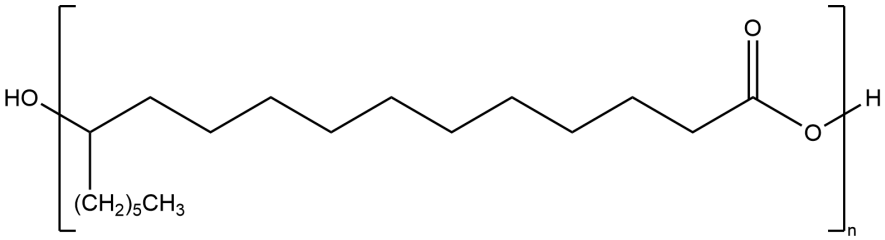
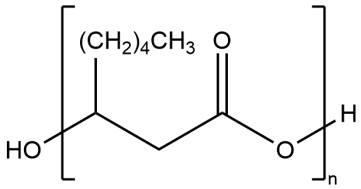
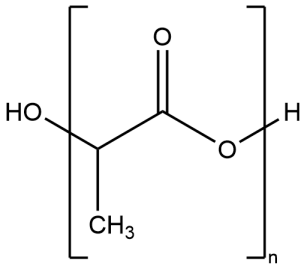
Ingredient	Definition	Function
Polyhydroxystearic Acid 27924-99-8 58128-22-6	Polyhydroxystearic Acid, defined as a polymer of hydroxystearic acid, generally conforms to the structure: 	Dispersing agents - nonsurfactant
Poly(3-Hydroxyoctanoic Acid)	Poly(3-Hydroxyoctanoic Acid) is the polymer of 3-hydroxyoctanoic acid produced through fermentation that conforms generally to the structure: 	Skin-conditioning agents - miscellaneous
Polylactic Acid 9051-89-2 26917-25-9 26811-96-1	Polylactic Acid, defined as a polymer of lactic acid, generally conforms to the structure: 	Abrasives

Table 2. Chemical properties of Polyhydroxystearic Acid and Polylactic Acid

Property	Value	Reference
	Polyhydroxystearic Acid	
Physical Form	Viscous liquid or waxy solid	9
Color (Gardner color standard)	3; yellow	9
Odor	Mild, bland	9
Molecular Weight (g/mol)	1243 (number average) 8243 (weight average)	7
Refractive Index (@ 25 °C)	1.4675	9
Specific Gravity (@ 25 ºC)	0.9333	9
Solubility		9
Soluble	castor oil, mineral oil, isododecane, isopropyl myristate, isononyl isononanoate, pentaerythrityl tetraethylhexanoate	
Insoluble	water, ethanol, propylene glycol, cyclopentasiloxane, dimethicone	
	Polylactic Acid	
Physical Form	Stiff, glassy material	8
Color	colorless	8
Glass Transition Temperature (°C)	55	8
Molecular Weight (g/mol)	53,000 – 800,000	8
Density (g/cm^3)	1.25	8
Solubility		8,10,11
Soluble	benzene, chloroform, furan, 1,4-dioxane, 1,3-dioxolane, pyridine, and tetrahydrofuran	
Insoluble	acetonitrile, alcohols, ethanol, methanol, and water	

Table 3. Frequency (2022)[19] and concentration (2021)[20] of use according to duration and exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Polyhydroxystearic Acid		Polylactic Acid	
Totals*	**265**	**0.014 – 14.2**	**18**	**0.084 - 5**
Duration of Use				
Leave-On	*259*	*0.014 – 14.2*	*13*	*0.084*
Rinse-Off	*6*	*NR*	*5*	*3.5 - 5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	62	0.12 - 8	3	NR
Incidental Ingestion	116	0.4 – 14.2	1	0.084
Incidental Inhalation-Spray	10[a]; 9[b]	0.5; 0.2 -8[a]	5[a]; 1[b]	NR
Incidental Inhalation-Powder	5; 9[b]	0.014 -0.88[c]	1[b]	NR
Dermal Contact	138	0.014 - 10	16	3.5 - 5
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	4	0.5 - 8	1	NR
Hair-Coloring	5	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	116	0.4 – 14.2	2	0.084
Baby Products	2	0.9	NR	NR

*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] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – none reported

Table 4. Ingredient not reported to be in use[19,20]

Poly(3-Hydroxyoctanoic Acid)

Table 5. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
Polylactic Acid film substrates	0.25 cm^2	NR	Chinese hamster ovary cell lines	Comet assay and in vitro cytokinesis-blocked micronucleus assay. Cells were exposed for 24 h to either the Polylactic Acid film, 0.25 µM doxorubicin (positive control), or no treatment (negative controls). The same protocol was used for the micronucleus assay, with the addition of 5 µg/ml cytochalasin-B for an additional 24 h prior to fixing and preparation of slides.	Not genotoxic in both tests	[34]
			IN VIVO			
Polylactic Acid film extracts	0, 50, 100, or 200 ml/kg	fetal bovine serum, containing RPMI-1640 and diluted in saline	Groups of 10 mice	Micronucleus test. Animals received an intraperitoneal injection of saline (control), followed by an injection of the test article, and a 2nd injection of the same treatment 24 h later. Cyclophosphamide (40 mg/kg) was used as the positive control.	Not genotoxic	[35]
95% Polylactic Acid	2 mm-thick, 4-mm diameter disc		Groups of 5 male rats	Micronucleus test. The discs were inserted in the calvarium of 2 groups, one observed for 90 d and the other observed for 120 d, before being killed. No test material was inserted for controls. Both control and treatment groups received the same surgical procedures and pre- and post-operative medications (0.5 mg/100 g ketamine and 0.025 ml/100g xylazine). Bone marrow was extracted and stained on slides to identify the presence of micronucleated polychromatic erythrocytes.	Not genotoxic	[36]

Abbreviations: NR – none reported; RPMI – Roswell Park Memorial Institute

Table 6. Dermal irritation and sensitization studies

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
Polylactic Acid film extracts	0.2 g	New Zealand white rabbits (2/group)	24-h skin irritation test. Fur was removed from the animal backs 24 h prior to the test, and sterile gauze was used to cover the skin area. Either saline, DNFB, or the Polylactic Acid extract were applied to the sterile gauze until it was fully soaked. The gauze was removed after 24 h and the skin condition was observed 1, 24, 48, and 72 h after patch removal. A primary irritation score index value was calculated using the primary skin irritation score for each animal divided by the total number of animals.	Not irritating; both rabbits treated with Polylactic Acid extracts had a primary irritation score of 0 and PII = 0.	[35]
			HUMAN		
Polyhydroxystearic Acid	0.2 g; tested neat	51 subjects	HRIPT; 9 occlusive, 24-h induction applications were made over a 3-wk period. Induction sites were scored 24 h after patch removal. After a 10-14 d non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications. The reactions were scored at 24 and 48 h after application.	Not irritating or sensitizing; no adverse reactions occurred.	[37]
Polyhydroxystearic Acid; 3.45% in a product	0.02 g, , tested neat	107 subjects	Modified Marzulli Maibach HRIPT; 9 occlusive applications were made to a 50 mm^2 area of the back over a 3-wk period. The 1st, 2nd, 4th, 5th, 7th, and 8th applications were made for 48 h, and the 3rd, 6th, and 9th applications were made for 72 h. After a 13-d non-treatment period, a single 48-h challenge application was made to the induction site and a previous untreated site. Reactions were scored on a 0-4 irritation scale between 15 and 35 min of patch removal during both the induction and challenge phases; challenge phase reactions were additionally evaluated 24 h and 48 h after application. An MII was calculated by dividing the sum of the quotations of the 9 induction readings by the number of subjects and readings performed.	Not irritating or sensitizing, MII = 0	[38]
Polylactic Acid; 4% in a product	0.02 ml, tested neat	104 subjects	Marzulli Maibach HRIPT; 9 occlusive, 48-h induction applications were made using 8 mm Finn chambers to the same site over a 3-wk period. Induction sites were evaluated for dermal reactions immediately prior to application of the next patch. After a 10-14 d non-treatment period, challenge applications were made for 48 h to the original test site and a previously untreated site in the same manner as the induction applications. Challenge sites were scored 48, 72, and 96 h after application.	Not irritating or sensitizing	[39]

Abbreviations: DNFB- dinitrofluorobenzene; HRIPT – human repeated patch test; MII – mean irritation index; PII – primary irritation index

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

DATE: April 11, 2022

SUBJECT: Polyhydroxystearic Acid

Phoenix Chemical, Inc. 2022. Pelemol® PHS-8 (INCI: Polyhydroxystearic Acid).

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PHOENIX CHEMICAL, INC. PHOENOMENON
151 Industrial Parkway • Branchburg, NJ 08876 • 908.707.0232 • Fax 908.707.0186 • www.phoenix-chem.com

PELEMOL® PHS-8

(INCI: Polyhydroxystearic Acid)

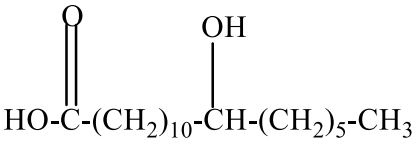
PELEMOL PHS-8 is a100% active, all vegetable derived polyester. It is a viscous, substantive, yellow liquid at ambient temperatures and as with any polymer, will tend to fractionate on cooling. Product clarity and homogeneity is restored on heating and stirring with no adverse effect on the product.

PELEMOL PHS-8 has many nucleophilic sites and, although oil soluble, will complex water via hydrogen bonding on the skin surface. It will, therefore, function as a skin conditioner and humectant. Its substantivity and solubility profile strongly suggests its use in color cosmetics. **PELEMOL PHS-8** also functions as a superior pigment wetting, grinding, and coating agent.

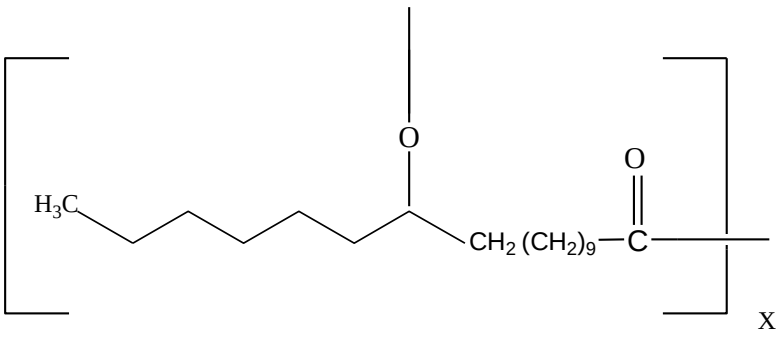
PELEMOL PHS-8 retains single terminal hydroxy and carboxy groups allowing for derivatization into many complex esters which will be the subject of patented technology.

PELEMOL PHS-8 is structurally described as**:**

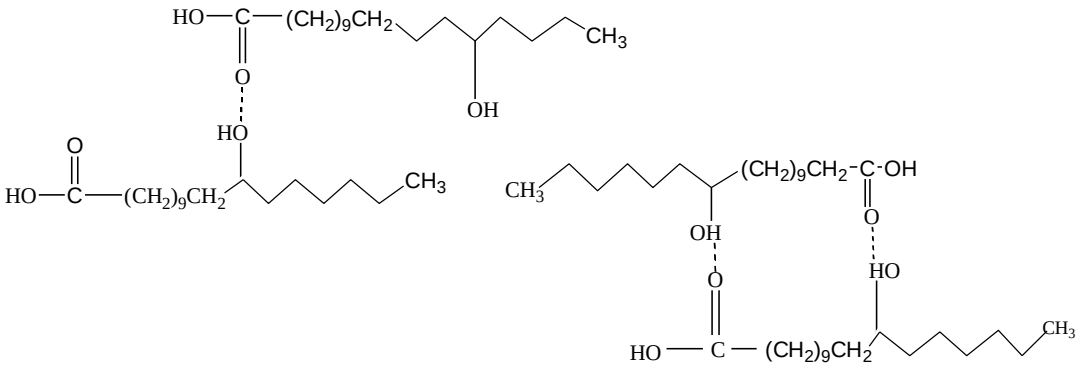
Hydroxystearic Acid



Polyhydroxystearic Acid



Gel Matrix Formation in Polyhydroxystearic Acid



PELEMOL PHS-8 (Polyhydroxystearic Acid) is a true polymeric ester; we can postulate that specific polar sites on the polymer chain will form a film in solution via hydrogen bonding with adjacent molecules to form multi-layered micelles in a polymeric liquid crystals pattern. It is this associative gel matrix formation that accounts for the superior liquid crystal emulsification properties of **PELEMOL PHS-8**.

Trade Name	**PELEMOL PHS-8**
INCI Name	Polyhydroxystearic Acid
CAS #	27924-99-8

APPLICATIONS

PELEMOL PHS-8 can be used in concentrations as much as 50% in lipsticks and its use is highly recommended in:

- Lipsticks
- Foundations
- Eye make-up
- Mascara
- Skin conditioners

TYPICAL PROPERTIES

Appearance @ 25°C	Viscous Liquid or Waxy Solid
Color (Gardner)	3
Odor	Mild, Bland
Acid Value mg KOH/gm	25
Hydroxyl Value mg KOH/gm	10
Refractive Index @ 25°C	1.4675
Specific Gravity @25°C	0.9333

*Product may separate on cooling or long-standing due to its tittering effects. Heat and stir product at 60°C to restore clarity and homogeneity at ambient temperatures before sampling and /or use. This has no adverse effects on the product.

SOLUBILITY

Water	i
Propylene Glycol	i
Ethanol	i
Mineral Oil	m
Isododecane	m
Isopropyl Myristate (Pelemol IPM)	m
Castor Oil	m
Cyclopentasiloxane(D_5)	i
Dimethicone (DC 200 Fluid, 100 cst.)	i
Isononyl Isononanoate (Pelemol IN-2)	m
Pentaerythrityl Tetraethylhexanoate (Pelemol PTO)	m

i= insoluble (at 5%)
m=miscible (soluble in all proportions)

SAFETY

* RIPT study (50 human subjects) when tested under occlusion, provides very favorable results for **PELEMOL PHS-8.**	
*Skin Irritation	NON-PRIMARY SKIN IRRITANT
*Skin Sensitization	NON-PRIMARY SKIN SENSITIZER

PELEMOL PHS-8 CAN BE DESCRIBED AS HYPOALLERGENIC

* Study conducted by AMA Labs., 216 Congers Rd. New City, NY 10956

Eye Irritation
** A HET-CAM study concluded that **PELEMOL PHS-8** has practically no ocular irritation potential.

** Study conducted by Consumer Product Testing Co., 70 New Dutch Lane, Fairfield, NJ 07004

02/09/2022

PHOENIX CHEMICAL, INC.
151 INDUSTRIAL PARKWAY • BRANCHBURG, N.J. 08876 • TEL: (908) 707-0232 • FAX: (908) 707-0186
www.phoenix-chem.com

10/22/2021

Re: PELEMOL PHS-8

Molecular weight or low molecular fraction:

1. Number average Molecular Weight (MW) is 1,243 Da.
2. Weight Average Molecular Weight (MW) is 8,243Da.
3. 20% of the molecular weight is less than 1,000 Da, attributable to Oligomers.

Signed on behalf of (company): **PHOENIX CHEMICAL INC.**

Signature:	
Name (Please Print):	Rolguens Saturne
Position:	Director Regulatory Affairs
Date:	10/22/2021

AMA LABORATORIES, INC.
216 Congers Road, Bldg. 5
New City, NY 10956-6261 USA
(845) 634-4330
Fax: (845) 634-5565
www.amalabs.com

50 HUMAN SUBJECT REPEAT INSULT PATCH TEST SKIN IRRITATION/SENSITIZATION EVALUATION (OCCLUSIVE PATCH)

Date: October 16, 2003

AMA Ref. No.: MS03.RIPT.K6377O.50.PCI

Sponsor: Phoenix Chemical, Inc.
60 Fourth Street
Somerville, New Jersey 08876

1.0 Objective:

Consumer products or raw materials designed for consistent reapplication to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certain individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/ sensitization potential if such exists.

2.0 Reference: The method is modified to test 50 panelists not the 200 cited in the reference Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, published by The Association of Food and Drug Officials of The United States. The method also employs nine inductive patchings and not the ten cited in the reference.

3.0 Test Material:

3.1 Test Material Description: Poly hydroxy stearic Acid

On September 4, 2003 two test samples labeled as PELEMOL PHS-8, Lot # B01893 and B02173 were received from Phoenix Chemical, Inc. and assigned Lab. Nos. K-6377 and K-6378.

3.2 Handling:

Upon arrival at AMA Laboratories, Inc., the test material is assigned a unique laboratory code number and entered into

a daily log identifying the lot number, sample description, sponsor, date received and tests requested.

Samples are retained for a period of three months beyond submission of final report unless otherwise specified by the sponsor or, if sample is known to be in support of governmental applications, representative retained samples are kept two years beyond final report submission.

Sample disposition is conducted in compliance with appropriate federal, state and local ordinances.

3.3 Test Material Evaluation Prerequesite:

Prior to induction of a human test panel, animal toxicology, microbiology and other in-vivo or in-vitro performance spectra may be required to assess the feasibility of commencement as dictated by an Institutional Review Board (IRB) described in Section 4.0.

3.31 Sponsor purports that prior to sample submission to AMA the following tests were conducted with no adverse results and that the test data are on file on their premises and have not been made available to AMA personnel:

- CTFA Preservative Efficacy Test of equivalent
- 90 Day Accelerated Stability and Container Compatability Study

4.0 Instututional Review Board:

Reference: CTR Title 21 Part 56, Subparts A, B, C, and D. The IRB of AMA Laboratories, Inc., consists of five or more individuals, chosen from within the company for technical expertise and from the local community for lay interaction. The list of IRB members is kept on file at AMA Laboratories, Inc. and is available for inspection during the hours of operation.

5.0 Panel Selection:

5.1 Standards for Inclusion in a Study:

-Individuals who are not currently under a doctor's care.
-Individuals free of any dermatological or systemic disorder which would interfere with the results, at the discretion of the Investigator.

-Individuals free of any acute or chronic disease that might interfere with or increase the risk of study participation.
-Individuals who will complete a preliminary medical history form mandated by AMA Laboratories, Inc. and are in general good health.
-Individuals who will read, understand and sign an informed consent document relating to the specific type of study they are subscribing. Consent forms are kept on file and are available for examination on the premises of AMA Laboratores, Inc. only.
-Individuals able to cooperate with the Investigator and research staff, be willing to have test materials applied according to the protocol, and complete the full course of the study.

5.2 Standards for Exclusion from a Study:

-Individuals under 18 years of age.
-Individuals who are currently under doctor's care.
-Individuals who are currently taking any medication (topical or systemic) that may mask or interfere with the test results.
-Subjects with a history of any acute or chronic disease that might interefe with or increase the risk associated with study participation.
-Individuals diagnosed with chronic skin allergies.
-Female vounteers who indicate that they are pregnant or nursing.

5.3 Recruitment:

Panel selection is accomplished by advertisements in local periodicals, community bulletin boards, phone silicitation, electronic media or any combination thereof.

5.4 Informed Consent and Medical History Forms:

An informed consent was obtained from each volunteer prior to initiating the study describing reasons for the study, possible adverse effects, associated risks and potential benefits of the treatment and their limits of liability. Panelists signed and dated the informed consent document to indicate their authorization to proceed and acknowledge their understanding of the contents. Each subject was assigned a permanent identification number and completed an extensive medical history form. These forms along with the

signed consent forms, are available for inspection on the premises of AMA Laboratories, Inc. only. Reference 21 CFR Ch. 1 Part 50, Subpart B.

The parties agree to comply with applicable state and federal privacy laws for the use and disclosure of a subject's personal health information by taking reasonable steps to protect the confidentiality of this information. This obligation shall survive the termination or expiration of this Agreement.

6.0 Population Demographics:

Number of subjects enrolled		59
Number of subjects completing study		51
Age Range		18– 74
Sex	Male	8
	Female	51
Race	Caucasian	42
	Hispanic	15
	Asian	0
	Black	2

7.0 Equipment:

-Patch Description: Parke-Davis Hypoallergenic Readi Bandages (20 x 20 mm Webril affixed to the center of a 40 x 40 mm adhesive bandage) or the equivalent.
-1 ml volumetric syringe without a needle.

8.0 Procedure:

-Subjects are requested to bathe or wash as usual before arrival at the facility.
-0.2 ml or 0.2 g of the test material is dispensed onto the occlusive, hypoallergenic patch.
-The patch is then applied directly to the skin of the infrascapular regions of the back, to the right or left of the midline and the subject Is dismissed with instructions not to wet or expose the test area to direct sunlight.
-After 24 hours the patch is removed by the panelist at home.This procedure is repeated until a series of nine consecutive 24 hour exposures have been made for every Monday, Wednesday and Friday for three consecutive weeks.
-In the event of an adverse reaction, the area of erythema and edema is measured. The edema is estimated by the evaluation of the skin with respect to the contour of the unaffected normal skin. Reactions are scored just before

applications two through nine and the next test date following application nine. In most instances this is approximately 24 hours after patch removal. Clients are notified immediately in the case of adverse reaction and determination is made as to treatment program if necessary.

- Subjects are then given a 10 - 14 day rest period after which a challenge or retest dose is applied once to a previously unexposed test site. The retest dose is equivalent to any one of the original nine exposures. Reactions are scored 24 and 48 hours after application.
- Comparison is made between the nine inductive responses and the retest dose.

9.0 Results:

Please refer to attached Tables.

10.0 Observations:

No adverse reactions of any kind were noted during the course of this study.

11.0 Archiving:

All original samples, raw data sheets, technician's notebooks, correspondence files and copies of final reports and remaining specimens are maintained on premises of AMA Laboratories, Inc. in limited access storage files marked "Archive". A duplicate disk copy of final reports is separately archived ina bank safe deposit vault.

12.0 Conclusions:

The test materials listed below when tested under occlusion as described herein, may be considered as **NON-PRIMARY IRRITANTS** and **NON-PRIMARY SENSITIZERS** to the skin according to the reference.

AMA Lab No.	Sample Description
K-6377	PELEMOL PHS-8, Lot # B01893
K-6378	
K-6382	

Howard L. Kaminsky, M.S., R. Ph.
Study Director

Diana Steixner, A.A.S.
Technician

Mary Ellen Perez
Technician

David R. Winne, B.S.
Quality Assurance Supervisor

10/16/03
Date

TABLE 1
SUMMARY OF RESULTS
(OCCLUSIVE PATCH)

AMA Lab. No.: K-6377
Client No.: PELEMOL PHS-8, Lot # B01893

No.	Subject ID	RACE	SEX	Response 1	2	3	4	5	6	7	8	9	Chall. 24 HR	Chall. 48 HR	Score
1	54 9626	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
2	64 5370	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
3	30 0199	C	F	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
4	44 1039	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
5	48 3054	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
6	48 1553	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
7	58 1279	C	F	0	0	0	0	0	0	Dc	Dc	Dc	Dc	Dc	N/A
8	60 3986	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
9	74 0522	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
10	64 6364	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
11	46 7887	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
12	60 0557	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
13	52 3850	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
14	26 0599	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
15	54 0175	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
16	55 9599	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
17	60 9426	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
18	68 7038	C	F	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
19	66 1030	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
20	56 7499	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
21	79 8021	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
22	70 1497	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
23	64 7579	B	F	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
24	62 7366	C	F	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
25	38 7924	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
26	34 1401	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
27	28 1559	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
28	25 8548	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
29	40 5828	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
30	28 5301	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
31	58 4587	B	F	0	0	0	0	0	0	0	0	0	0	0	0.0
32	32 4178	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0

TABLE 1 (CONT'D)
SUMMARY OF RESULTS
(OCCLUSIVE PATCH)

AMA Lab. No.: K-6377
Client No.: PELEMOL PHS-8, Lot # B01893

No.	Subject ID	RACE	SEX	Response									Chall.		Score
				1	2	3	4	5	6	7	8	9	24 HR	48 HR	
33	52 3393	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
34	56 6594	C	F	0	0	0	0	0	0	0	0	0	Dc	Dc	N/A
35	80 2120	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
36	34 7142	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
37	46 3564	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
38	34 7962	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
39	26 0992	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
40	54 1935	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
41	36 8248	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
42	36 4212	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
43	40 2487	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
44	54 4669	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
45	38 0044	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
46	68 1557	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
47	48 3275	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
48	98 7654	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
49	68 4139	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
50	36 0202	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
51	22 4828	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
52	11 5901	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
53	72 6778	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
54	27 7158	H	F	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
55	32 0178	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
56	72 2622	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
57	54 6626	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
58	32 3937	C	F	0	0	0	0	0	Dc	Dc	Dc	Dc	Dc	Dc	N/A
59	58 3527	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0

Evaluation Period:

This study was conducted from September 10, 2003 through October 15, 2003.

Scoring Scale And Definition Of Symbols Shown In Tables:

0 -No evidence of any effect

? -(Barely perceptible) minimal faint (light pink) uniform or spotty erythema

1 -(Mild) pink uniform erythema covering most of 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

D -Patch eliminated due to severe reaction

Dc -Discontinued due to absence of subject on application date

M -Patch applied to an adjacent site after strong test reaction

NA -Score is not calculated for subjects discontinued before challenge

S -Skin stained from pigment in product

T - Tan

NOTE: All technical employees of AMA LABORATORIES, INC. are required to take and pass a visual discrimination examination conducted by a Board Certified Ophthalmologist using the Farnsworth-Munsell100 Hue Test as published; which determines a person's ability to discern color against a black background. This test was additionally modified to include a flesh tone background more nearly approaching actual use conditions, wherein erythematous skin is graded according to intensity.

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: April 15, 2022

SUBJECT: Polylactic Acid and Polyhydroxystearic Acid

Anonymous. 2014. Repeated insult patch test (RIPT) - Marzulli Maibach method (product contains 4% Polylactic Acid).

Anonymous. 2021. Modified Marzulli-Maibach protocol - Human repeated insult patch test with challenge (product contains 3.45% Polyhydroxystearic Acid).

[redacted]

Report Status: Final Report
Report Date: July 14, 2014

[redacted]

product contains 4% Polylactic Acid

This report consists of 16 pages including appendices.

Study Title: Repeated Insult Patch Test (RIPT) – Marzulli Maibach Method

Study Dates: May 19, 2014 – June 27, 2014

Sponsor: [redacted]

Investigational Product:

Attention:

Principal Investigator/
Dermatologist:

Investigating Laboratory:

[redacted]

7/15/14
Date

7/15/14
Date

7/14/14
Date

[redacted]

Table of Contents

[redacted]

[redacted]

1.0 SUMMARY

This study was initiated with 112 subjects. Eight subjects discontinued study participation for reasons unrelated to the investigational product. A total of 104 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I. No clinically significant dermal reactions were observed during the study.

Based on the test population of 104 subjects and under the conditions of this study, the investigational product identified as [redacted] did not demonstrate a potential for eliciting dermal irritation or inducing sensitization.

2.0 INTRODUCTION

Repeated insult patch evaluation is a predictive patch study that can detect weak sensitizers requiring 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.

3.0 PURPOSE

The purpose of this study was to confirm that the application of a cosmetic product to the back of volunteer subjects, under maximized conditions of exposure, does not induce delayed contact sensitization. This study was carried out on a cosmetic product whose safety had been assessed by a toxicologist, with the aim to further confirm safety of this product which will be used by a large number of consumers under normal and reasonably foreseeable use conditions.

4.0 STUDY MATERIALS

4.1 INVESTIGATIONAL PRODUCT

[redacted]

[redacted]

[redacted]

4.2 TYPE OF PATCH

Occlusive Finn Chamber (manufactured by Allerderm, Phoenix, AZ or equivalent) formed of an aluminum cup (8 mm), which provides an isolation chamber for the investigational product, on Scanpore occlusive tape.

4.3 INVESTIGATIONAL PRODUCT APPLICATION

A measured dose of approximately 0.02 ml of the investigational product was applied to the occlusive patch (Finn Chamber).

5.0 STUDY DATES

This study was initiated on May 19, 2014 and was completed on June 27, 2014.

6.0 SUBJECT SELECTION

A subject was eligible for enrollment provided the following criteria were met.

6.1 INCLUSION CRITERIA

a) Male and female subjects between the ages of 18 and 70 years;

b) Subjects who do not exhibit any skin disease which might be confused with a skin reaction from the investigational product;

c) Subjects willing to avoid exposing the test sites to excessive sun or moisture;

d) Subject agrees to refrain from getting patches wet during the course of the study (including participating in sports which may induce excessive perspiration);

e) Subjects willing to sign an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

f) Subjects who have completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

g) Subjects in generally good health who have a current Subject Profile/Medical History on file;

h) Subjects who are dependable and able to follow directions as outlined in the protocol.

[redacted]

[redacted]

6.2 NON-INCLUSION CRITERIA

a) Subjects that are known to be pregnant or nursing or plan to become pregnant during the test period;

b) Subjects reporting allergies to adhesives, cosmetics, toiletries or personal care products;

c) Subject has received excessive or intensive sun exposure within one month prior to study initiations;

d) Subject is currently participating in another clinical study;

e) Subject is an employee of [redacted]

f) Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

g) Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

6.3 SUBJECT IDENTIFICATION

All subjects were initially identified by a permanent [redacted] identification number. Subjects who met the qualification criteria were assigned a study subject number. This subject number was assigned in sequence as subjects were enrolled in the study. A master roster was kept of the permanent [redacted] identification number and the corresponding study subject number.

7.0 INFORMED CONSENT

The study procedures were explained to all subjects intending to participate. All subjects were completely informed about pertinent details and purpose of the study, according to the informed consent guidelines. Subjects were given the opportunity to ask any questions. Two copies of an Informed Consent Form were read and signed by each subject prior to study initiation. The Investigator (or designee) signed and dated the consent form attesting that the requirements for informed consent had been satisfied. One copy was given to the subject and the other was retained in the study folder.

8.0 TEST METHOD

At the first visit, inclusion/non-inclusion criteria were verified and Informed Consent obtained. The back of each subject was examined for the absence of irritation, sunburn, scars, and excessive tattoos. Qualified subjects were enrolled for participation. Prior to

[redacted]

[redacted]

the application of the patch, the test area was wiped with distilled water and allowed to dry. The investigational product, which was prepared as described in Section 4.1, was applied to the upper back, between the scapulae and the waist, lateral to the midline.

The investigational product was applied to the same site three times per week (Monday, Wednesday, and Friday) for a total of nine applications. However, the schedule may have been modified to accommodate inclement weather, holidays, or missed applications. At the discretion of the Study Manager, the investigational product may have been applied on two consecutive days during the Induction Phase or a makeup day may have been added at the end of the Induction Phase.

Each site was marked with a gentian violet surgical marker to ensure the continuity of patch application. The patches were removed by a [redacted]clinician after 48 hours, with the exception of patches applied on Friday. Friday patches were removed by the subject, after approximately 48 hours, on Sunday. Each site was evaluated for dermal reactions just prior to the application of the next patch, according to the dermal scoring system (Section 9.0). The schedule of patch applications/dermal grading is presented below:

Procedure	Visit													
	Induction Phase										Challenge Phase			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Patch Application	X	X	X	X	X	X	X	X	X		X			
Dermal Grading of Test Site		X	X	X	X	X	X	X	X	X		X	X	X

If at any time during the Induction Phase of the study a test site was observed to exhibit an evaluation score of "++" or greater, the application of investigational product to this site was moved to an adjacent virgin site, and, at the discretion of the Study Manager, the patch type and/or test condition may have been changed. The new adjacent site, referenced as an alternate site, was scored for all Induction Phase study visits subsequent to a 48-hour investigational product exposure at the alternate site. The original patch application location was evaluated and scored until the reaction resolved and/or until the final study visit. At the discretion of the Study Manager, patch sites with scores less than a ++ may have been changed to a new test site location.

If a "++" reaction or greater occurred on the changed site, patching with the investigational product was discontinued for the remainder of the Induction Phase, but the subject was challenged on the appropriate day of the study.

At the discretion of the Study Manager, any subject exhibiting a significant reaction at the beginning of the Induction Phase may have been classified as "pre-sensitized" to an ingredient(s) contained in the investigational product and may have been discontinued from further patching of the investigational product.

[redacted]

[redacted]

During the course of the study, all sites graded a "+" or greater were confirmed by a second clinician.

Approximately 10 to 14 days following the Induction Phase, challenge patches were applied to the original test site and a virgin site on the back, following the same procedure described for the Induction Phase. Alternate test sites, which were assigned during the Induction Phase for patch type changes, were also patched during the Challenge Phase with the same patch type as for the Induction Phase. After 48 hours, patches on the original and virgin sites were removed by a [redacted] clinician, and the sites were evaluated and scored. Subjects were required to return for additional evaluations of the test sites at 72 and 96 hours after application.

9.0 DERMAL SCORING

All test sites were evaluated and scored according to the following grading system during the Induction and Challenge Phases of the study:

Dermal Score		
-	=	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

10.0 TEST RESULTS

10.1 SUBJECT NUMBERS

This study was initiated with 112 subjects. Eight subjects discontinued study participation for reasons unrelated to the investigational product:

Subject #	Reason for Discontinuation
1	Lost to follow up
3	Lost to follow up
60	Lost to follow up
66	Withdrew Consent
89	Schedule conflict
96	Lost to follow up
98	Lost to follow up
105	Schedule conflict

One subject (#55) missed the 9th Induction reading. A total of 104 subjects completed the study.

[redacted]

[redacted]

10.2 DEMOGRAPHY

A total of 112 male and female subjects between the ages of 19 and 70 years were enrolled for participation. A summary of demographic information appears below:

Age		Gender	
Mean Age	51.08	Females	85 (76%)
St. Dev.	12.32	Males	27 (24%)
Min.	19		
Max.	70		

10.3 DERMAL ASSESSMENTS

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I. No clinically significant dermal reactions were observed during the course of the study.

10.4 ADVERSE EVENTS

There were no adverse events reported during the course of the study.

10.5 PROTOCOL AMENDMENTS

No protocol amendments were issued during the course of the study.

10.6 PROTOCOL DEVIATIONS

The following deviation occurred during the study:

- Subject #55 did not return for the 9th Induction evaluation

This deviation did not affect the safety of the subject and had no impact on the scientific validity or outcome of the study. Since although the subject was not scored; the subject received 9 induction patches. The subject was re-instructed in the importance of keeping all study appointments.

[redacted]

[redacted]

11.0 CONCLUSION

Based on the test population of 104 subjects and under the conditions of this study, the investigational product identified as [redacted] did not demonstrate a potential for eliciting dermal irritation or inducing sensitization.

12.0 RECORD AND INVESTIGATIONAL PRODUCT RETENTION

All study records and remaining investigational products will be retained at the following location:

[redacted]

All study documents will be retained on file at [redacted] for a period of ten years. Documents will be shredded after the retention period has expired upon written agreement from the Sponsor. Alternatively, original study documentation will be returned to the Sponsor if written notification of the request is received after study conclusion and subject to fees associated with the preparation and mailing of documents to the Sponsor.

All unused investigational products will be retained by [redacted] for a period of 6 months and then destroyed according to [redacted] Standard Operating Procedures.

13.0 REFERENCES

Marzulli, F. N. and Maibach, H. I. 1973. *Antimicrobials: Experimental contact sensitization in man. J. Soc. Cosmet. Chem.* 24:399-421

Marzulli. F. N. and Maibach, H. I. 1974a. *Status of topical parabens: Skin hypersensitivity. Int. J. Dermatol.* 13:397-399

Marzulli, F. N. and Maibach, H. I. 1974b. The use of graded concentrations in studying skin sensitizers: Experimental contact sensitization in man. *Food Cosmet. Toxicol. 12:219-227. Human Patch Tests, Proc. Sci. Sect. Toilet Goods Assoc.*, 19:46-49, 1953.

[redacted]

[redacted]

TABLE I
Tabulation of Individual Scores

Investigational Product :	[redacted]

	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
Subject Number	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
1	-	-	-	-	Discontinued										
2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-	Discontinued													
4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
26	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

[redacted]

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Investigational Product :	[redacted]

	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
Subject Number	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
31	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
32	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
35	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
36	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
37	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
38	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
39	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
40	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
43	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
45	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
47	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
49	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
51	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
52	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
53	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
54	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
55	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-
56	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
57	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
58	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
59	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
60	-	-	-	-	-	Discontinued									

O = Original Site
V = Virgin Site
X = Subject Absent

[redacted]

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Investigational Product :	[redacted]

	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
Subject Number	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
61	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
62	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
64	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
66	-	Discontinued													
67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
68	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
69	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
70	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
71	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
73	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
74	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
75	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
76	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
77	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
78	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
79	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
80	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
81	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
82	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
83	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
84	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
85	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
86	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
87	-	-	-	-	-	-	-	-	-	-	-	-	?	-	-
88	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
89	-	-	Discontinued												
90	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

[redacted]

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Investigational Product :	[redacted]

	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
Subject Number	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
91	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
92	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
93	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
94	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
95	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
96	Discontinued														
97	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
98	-	-	-	-	-	-	-	Discontinued							
99	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
100	-	-	-	-	-	?	-	-	-	-	-	-	-	-	-
101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
105	-	Discontinued													
106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
108	-	-	-	-	-	-	-	-	-	-	-	-	?	-	-
109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

[redacted]

[redacted]

[redacted]

[redacted]

REPORT: SENSITIZATION AND CUTANEOUS COMPATIBILITY STUDY

[redacted]

MODIFIED MARZULLI-MAIBACH PROTOCOL – HUMAN REPEATED INSULT PATCH TEST WITH CHALLENGE
TCFS PSC

product contains 3.45% Polyhydroxystearic Acid

INVESTIGATIONAL PRODUCT	:	[redacted]
PROTOCOLS	:	[redacted]
REPORT	:	[redacted]
BEGINNING OF THE OBSERVATIONS	:	19 January 2021
END OF OBSERVATIONS	:	06 March 2021

SAFETY ASSESSOR	DEPUTY TECHNICAL AND SCIENTIFIC MANAGER	DERMATOLOGISTS
[redacted]		

[redacted]

[redacted]

TABLE OF CONTENTS

AUTHENTICATION

The study subject of the present report was conducted under my responsibility, in compliance with standard and specific study protocols, in accordance with [redacted] and in the spirit of the general principles of the Good Clinical Practices (ICH Topic E6 (R2): EMA/CPMP/ICH/135/1995).

I assume the responsibility of the validity of all raw data obtained during this study and mentioned in the present report.

[redacted]

I have read this report, I certify that these data are an accurate reflection of the results obtained and I agree with its content.

[redacted]

[redacted]

SUMMARY OF THE REPORT

SPONSOR: [redacted] INVESTIGATIONAL PRODUCT:

SENSITIZATION AND CUTANEOUS COMPATIBILITY STUDY

MODIFIED MARZULLI-MAIBACH PROTOCOL – HUMAN REPEATED INSULT PATCH TEST WITH CHALLENGE
TCFS PSC

INTRODUCTION	The study consists in the repeated dermal application of the investigational product to healthy human volunteer subjects under conditions which exaggerate the normal conditions of product use. It is carried out on cosmetic product whose safety had been assured by a toxicologist, with the aim to further confirm safety of this product which will be used by a large number of consumers under normal and reasonably foreseeable use conditions. The maximization of exposure under the test conditions (occlusion, extended contact time etc.) makes it possible to identify substances whose weak allergenic potential may be expressed only in the finished product matrix.
STUDY OBJECTIVES	The main objective of the study is to confirm that the application of a cosmetic product, to healthy volunteer subjects, under maximized conditions of exposure, does not induce delayed contact sensitization. Secondarily, skin compatibility of the product may be evaluated during the study.
STUDY RELEVANCE	Cutaneous allergy is an individual phenomenon, of immune origin, which setting off requires 3 phases (penetration of the foreign substance into the skin and formation of the allergen; development of the immune reaction; activation of the reaction, by a new application of the allergenic molecule to the skin). These 3 phases are thus required to check, in 50 or 100 subjects, the absence of delayed cutaneous sensitizing potential of a finished cosmetic investigational product, and are the basis of the method described by Marzulli and Maibach *(protocol in conformity to note dated 4 August 1997 of the French "Répression des Fraudes" to the "Fédération Française des Industries de la Parfumerie" and performed in compliance with the general principles of the AFSSaPS recommendations of December 2008 on the Final Clinical Safety Test - TCFS PSC)*.

INCLUSION CRITERIA SPECIFIC TO THE STUDY *(in addition to the criteria given in the standard study protocol)*	To be eligible, each subject must satisfy all the criteria written in the standard study protocol [redacted] and the specific following ones: . *Number of subjects:* 100 subjects divided in two panels of 50 subjects receiving each 10 investigational products (the product distribution being indicated in the application scheme of the Case Report Form). . *Selection of subjects:* exclusive selection of 100 valid cases (a valid case will be defined as a subject who respects the following: . Application of the investigational product all along the study in respect with the frequency . Subject participation to all visits and clinical examinations as requested in the study protocol . Absence of any concomitant treatment interfering with the results of the study, according to the Investigator However, a subject who has presented with significant reactions (moderate erythema and/or infiltration and/or papules and/or vesicles) twice during the induction phase, inducing a stop of application, but who received the challenge phase application after decision of the Dermatologist Investigator and the Sponsor, will be considered as a valid case even though he had not followed the previous procedure.)
NON-INCLUSION CRITERIA SPECIFIC TO THE STUDY (*in addition to the criteria given in the standard study protocol*)	To be eligible, each subject must not meet any criterion written in the standard protocol cited above.
METHODOLOGY	**- Modes of application:** . *area*: back . *quantity*: 0.02 g over a 50 mm² surface (occlusive patch: Small Finn Chambers on Scanpor). . *conditions of application*: investigational product as supplied, under occlusive patch (Finn Chambers on Scanpor) or semi-occlusive (Strukmyer Medical, U.S.A.) if reactions occurred during the induction period. . *frequency and duration*: . *induction phase*: 9 applications spread out over 3 weeks as follows: 1st week: Day 0 (Tuesday: 1st application), Day 2 (Thursday), Day 4 (Saturday), 2nd week: Day 7 (Tuesday), Day 9 (Thursday), Day 11 (Saturday), 3rd week: Day 14 (Tuesday), Day 16 (Thursday), Day 18 (Saturday) Duration of exposure: 48 ± 4 hours for the 1st, 2nd, 4th, 5th, 7th and 8th applications and 72 ± 4 hours for the week-ends (3rd, 6th and 9th applications). . *rest phase*: the subjects are not submitted to any application from Day 22 (Wednesday) to Day 34 (Monday) inclusive, i.e. for a 13-day period. . *challenge phase*: single application on 2 sites (virgin and induced sites) on Day 35 (Tuesday) for 48 ± 4 hours. *N.B.: the patches are removed by the Laboratory staff or by the subject at home.*

METHODOLOGY *(con't)*	- **Modes of evaluation:** - *Clinical observations*: readings performed, according to the Sponsor's specificities (D2, D37 and D39), by the Dermatologist Investigator: . *Induction phase:* between 15 and 35 min, after removal of the patches . *"challenge" phase:* between 15 and 35 min, 24 ± 3 hours (in case of reaction (erythema score ≥ 2) during previous reading), as well as 48 ± 4 hours, after removal of the patches or more if this is necessary in order to fully evaluate observed reactions. - *Grading*, according to a given numerical scale (irritation scale: 0 to 4 & scale of the International Contact Dermatitis Research Group (I.C.D.R.G.): 0 to 3 [+++]).
ANALYSIS OF THE RESULTS AND EVALUATION CRITERIA	- *Determination of the Mean Irritation Index (M.I.I.):* equal to the sum of the quotations of the 9 readings of the induction phase divided by the number of subjects and of readings performed. - *Interpretation of the results obtained,* under the experimental conditions adopted: . **for cumulative irritation**: evaluated from the irritative (erythema) reactions observed (number, intensity, and frequency). Classification of the investigational product ("non-irritant" to "severely irritant") and comparison to that established for a selected reference product, to the untreated control site or with the results of the [redacted] internal database. . **for the delayed cutaneous sensitizing potential**: A site where erythema is graded 2 or more during the "challenge" phase, with or without palpable lesions, must be evaluated on subsequent days to note whether the reaction decreases or increases in order to better differentiate between an allergic and an irritant reaction. A rapidly decreasing reaction is indicative of irritation (decrescendo reaction). A reaction with infiltration/oedema that persists and/or increases over time usually indicates an allergic reaction (crescendo reaction), and additional studies ("rechallenge" and/or R.O.A.T.: Repeated Open Application Test) could be performed 3 to 6 weeks after the first appearance of the challenge reaction and after all reactions have ceased. . Also on the basis of the type of investigational product and the [redacted] statistics (positioning of the cumulative irritation and/or sensitisation in comparison with investigational products of the same type).

RESULTS AND CONCLUSION

STUDIED POPULATION

Number of subjects recruited	146
Number of subjects who came to [redacted]	107
Number of subjects not included by the Dermatologist Investigator	0
Number of subjects included by the Dermatologist Investigator	107
Number of subjects discontinued from the study . before the 1st reading . during the induction phase . during the rest phase . during the challenge phase	3 0 2 (n° 28 and n° 39) 0 1 (n° 34)
- Non related adverse event - Non related serious adverse event - Related adverse event - Related serious adverse event - Concomitant treatment(s) incompatible with the study - Consent withdrawal by the subject - Lost to follow up - Emergence of a non-inclusion criterion - Decision of the Dermatologist Investigator - Violation of the protocol	1 (n° 28) 0 0 0 0 1 (n° 34) 0 0 0 1 (n° 39)
Number of subjects for the analysis of the results . for the evaluation of Primary Irritation . for the evaluation of Cumulative Irritation . for the evaluation of Delayed Cutaneous Sensitization	 107 105 104

The physical characteristics of the subjects are summarized in the following table:

Subjects	Primary Irritation	Cumulative Irritation	Cutaneous Sensitization
Number	107	105	104
Females	76	75	74
Males	31	30	30
Age minimum	19	19	19
Age maximum	64	64	64

RESULTS

Percentage of subjects having presented with one or several slight to severe irritation reactions (score ≥ 2), during the induction	0%
Mean Irritation Index (M.I.I.) of the induction Classification of the investigational product	0 ■ non-irritant □ slightly irritant □ moderately irritant □ very irritant □ severely irritant
Percentage of the sensitisation reactions observed	0%
Reactions considered as serious adverse events linked to the investigational product	0%

No pathological irritation or sensitization reaction significant of a cutaneous intolerance was noted.

The Mean Irritation Index (M.I.I.), obtained during the induction was equal to **0**, and compared to the one obtained with the control (patch alone, without any investigational product) applied under the same conditions, thus enabled to classify arbitrarily the applications of these investigational products as "**non-irritant**".

CONCLUSION

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of the investigational product designated as [redacted], under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitization.

[redacted]

1. INTRODUCTION

The study consists in the repeated dermal application of the investigational product to healthy human volunteer subjects under conditions which exaggerate the normal conditions of product use. It is carried out on cosmetic product whose safety has been assured by a toxicologist, with the aim to further confirm safety of this product which will be used by a large number of consumers under normal and reasonably foreseeable use conditions.
The maximization of exposure under the test conditions (occlusion, extended contact time etc.) makes it possible to identify substances whose weak allergenic potential may be expressed only in the finished product matrix.

2. STUDY OBJECTIVE

The main objective of the study is to confirm that the application, of cosmetic product, to healthy volunteer subjects, under maximized conditions of exposure, does not induce delayed contact sensitization.

Secondarily, skin compatibility of the product may be evaluated during the study.

3. STUDY RELEVANCE

Cutaneous allergy is an individual phenomenon, of immune origin, which triggering requires 3 phases:
. penetration of the foreign substance (hapten) into the skin and formation of the allergen;
. development of the immune reaction;
. triggering of the reaction, by a new application of the allergenic molecule to the skin.
These 3 phases are thus required to check the absence of sensitizing potential of an investigational product, and are at the root of the method described by Marzulli and Maibach *(protocol in compliance with the note of 4 August 1997 of the "Répression des Fraudes" à la "Fédération Française des Industries de la Parfumerie" and performed in compliance with the general principles of the AFSSaPS recommendations of December 2008 on the Final Clinical Safety Test - TCFS PSC):* repeated applications of the investigational product, by occlusive epicutaneous route, for 48 ± 4 or 72 ± 4 hours and for 3 consecutive weeks (induction phase), followed by a rest phase and by a new application under occlusion, for 48 ± 4 hours (challenge phase, during which cutaneous macroscopic examinations are performed according to the International Contact Dermatitis Research Group scale: I.C.D.R.G.).

The realisation of this study under medical control, on a limited number of people thus enables to complete the data relative to the safety of a product by studying it under maximized exposure conditions.

4. PRINCIPLE

- Induction phase: during which the "preparing" or "sensitizing" contacts between epidermis and investigational product may occur, which will possibly induce the allergical process without showing evidence of any clinical manifestation of hypersensitivity:

. 9 consecutive applications, to the same area, of about 0.02 g, per subject, of the investigational product, by occlusive epicutaneous route (Finn Chambers on Scanpor) or semi-occlusive epicutaneous route (Strukmyer Medical, U.S.A.) if reactions occur, for 48 ± 4 hours or 72 ± 4 hours for the first 3 week-ends, to the skin of the back of healthy adult subjects, of both sexes.

- Rest phase: or incubation period during which the cells' transformations possibly go on, leading to the modification of reactivity:

. 13 days without any application.

- "Challenge" phase: corresponding to the contact between the epidermis and the investigational product applied during the induction phase and which aim is to reveal a clinical manifestation of induced immunological hypersensitivity:

. single application of about 0.02 g, per subject, of the investigational product, by occlusive epicutaneous route (Finn Chambers on Scanpor) for 48 ± 4 hours, on 2 areas on the skin of the back of the subjects (i.e., the same area as the one used for the induction and on an untreated symmetrical area).

The cutaneous reaction, control of the primary and cumulative irritations, is evaluated by the macroscopic examination of the reactions possibly observed between 15 and 35 minutes after removal of each patch corresponding to the induction phase.

The cutaneous reaction, control of the sensitization, is evaluated by the macroscopic examination of the reactions possibly noted, between 15 and 35 minutes, 24 ± 3 hours (in case of reaction (erythema score ≥ 2) during previous reading), as well as 48 ± 4 hours after removal of the patches corresponding to the "challenge" application, or more if necessary. All adverse reactions are graded until resolution. Subjects must notify of any delayed skin reactions on the test site occurring after the 48-hour grading. The site is then re-examined by the Dermatologist.

These examinations are performed by comparison to the reactions possibly obtained with a patch alone (without investigational product), or if necessary with a vehicle known as neutral, non irritant, non sensitizing and non comedogenic, applied in parallel under the same conditions, as a "negative" control.

Analysis and interpretation of the results are performed depending on the data obtained under the experimental conditions adopted in comparison to that established for a selected reference product, to the untreated control site or with the results of the [redacted] internal database.

5. INVESTIGATIONAL PRODUCT

Designation/Investigational product category	[redacted]
Formula	
Batch nº (including manufacturing date)	
Physical form	
Colour	
[redacted]	
Packaging	
Quantity supplied (packaging included)	
Quantity used	
Date of receipt	12 January 2021
Analytical control	The conformity of the investigational product with the labelling was guaranteed by the Sponsor. In addition information on the investigational products was provided to the investigational laboratory (colour, physical form). For this type of study, no analytical dosage was made and neither stability, nor absorption of the investigational product was evaluated by [redacted]
Storage	Under lock and key, at room temperature protected from heat (between + 15°C and + 25° C). The used and unused investigational products were destroyed at the end of the study. A sample of the investigational product or at least a sufficient quantity of the product used in the study was kept in the concerned facility [redacted] for 6 months as of the date of dispatch of the final report. From this date and unless advised of the contrary by the Sponsor, the investigational product will be destroyed.
Particular precaution(s)	In the absence of information from the Sponsor about a possible interaction with the other investigational products, no particular precaution was taken during the positioning of this product on the subjects' back.

6. ETHICS

6.1. Standard protocol

The [redacted] the following documents on an annual basis:
- The standard protocol concerning this standard study
- Standard forms: The written informed consent form, the Case Report Form (CRF) and the subject information sheet if any

If needed, the [redacted] may ask for additional information about the conduct of a study.

6.2. Specific study protocol

Before the beginning of the study, the [redacted] has reviewed the following documents concerning the study:
- The standard protocol and the specific study protocol
- The written informed consent form and the subject information sheet
- The Case Report Form (CRF)
- Qualitative composition of the investigational product(s), only upon request
- Any relevant and available safety data concerning the investigational product(s)

If needed, the [redacted] may ask for additional information (i.e. Investigator's current CV, information about payments etc.).

7. SUBJECTS

7.1. Principle of selection, recruitment, admission and inclusion

The procedure for selection, recruitment and admission of the subjects who accepted to participate in this study, after signed informed consent form, was elaborated to give him/her clear and precise information, enabling him/her to appreciate the aim and the consequences of his/her consent.

This procedure included in particular:
- The verification of the identity of the subjects (presentation of an official document)
- A preliminary interview during which the subjects were adequately informed of the objectives, methods, the potential risks of the study and the discomfort it may entail. The language used was non-technical as possible and understandable. Neither the Dermatologist Investigator, nor the staff, in their oral and written communication didn't coerce or unduly influence the subject to participate or to continue to participate in the study. The informed consent discussions with the subjects (written in a subject information sheet and/or written informed consent form) included the following items, as a minimum :
. That the study involves research
. That the subject will not participate in another study throughout the whole period of the current study
. That the subject is covered by medical insurance
. That the subject must have a fixed abode
. The purpose of the study
. The expected duration of the study
. The approximate number of subjects involved in the study

. The study design, experimental aspects and test constraints
. The subject's compliance to the study protocol
. Any restrictions concerning activities and medications
. Dates, locations, times and duration of visits
. The reasonable foreseeable risks or inconveniences to the subjects
. The person to contact for further information regarding the study and the rights of the subjects and who to contact in the event of study-related injury with the corresponding 24/24 hours and 7/7 days contact telephone number
. That in the event of a significant reaction occurring during the course of the study the subject will immediately contact [redacted] which will carry out a clinical examination as quickly as possible
. That photograph(s) may be taken (avoiding as much as possible the subject to be identifiable) and used in connection with the study. In case where he/she could be recognizable, the subject will be asked to give a written authorization
. That the subject may be asked to take part in a follow-up test to complete the study
. Indemnity for participation
. That the subject's participation in a study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without any legal consequences
. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available
. That the Monitors, the Auditors, the Independent Ethics Committee and the Regulatory Authorities will be granted direct access to the subject's original data without violating the confidentiality of the subject, to the extent permitted by the laws and regulations and that, by signing a written informed consent form, the subject is authorizing such access.
- The signature of an informed consent form by the subject. The Dermatologist Investigator, or a person designated by the Investigator, provided the subject sufficient time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. Two original copies of the written informed consent form have to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The subject has to receive one original copy of the signed and dated written informed consent form and any other information. [redacted] retained in the study records the other original copy of the subject's signed written informed consent form.
- The notification of his/her taking over by the insurance in civil liability subscribed independently by the Sponsor and [redacted], once the subject has been definitely admitted in the study by the Dermatologists.

The subject recruited for this study was previously selected by the responsible for recruitment and selection, on the basis of a medical examination performed for the inclusion in the panel of [redacted] (medical examination, based on the general inclusion and general non-inclusion criteria defined in the [redacted] procedures).
The final inclusion of the subject in the present study was determined by the Dermatologists, from a pre-study medical auto-questionnaire and from a clinical medical examination specific to the study, performed just before its start, on the basis of the inclusion and non-inclusion criteria specific to the study, as well as the prohibition and restriction concepts defined in the protocol.

7.2. Number of subjects requested for the study

The required number of subjects depends on the risk considered as acceptable to wrongly conclude that the product does not cause delayed contact allergy reaction (α) through it is sensitizing and on the prevalence in the appearance of delayed contact allergy reactions in the considered population (p).
Should no reaction be observed for all the subjects of the study, the number of subjects required (n) is:

$$n = \frac{\log(\alpha)}{\log(1-p)}$$

. The number of 50 subjects is used to obtain, for a value of p equivalent to 0.058, a risk of α of 5% (or for p = 0.045, a risk of 10%).
. The number of 100 subjects is used to obtain, for a value of p equivalent to 0.030, a risk of α of 5% (or for p = 0.023, a risk of 10%).
. The number of 200 subjects is used to obtain, for a value of p equivalent to 0.015, a risk of α of 5% (or for p = 0.012, a risk of 10%).

The number of subjects included in the study was sufficient to obtain 100 valid cases. A "valid case" is defined as a subject who has respected the following:
. Application of the investigational product all along the study with respect to the frequency
. Subject participation to all the visits and clinical examination
. Absence of any concomitant treatment interfering with the results of the study, according to the Dermatologist Investigator

However, a subject who had presented with significant reactions (moderate erythema and/or infiltration and/or papules and/or vesicles) twice during the induction phase, inducing a stop of application, but who received the challenge phase application after decision of the Investigator Dermatologist and the Sponsor, could be considered as a valid case even though he had not followed the previous procedure.

7.3. Inclusion criteria

These criteria were evaluated on the basis of a questionnaire and clinical examination listed in the case report form.

To be eligible, each subject satisfied the following:

7.3.1. General inclusion criteria

- Origin: Caucasian
  Justification for origin: the white colour of Caucasians' skin allows easier evaluation of the cutaneous reactions.

- Weight: included within the limits of the scale indicated in the Standard Operating Procedure of [redacted]

- Subject without history of reactions to cosmetic products.

7.3.2. Inclusion criteria specific to the study

- Healthy subjects aged between 18 and 70 years old *(the 60-70 age range should not exceed 10% of the total number of subjects).*

- Subjects with phototypes I, II, III and IV.

- Males and females.

- Female subjects: having used an effective contraception for at least 3 months before the beginning of the study and who maintained it throughout the study.

- Subjects whose medical examination confirmed their suitability for participation in this study.

- Subjects, whose wash-out period was 4 months minimum time-lapse from any other HRIPT study (no more than 3 participations per year in HRIPT studies). In addition, subject's wash-out period was 1 month minimum time-lapse from the last participation in any clinical study involving patch on the back.

- Subjects covered by medical insurance.

- Provide signed Informed Consent.

7.4. Non-inclusion criteria

These criteria were evaluated on the basis of a questionnaire and clinical examination listed in the case report form.

To be eligible, each subject didn't satisfy the following:

7.4.1. General non-inclusion criteria

- Subject of whom the health condition has changed since the inclusion visit in the [redacted] and/or makes, the subject ineligible or places the subject at undue risk

- Subject presenting with an "atopic" background, that is to say presenting with:
  . either TWO familial past history (among: mother, father, brother(s) and sister(s)) for the following affections: (1) atopic dermatitis, (2) allergic asthma in the 1st half of life, (3) recognised pollinosis,(4) dermo-respiratory syndrome;
  . or personal past history (at least ONE criterion) among the following affections: (1) constitutional eczema, mostly appearing during the childhood and mostly located into the skin folds, (2) recurrent periodic asthma in the childhood or pre-teenage years (no asthma crisis should have occurred during the last 6 months), (3) recurrent periodic (chronic) conjunctivitis, (4) documented (allergological examination + prick tests) or non documented pneumallergen related (pollens, acaridae, animals) allergic rhinitis.

- Subject with documented history of contact allergy.

- Subject having undergone surgery, chemical or physical treatment to the concerned area in the last 2 months (or in the last 24 months for liposuction, if concerned by study application areas)

- Subject having modified his/her cosmetic habits (on the areas concerned by the study) during the last 2 weeks, which makes him/her ineligible;

- Subject having applied a cosmetic product (other than the usual cleanser) on the areas concerned by the study, on the inclusion day of the study

- Subject whose health condition, in the Dermatologist Investigator judgement, makes him/her ineligible or places him/her at undue risk (if the potential subject is under the care of a physician, approval to participate may be sought from that physician, at the Dermatologist Investigator's discretion and/or in accordance with regulatory requirements)

- Subject presenting with a redhibitory affection for this type of study

- Subject whose medical treatment which is, in the Dermatologist Investigator judgement, inconsistent with the participation in the study and that thus makes him/her ineligible (in particular for anti-inflammatories, applied on the test area within the 2 weeks before the beginning of the study, antihistamines, antibiotics, steroids, beta blockers (including collyrium) and corticoids…).

- Subject having *a skin disease,* and in particular: skin cancer or history of skin cancer, urticaria, œdema, eczema, recurrent herpes, herpes zoster having erupted in the last 3 months, pityriasis versicolour, common acne with a sudden rise of inflammation or nodular or kystic acne, psoriasis, ichthyosis, lichen planus, chronic lupus erythematosis, keloid scars, severe pigmentation disorders

(vitiligo, chloasma, multiple lentigines, numerous or congenital nevi, especially if they are of large size), hyperhidrosis, dorsal hyperpilosity, residual hyperpigmentation on the back following photobiology studies (photo-irritation …), keratosis pilaris, severe dermographism that could compromise evaluation of skin reactions.

- Subject with a history of severe reactions to sun exposure (phototoxicity, photoallergie, solar urticaria ...)

7.4.2 Non-inclusion criteria specific to the study

- Subject under immunosuppressive treatment and/or having an organ transplant;

- Subject currently taking topical or systemic anti inflammatory drugs for a defined medical condition, e.g. aspirin, ibuprofen, corticosteroids;

- Subject having intensive treatment with retinoids less than 3 months before the current HRIPT;

- Subject having an immune deficiency or autoimmune disease;

- Subject being vaccinated in the last 3 weeks preceding the start of the study or intention to be vaccinated during the course of the study.

- Subject with history of cancer (ex.: history of skin cancer, treatment for malignancy of any kind, mastectomy…);

- Subject having an insulino-dependent diabetes;

- Subject being an asthma sufferer;

- Subject either lactating or known to be pregnant;

- Subject having applied within the last two months of any anti-inflammatory drug to the skin area to be used in testing;

- Subjects with clinically significant active dermatitis or skin disease anywhere on the body (excluding facial acne);

- Subject with background of allergy (Drugs, cosmetics, food…) that makes the subject ineligible or places him/her at undue risk;

- Subject having skin disorders (scars, moles or other blemishes / abnormalities) affecting the test area which, in the Dermatologist Investigator's / designee's judgement, would interfere with grading / assessment on skin responses;

- Subject having an intensive exposure to sunlight (natural or artificial), during the month preceding the start of the study.

- Subject with clinically significant dermographism that could compromise the evaluation of skin reactions;

- Subject with known excessive skin reactivity to patch materials;

- Subject having a condition or medication which, in the Dermatologist Investigator's judgement, makes the subject ineligible or places the subject at undue risk (if the potential subject is under the care of physician, approval to participate may be sought from that physician, at the Dermatologist Investigator's discretion and/or in accordance with the regulatory requirements);

- Subject currently participating in another clinical study of any kind;

- Subject unwilling or not able to comply with protocol requirements;

- Subject deprived from his/her freedom by administrative or legal decision or who are under guardianship;

- Subject who cannot be contacted in case of emergency;

- Subject who cannot justify of a fixed abode;

- Subject being an [redacted] employee.

7.5. Test constraints

. The subjects were instructed not to change as far as possible their routine lifestyle, e.g. food, smoking, exercise, etc.
. The subjects were required to visit [redacted]13 times. Additional sessions were envisaged if necessary.
. During the induction and challenge phases, the subjects should not wet the patches sites, they had to refrain from practicing sport which may induce excessive perspiration, should not apply product(s) to the test area, and should inform the Dermatologist Investigator in the event of any use of medication or vaccination.
. Throughout the entire test and for 2 weeks after the study, the subjects should avoid UV exposure (natural or artificial);
. The subjects were instructed not to take part in any other study in the course of this study, and should not be included in any other HRIPT study during 4 months following the end of the current HRIPT. In addition, subjects should not participate in any other study involving patch on the back during a one-month period following the end of the current HRIPT.

7.6. Concomitant medications

Any information (commercial name, galenic form, administration regimen, start date and end date, indication) relating to concomitant medication were recorded in a "Concomitant Medication" paragraph in the Case Report Form. Subjects taking concomitant medications likely to interfere with the results of the study (see non-inclusion criteria of the protocol) could be excluded from the data analysis.

8. CLINICAL STUDY (EXPERIMENTAL DESIGN)

8.1. Application

8.1.1 Application area

The applications of the investigational product were performed on a surface of about 50 mm² (8 mm in diameter) on the one hand, for the induction on the left side of the spine, and on the other hand, for the challenge phase, on one side and the other of the spine (induction area and "blank" area), between the hips and shoulders, as much as possible on the upper back. If not possible, other areas on the back where frictions with clothes are limited, such as the lower back, were used. These areas had been submitted beforehand to a specific examination, at the occasion of the final inclusion **by the Dermatologist Investigator**, that is to say just before the start of the study on D0 in order to keep only surfaces free of scars, tattoos, beauty spots, warts or any other cutaneous disease.
As several products were tested during the same study, the patches were applied at least 1 cm apart.
No randomisation or rotation of the patches was involved in this study.

8.1.2. Preparation of the application area

The surface defined above was previously cleaned with distilled water, then dried with cotton-wool cellulose paper.

8.1.3. Patches

The applications of the investigational product were performed under occlusive patches (Small Finn Chambers on Scanpor, delivered by Smart Practice, USA) during the whole study or applied at the monitor's request under semi-occlusive patch (Strukmyer Medical, U.S.A.) in the case of reaction.
The "Finn Chamber" makes an isolation chamber which ensures a good occlusion limited to the application area of the investigational product: it is composed of an 8 mm-diameter aluminium cupule covering a contact surface of 50 mm².

Each cupule is individually mounted onto an adhesive tape (Scanpor: Norgesplaster A/S Norway) applied in order to create the same pressure on the whole cupule.

Being under a cream form, the investigational product (or the preparation) was directly put into the cupule which was filled to 2/3 of its volume.

Except if superior evaporation time was required, the shelf life of the investigational product on the patch did not exceed 20 minutes.

8.1.4. Dose level and concentration

- About 0.02 g, per subject, weighed with a 0.1 mg precision balance (Mettler Toledo AG204 DR), connected to a printer for the printing of weighing tickets.

- Justification for the dose level: it is the capacity of the cupule indicated by the manufacturer of the patches.

8.1.5. Administration route

- Route: local epicutaneous

- Justification for the route: normal route for this type of study.

8.1.6. Application modalities

8.1.6.1. Induction phase

- Application area: back, between the hips and the shoulders, on the left side of the spine and always on the same area.

- Investigational products applied: the previously identified patches were carefully applied to the skin of the back, using several "ribbons" composed of 2 parallel rows, having a number of several isolation chambers corresponding to the number of investigational products.
Isolation chamber alone (without investigational product) was also affixed under the same conditions to act as a negative control.

- Frequency and administration time: 9 applications spread out over 3 weeks (3 applications per week) as follows:

1st week : Day 0 (Tuesday: 1st application), Day 2 (Thursday), Day 4 (Saturday),
2nd week : Day 7 (Tuesday), Day 9 (Thursday), Day 11 (Saturday),
3rd week : Day 14 (Tuesday), Day 16 (Thursday), Day 18 (Saturday).

If one session was missed, a make-up patch was applied to the corresponding subjects at the end of the induction phase.

- Duration of exposure: 48 ± 4 hours (1st, 2nd, 4th, 5th, 7th and 8th applications) or 72 ± 4 hours (3rd, 6th and 9th applications).

During the last patch removal, the application area of each product was marked off on the skin (using transparent cards with anatomic marks), in order to find the precise areas for the "challenge" phase.

The patches were never left on for more than 72 ± 4 hours.

8.1.6.2. Rest phase

The subjects were not submitted to any application from Day 22 (Wednesday) to Day 34 (Monday) inclusive, i.e. for a 13 day period.

The subjects were asked to inform the Investigator of any reaction occurring during the rest phase.

8.1.6.3. "Challenge" phase

Prior to the challenge phase application, a careful examination of the test areas was made and the subjects were questioned about any changes in their health and on any medication taken since their last visit.

The investigational product was not reapplied as long as an erythema score is ≥ 2. An additional one week rest period could be necessary.

- **Application area**: back, between the hips and the shoulders, on the left and right side of the spine, on the same area as the one for the induction (induced site), precisely marked off, as well as on a symmetric area (on the right of the spine), having never received any product (virgin site).

- **Investigational product applied**: the investigational product (left and right side of the spine), as well as one patch alone (without investigational product) applied under the same conditions, to act as "negative" control under the same condition (type of patch, …) as during the induction phase.

- **Frequency and administration time point**: single application on Day 35 (Tuesday).

- **Duration of exposure:** 48 ± 4 hours.

8.2. Observations and clinical examinations

8.2.1. Reading times

The cutaneous examinations were performed on the one hand, during the induction, between 15 to 35 minutes after removal of the patches of the investigational product, in order to appraise their possible irritation potential and on the other hand, between 15 to 35 minutes, 24 ± 3hours (in case of reaction (erythema score ≥ 2) during previous reading) and 48 ± 4 hours after removal of the patches corresponding to the "challenge" phase (i.e. on D37, D38 and D39: examinations performed by the Dermatologist) to evaluate their possible sensitizing potential.

In all cases, during the challenge phase, any late cutaneous reaction on the test area, after the reading at time point 96 hours (that is to say 48 hours after the removal), must be reported by the subject who must come back to the laboratory for an evaluation of the site by the Dermatologist Investigator.

8.2.2. Evaluation of the sensitizing potential and of the cutaneous compatibility

The cutaneous reactions possibly observed during the induction and the "challenge" phase were evaluated, for each subject and for each product, according to the 3 following scales (provided by the Sponsor of the Study):

(E) Erythema

No visible erythema 0
Mild erythema (faint pink) 1
Moderate erythema (well defined) 2
Severe erythema 3
Caustic erythema - erosive aspect and/or necrotic aspect 4

(A) Scale of the International Contact Dermatitis Research Group: I.C.D.R.G.

No reaction* ..... 0 (-)
Weak positive reaction: erythema, infiltration, possibly papules ..... 1 (+)
Strong positive reaction: erythema, infiltration, papules, vesicles ..... 2 (++)
Extreme positive reaction: intense erythema, infiltration,
Vesicles may coalesce to form a blister ..... 3 (+++)

* *no reaction according to the I.C.D.R.G.*
for the doubtful reactions (?+), score for Erythema only.

(M) Supplementary mentions / other reactions

H / Oe = Homogeneous infiltration / oedema from 1 to 3 [1 = slight; 2 = moderate; 3 = severe]
P = Papules (to precise the number)
V = Vesicles (to precise the number)
B = Bullae (to precise the number)
Pe = Petechiae
S = Spreading beyond the patch area (infiltration or erythema)
SV = Soap effect (shiny skin possibly wrinkles)
F = Fissuring
D = Desquamation
Dr = Dryness
C = Skin coloration – hyperpigmentation (to precise the colour)
HY = Hypopigmentation
Fr = Follicular reaction
NA = Product not applied
T = Tape reaction
I = Itching at the test site
Er = Erosion
* = Additional free comments
N9G = No 9th reading
Cr = Exudation and/or surface encrustation
X = Succeeding patch not applied and succeeding grade (in brackets or on a new line) denotes a residual reaction
- or Abs = Absent subject
° = Discontinuation during the study
MU = Make-up patch.

8.2.3. Dermatologist involvement and qualification of study personnel

The dermatologist personally conducted at least the following phases:
Day 1: Inclusion of the subjects and medical examination
Day 3: Readings of the cutaneous reactions after patches removal
All clinical examinations after patches removal during challenge phase
Confirmation and follow-up of all suspected allergic reactions (score 2 and higher from ICDRG scale) during all the study
All the rechallenge phase, if any

All study personnel involved in the study was appropriately trained and qualified. A specific attention should be given to the training of study personnel involved in the grading of reactions.

8.2.4. Security

If the adhesive of the patch provokes an intolerance leading to the stop of the applications to the concerned area, the patch is not applied to the same site as the one used for the previous application, but to a site located near it.

At the first sign of significant irritation, during the induction, graded as erythema “2” – moderate to strong, or graded as erythema “1” associated with any other intolerance sign judged significant) observed on the application area of an investigational product, when removing the patches, the Sponsor was informed immediately and the treatment was moved to an adjacent site. The test site was only changed once. In addition, in case of strong irritation, the type of patch might be modified (form occlusive to semi-occlusive when concerned). The original patch test site should be scored in parallel with the new test site until completion of the test. The scores for both sites were clearly documented. In case of application to an adjacent site during the induction period, the “induced site” for the challenge phase was the site having received most applications.

In the exceptional and unforeseen event of the product proving too irritating for the selected patching regime, the Sponsor was informed immediately in order to consider modifying the protocol according to the product type (open application, reduction of the time the patch is worn, semi-occlusion instead of occlusion, reduced investigational product concentration, quantity applied, etc.)

In the case where there is suspicion of an allergic type of reaction, the investigational product was not applied again and the case was discussed immediately with the Sponsor. The decision to reapply or not the product in the challenge phase was taken jointly by the Investigator and the Sponsor.

During the rest phase, the subjects were asked to inform the Dermatologist Investigator of any reactions which occurred.

The investigational product was not reapplied as long as an erythema score is ≥ 2. An additional 1-week rest period was necessary.

A photograph is taken and sent to the Sponsor in the case of a marked reaction (induction or challenge).

If the applications provoke a severe or unforeseeable intolerance, the subject must immediately inform the Dermatologist Investigator: this one will proceed, in the shortest delay, to a medical examination and [redacted]informs the Sponsor of the consequences on the evolution of the study.

8.3. Removal of subjects from study or data analysis

Reasons for which a subject could be discontinued from the clinical study or withdrawn from the data analysis will be one of the following:

- Adverse event,
- Serious adverse event,
- Concomitant treatment(s) incompatible with the study or likely to interfere with the results of the study,
- Consent withdrawal by the subject*,
- Lost to follow up,
- Emergence of a non inclusion criterion,
- Decision of the Dermatologist Investigator (for reason of a subject well being for example),
- Violation of the protocol.

** All the subjects were informed of the fact that they can willingly and freely withdraw from the study, if they wish to do so, at any time and without having to give any reason.*

Any relevant information about the subjects has to be recorded in the CRF to decide whether or not the subject should be withdrawn.

Any discontinuation in the participation of a subject during the study is mentioned in the report and the reasons for this discontinuation are precised.

Any premature discontinuation linked to a Serious Adverse Event had to be followed-up (until final outcome) and this information had to be sent to the Sponsor within 24 hours.

In the case where the subject did not present for a visit, the Investigator or designee had to attempt to contact the subject by telephone on two occasions. These attempts had to be recorded in the Case Report Form. In the absence of any response, the subject was considered as “lost to follow up” and this decision was documented in the Case Report Form.

If the number of discontinuation or non presentations at the beginning of the study was higher than 10%, the subjects were replaced so that the data are available in at least 90% of the subjects, except if this discontinuation was due to a severe intolerance to the investigational product.

8.4. Data analysis and interpretation of the results

Analysis and interpretation of the results were performed according to the data obtained under the experimental conditions adopted (valid cases).

8.4.1. Sensitizing potential

For the analysis of the sensitizing potential, only the subjects having participated in the challenge stage and having respected the protocol were taken into account.
The interpretation of the sensitizing potential was made from results in compliance to the I.C.D.R.G. scale (see chapter. 8.2.2.).
Sensitizing potential of the Investigational product was evaluated on the basis of weight-of-evidence, taking into account all reactions observed in all subjects during the course of the study (induction, challenge and rechallenge if any).
A site where erythema is graded 2 or more during the "challenge" phase, with or without palpable lesions, must be evaluated on subsequent days to note whether the reaction decreases or increases in order to better differentiate between an allergic and an irritant reaction. A rapidly decreasing reaction is indicative of irritation (decrescendo reaction). A reaction with infiltration/oedema that persists and/or increases over time usually indicates an allergic reaction.

8.4.2. Cutaneous compatibility

All the subjects included were taken into account for the analysis of the cutaneous compatibility, whatever the number of times they visited the Investigator, during the induction stage.

This analysis was completed by the calculation of the Mean Irritation Index (M.I.I.), equal to the sum of the quotations of the 9 readings corresponding to the induction divided by the number of subjects included in this study (having participated in the whole induction phase) and the number of readings performed:

$$\text{M.I.I.} = \frac{\Sigma \text{ quotations of the 9 readings (all the subjects)}}{\text{Number of subjects x 9 (readings)}}$$

For this index calculation, it was defined that:

- if a subject is absent for an examination, the quotation of the day of absence is identical to the one of the day before;
- if an application is stopped because of a too severe reaction, the maximum quotation (4) is attributed on the day following the stop of the investigational product application for the considered area and this, until the end of the tolerance test;
- if the applications are stopped for any other reason, the quotations of the subject are excluded of the indices calculation.

The M.I.I. thus obtained enabled the classification of the investigational products ("non-irritant", "slightly irritant", "moderately irritant", "very irritant", "severely irritant") in comparison to that established for a selected reference product, to the untreated control site or with the results of the [redacted] internal database.

8.4.3. Adverse Events

8.4.3.1. Definition

An adverse event (AE) is defined as:
- any unfavourable and unintended event or degradation of the medical conditions (in comparison with those noted during the initial examination), occurring during the period of application of the investigational product(s) (between the inclusion in the study and the end of the study), not related to the investigational product(s) application: disease, accident, food intoxication, …
- any reaction or event related to the application of the investigational product(s) (definitely related (very probable or certain), probably related, possibly related or unlikely related (doubtful)) or unrelated to investigational product(s) application, which by its nature, its intensity or its appearance frequency leads to a modification of the application modalities of the investigational product(s) (rhythm, quantity, application area, …), and/or a discontinuation from the study (withdrawal of the consent by the subject or discontinuation on decision of the Dermatologist Investigator).

8.4.3.2. Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse event, regardless of cause or relationship to the investigational product, which:
- Results in death.
- Is life-threatening (i.e., an event which, in the view of the Dermatologist Investigator, places the subject at immediate risk of death from the reaction as soon as it occurs; it does not refer to an event which hypothetically may cause death if it had been more severe).
- Requires hospitalisation or prolonged hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly.
- Also considered an SAE is any other important medical event that jeopardises the subject or requires intervention to prevent one of the outcomes listed in this definition above.

As soon as [redacted] knows that an AE or SAE has occurred, the Sponsor must be informed either immediately for a serious adverse event or within 48 hours for a non serious adverse event.
The AEor SAE should be collected in the appropriate form at the end of the case report form along with the date of onset, site and duration of event, any action taken, outcome and an assessment of causality and severity. If the AE is still going on the final visit, the Dermatologist Investigator has to follow-up the event until complete outcome.

If an AE or SAE occurred, the Dermatologist Investigator has to determine the action to take and the appropriate measures on a case-by case basis, to ensure safety of the subjects taking part in the study.

The Investigator may stop the study if the study reveals a risk to the health of the subjects. In such case, the Sponsor should be notified within 24 hours of the action(s) taken.

The Investigator may decide to exclude a subject (permanently or temporarily) in the course of the study, if the subject experiences AE or SAE incompatible with proper observance of the protocol, for example contracts an illness requiring treatment that may interfere with the study and affect interpretation of the results.

8.4.3.3. Causality

The Dermatologist Investigator assesses the relationship (causality) of an AE to the investigational product according to the following definitions:

- **Definitely related (very probable or certain)**
  No uncertainty about the relationship between the event and investigational product application.
  The event follows a definite reasonable temporal sequence from the time of the investigational product application and improves upon stopping the dose of the investigational product. A re-challenge is positive. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject. The event follows a known response pattern to the investigational product.

- **Probably related**
  High degree of certainty about the relationship between the event and investigational product application.
  The event follows a reasonable temporal sequence from the time of the investigational product application and improves upon stopping the dose of the investigational product. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject.

- **Possibly related**
  Unlikely but cannot rule out with certainty the relationship between the event and investigational product application.
  The event may follow a reasonable temporal sequence from the time of the investigational product application. The event may be produced by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.

- **Unlikely related (doubtful)**
  Clinical event has an unlikely relationship with the investigational product application.
  There is no reasonable temporal association between the investigational product and the suspected event and the event could be reasonably produced by the subject's clinical state or other modes of therapy administered to the subject.

- **Unrelated (not linked)**
  Clinical event is clearly not due to investigational product application.
  There is no reasonable temporal relationship between the investigational product application and the suspected event (e.g., event occurs before investigational product application) or no reasonable causality, such as an accident, which cannot remotely be related to study participation (e.g., injuries sustained in a car accident).

8.4.3.4. Severity

The Dermatologist Investigator assesses the severity of each AE according to the following definitions:

- **Slight**
  Subject is aware (fully or partly) of the sign or symptom, but it is easily tolerated and does not interfere at all with the subject’s daily activity.

- **Mild**
Subject is aware of the sign or symptom, but it is rather well tolerated and does not interfere with the subject’s daily activity.

- **Moderate**
  Event causes discomfort enough to interfere with the subject's usual activities.

- **Severe**
  Incapacitating; subject is unable to perform usual activity.

8.4.4. Subject follow-up after the study

Subjects having presented with an allergic type reaction during the study has to be withdrawn from the panel of [redacted]

At a minimum, [redacted] gave to these subjects a document mentioning:
- Substance(s) concerned or "suspected" (if the relationship between the reactions linked to the finished product and breakdown substances was not established with certainty): INCI name and nature (function).
- Recommendations, prudence advice concerning the use of some categories of cosmetic products and action to be taken in case of reaction (consultation of the attending physician and/or of a dermatologist and/or of an allergist).

All additional follow-up described in the [redacted] procedures were ensured.

9. REGULATIONS, CONFIDENTIALITY AND LEGAL FORMALITIES

9.1. Regulations

This study was performed in agreement with the most recent recommendations of the World Medical Association (Declaration of Helsinki 1964, last amendment in force).

9.2. Confidentiality

Any information regarding the health condition of the subjects and the results of the clinical examinations, performed before the start of treatment, for their recruitment, their selection and inclusion, were submitted to the rules of the medical secrecy: in no case this information was given to the Sponsor with their identity.
To ensure preservation of the subjects' anonymity, they were identified by a code using 5 letters (and 2 digits if necessary when the letter code is already given to another subject), corresponding to the first 3 letters of their surname, then the first 2 letters of their first name, and for the study, by a number corresponding to their inclusion order in the study when eligible for the study.
At the end of the study, the page named "Subject Identification Form", in which the name and address of the subject were mentioned, was taken from the case report form and destroyed.
The Dermatologist Investigator/Institution should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority(ies).
The Monitor(s), the Auditor(s), the [redacted], and the Regulatory Authority(ies) were granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
Should the raw data be sent to the Sponsor, the confidential data of the informed consent form, as well as of the the information sheet, were masked.

9.3. Legal formalities

[redacted]

9.3.2. Subscription of insurance by the Sponsor

The Sponsor subscribed an insurance to guarantee its civil liability vis-à-vis the subjects: AIG Europe LTD, General Liability policy n° 7.109.393.

9.3.3. Data recording and archiving

All study documents (instructions for handling and storage and other documents related to investigational, product(s) preparation and application, safety Certificate for investigational product(s) signed by a safety assessor, confirming their safety in the study, the qualitative composition of the investigational product(s) if any), raw data (case report forms, signed informed consent forms and any other written instructions given to the subjects (as subject information sheet)), as well as the original documents of the compilation and a copy of the protocol, insurance statement, signed agreement between Sponsor and investigational laboratory, documented approval by the [redacted], the report (and amendments if any), are kept for 10 years, at the following addresses:

[redacted]

One copy of the compilation and the original documents (study documents, statistics, final protocol (protocol amendments if any), final report (all different versions and/or report amendments if any) and summaries) are kept for 10 years at the following addresses:

[redacted]

Once this period is over, the Sponsor will be contacted regarding its archives. No archive destroying will be done without the written agreement from the Sponsor.

[redacted]

9.3.7. Opinion from the Independent Ethical Committee

A favourable opinion of the Independent Ethical Committee based upon the type of the study, was obtained on an annual basis.

10. BIBLIOGRAPHICAL REFERENCES

- Marzulli F.N. and Maibach H.I. Contact allergy, predictive testing in man. Contact Dermatitis, 1976, 2, 1 - 17

- I.C.D.R.G. = The International Contact Dermatitis Research Group., Fregert S. Manual of Contact Dermatitis 2nd Edition

- ICH Topic E6(R2) "Note for guidance on good clinical practice" (EMA/CPMP/ICH/135/1995) - ICH Harmonized tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

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- Declaration of Helsinki adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and, last amendment in force.

- Le Coz Christophe-J., Muller Beatrice and Donnay Carole, Marking patch tests sites: description of a practical, clean, durable and inexpensive method Contact Dermatitis, 2004, 49, 284-286

- ICDRG, the International Contact Dermatitis Research Group, Fregert S. Manual of Contact Dermatitis, 2nd Edition

- Final clinical safety test of a cosmetic investigational product to confirm the absence of delayed cutaneous sensitizing potential, Recommendations to research sponsors and to service providers, TCFS PSC, AFSSaPS, final version of December 2008

11. RESULTS

11.1. Amendments and protocol compliance

11.1.1. Amendments

One amendment to the protocol was issued during the course of this study.

Amendment N°	Date	Reasons for the amendment
B201858AE1	19 March 2021	- Due to recruitment problems in order to obtain results on at least 100 subjects, a 2nd group of 29 subjects (n° 42 to n° 55 and n° 93 to n° 107 has been recruited to Day 8 (26/02/2021).

11.1.2. Protocol compliance

No phototype I
-One subject (n° 76) presented with a deviation to the protocol concerning application time and/or reading on D14: 50 minutes more than the 48 ± 4 h specified in the protocol
-One subject (n° 77) presented with a deviation to the protocol concerning application time and/or reading on D14: 25 minutes more than the 48 ± 4 h specified in the protocol
-One subject (n° 91) presented with a deviation to the protocol concerning application time and/or reading on D4: 5 hours and 25 minutes less than the 48 ± 4 h specified in the protocol
-One subject (n° 92) presented with a deviation to the protocol concerning application time and/or reading on D16: 10 minutes more than the 48 ± 4 h specified in the protocol
-One subject (n° 101) presented with a deviation to the protocol concerning application time and/or reading on D9: 10 minutes more than the 48 ± 4 h specified in the protocol
- One subject (n° 95) missed application on D7. Make-up patch was applied on D21.

These deviations are not considered to have affected, in a notable way, the quality or the interpretation of the results obtained.

11.2. Subjects

Number of subjects recruited	146
Number of subjects who came to [redacted]	107
Number of subjects not included by the Dermatologist Investigator	0
Number of subjects included by the Dermatologist Investigator	107
Number of subjects discontinued from the study . before the 1st reading . during the induction phase . during the rest phase . during the challenge phase	3 0 2 (n° 28 and n° 39) 0 1 (n° 34)
- Non related adverse event - Non related serious adverse event - Related adverse event - Related serious adverse event - Concomitant treatment(s) incompatible with the study - Consent withdrawal by the subject - Lost to follow up - Emergence of a non-inclusion criterion - Decision of the Dermatologist Investigator - Violation of the protocol	1 (n° 28) 0 0 0 0 1 (n° 34) 0 0 0 1 (n° 39)
Number of subjects for the analysis of the results . for the evaluation of Primary Irritation . for the evaluation of Cumulative Irritation . for the evaluation of Delayed Cutaneous Sensitization	 107 105 104

The physical characteristics of the subjects are summarized in the following table:

Subjects	Primary Irritation	Cumulative Irritation	Cutaneous Sensitization
Number	107	105	104
Females	76	75	74
Males	31	30	30
Age minimum	19	19	19
Age maximum	64	64	64

11.3. Results

The observations and clinical examinations are listed in the following appendix (Tables I to VII).

Percentage of subjects having presented with one or several slight to severe irritation reactions (score ≥ 2), during the induction	0%
Mean Irritation Index (M.I.I.) of the induction	0
Classification of the investigational product	■ non-irritant □ slightly irritant □ moderately irritant □ very irritant □ severely irritant
Percentage of the sensitisation reactions observed	0%
Reactions considered as serious adverse events linked to the investigational product	0%

No pathological irritation or sensitization reaction significant of a cutaneous intolerance was noted.

The Mean Irritation Index (M.I.I.), obtained during the induction was equal to **0**, and compared to the one obtained with the control (patch alone, without any investigational product) applied under the same conditions, thus enabled to classify arbitrarily the applications of these investigational products as "**non-irritant**".

12. CONCLUSION

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of the investigational product designated as [redacted], under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitization.

APPENDIX 1:
RESULTS

TABLE I: SUBJECTS' CHARACTERISTICS

SUBJECT N°	CODE	AGE	GENDER	PHOTOTYPE	SUBJECT N°	CODE	AGE	GENDER	PHOTOTYPE	SUBJECT N°	CODE	AGE	GENDER	PHOTOTYPE
01	[redacted]			III	41	[redacted]			II	81	[redacted]			III
02				III	42				III	82				III
03				III	43				III	83				III
04				III	44				III	84				III
05				III	45				II	85				IV
06				II	46				III	86				II
07				III	47				III	87				III
08				III	48				III	88				III
09				III	49				III	89				III
10				III	50				III	90				III
11				II	51				III	91				III
12				III	52				III	92				III
13				III	53				II	93				III
14				II	54				II	94				III
15				III	55				II	95				II
16				III	56				III	96				IV
17				III	57				III	97				II
18				III	58				III	98				II
19				IV	59				III	99				III
20				III	60				II	100				III
21				III	61				II	101				III
22				II	62				II	102				III
23				II	63				II	103				II
24				III	64				III	104				II
25				II	65				II	105				III
26				II	66				III	106				III
27				III	67				III	107				II
28				II	68				IV	108				
29				III	69				IV	109				
30				III	70				III	110				
31				III	71				II	111				
32				III	72				II	112				
33				III	73				III	113				
34				III	74				III	114				
35				III	75				III	115				
36				III	76				II	116				
37				III	77				IV	117				
38				II	78				IV	118				
39				III	79				III	119				
40				III	80				II	120				

TABLE II: INDUCTION PHASE - CONTROL

ALLERGY [A] AND IRRITATION [E]

SUB. N°		IRRITATION REACTIONS (E: 0 to 4) and SCORE ICDRG (A: 0 to 3)																				Σ QUOT	
		DAYS																					
		2		4		7		9		11		14		16		18		21		23			
		A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E
01		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
02		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
03		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
04		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
05		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
06		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
07		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
08		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
09		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
10		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
11		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
12		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
13		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
14		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
15		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
16		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
17		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
18		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
19		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
20		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
21		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
22		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
23		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
24		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
25		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
26		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
27		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
28		0	0	0	0	0	0	0	0	°	°	°	°	°	°	°	°	°	°			-	°
	M									°		°		°		°		°					
29		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
30		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						

TABLE II: INDUCTION PHASE - CONTROL (cont')

ALLERGY [A] AND IRRITATION [E]

SUB. N°	IRRITATION REACTIONS (E: 0 to 4) and SCORE ICDRG (A: 0 to 3)																				Σ QUOT	
	DAYS																					
	2		4		7		9		11		14		16		18		21		23			
	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
39	0	0	0	0	°	°	°	°	°	°	°	°	°	°	°	°	°	°			-	°
M					°		°		°		°		°		°		°					
40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
51	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
52	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
54	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
55	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
56	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
58	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
59	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						

TABLE II: INDUCTION PHASE - CONTROL (cont')

ALLERGY [A] AND IRRITATION [E]

SUB. N°	IRRITATION REACTIONS (E: 0 to 4) and SCORE ICDRG (A: 0 to 3)																				Σ QUOT	
	DAYS																					
	2		4		7		9		11		14		16		18		21		23			
	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E
61	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
62	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
63	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
64	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
65	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
66	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
67	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
69	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
71	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
72	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
73	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
74	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
75	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
76	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
77	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
78	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
79	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
81	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
82	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
83	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
84	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
86	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
87	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
88	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
89	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						

TABLE II: INDUCTION PHASE - CONTROL (cont')

ALLERGY [A] AND IRRITATION [E]

SUB. N°	IRRITATION REACTIONS (E: 0 to 4) and SCORE ICDRG (A: 0 to 3)																				Σ QUOT	
	DAYS																					
	2		4		7		9		11		14		16		18		21		21			
	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E
91	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
92	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
93	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
94	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
95	0	0	0	0	Abs	Abs	0	0	0	0	0	0	0	0	0	0	MU0	MU0	MU0	MU0	-	0
M																						
96	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
97	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
98	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
101	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
102	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
103	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
104	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
105	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
106	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
107	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						

TOTAL [E] = 0
M.I.I. = 0.00
Conclusion : Non Irritant

TABLE III: INDUCTION PHASE – INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUB. N°	IRRITATION REACTIONS (E: 0 to 4) and SCORE ICDRG (A: 0 to 3)																				Σ QUOT	
	DAYS																					
	2		4		7		9		11		14		16		18		21		23			
	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E
01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
04	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
05	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
08	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
09	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
28	0	0	0	0	0	0	0	0	°	°	°	°	°	°	°	°	°	°			-	°
M									°		°		°		°		°					
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						

TABLE III: INDUCTION PHASE – INVESTIGATIONAL PRODUCT (cont')

ALLERGY [A] AND IRRITATION [E]

SUB. N°		IRRITATION REACTIONS (E: 0 to 4) and SCORE ICDRG (A: 0 to 3)																				Σ QUOT	
		DAYS																					
		2		4		7		9		11		14		16		18		21		23			
		A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E
31		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
32		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
33		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
34		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
35		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
36		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
37		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
38		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
39		0	0	0	0	°	°	°	°	°	°	°	°	°	°	°	°	°	°			-	°
	M						°		°		°		°		°		°		°				
40		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
41		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
42		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
43		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
44		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
45		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
46		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
47		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
48		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
49		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
50		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
51		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
52		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
53		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
54		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
55		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
56		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
57		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
58		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
59		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						
60		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
	M																						

TABLE III: INDUCTION PHASE – INVESTIGATIONAL PRODUCT (cont')

ALLERGY [A] AND IRRITATION [E]

SUB. N°	IRRITATION REACTIONS (E: 0 to 4) and SCORE ICDRG (A: 0 to 3)																				Σ QUOT	
	DAYS																					
	2		4		7		9		11		14		16		18		21		23			
	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E
61	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
62	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
63	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
64	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
65	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
66	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
67	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
69	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
71	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
72	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
73	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
74	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
75	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
76	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
77	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
78	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
79	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
81	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
82	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
83	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
84	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
86	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
87	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
88	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
89	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						

TABLE III: INDUCTION PHASE – INVESTIGATIONAL PRODUCT (cont')

ALLERGY [A] AND IRRITATION [E]

SUB. N°	IRRITATION REACTIONS (E: 0 to 4) and SCORE ICDRG (A: 0 to 3)																				Σ QUOT	
	DAYS																					
	2		4		7		9		11		14		16		18		21		23			
	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E	A	E
91	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
92	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
93	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
94	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
95	0	0	0	0	Abs	Abs	0	0	0	0	0	0	0	0	0	0	MU0	MU0	MU0	MU0	-	0
M																						
96	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
97	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
98	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
101	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
102	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
103	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
104	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
105	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
106	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						
107	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			-	0
M																						

TOTAL [E] = 0

M.I.I. = 0.00

Conclusion : Non Irritant

TABLE IV: CHALLENGE PHASE – CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJECT N°	IRRITATION REACTION (E: 0 to 4) and ICDRG SCORE (A: 0 to 3)												CONCLUSION + (sensitization) - (no sensitization)
	15 - 35 min						48h ± 4h						
	Induction Site			Virgin Site			Induction Site			Virgin Site			
	A	E	M	A	E	M	A	E	M	A	E	M	
1	0	0	-	0	0	-	0	0	-	0	0	-	-
2	0	0	-	0	0	-	0	0	-	0	0	-	-
3	0	0	-	0	0	-	0	0	-	0	0	-	-
4	0	0	-	0	0	-	0	0	-	0	0	-	-
5	0	0	-	0	0	-	0	0	-	0	0	-	-
6	0	0	-	0	0	-	0	0	-	0	0	-	-
7	0	0	-	0	0	-	0	0	-	0	0	-	-
8	0	0	-	0	0	-	0	0	-	0	0	-	-
9	0	0	-	0	0	-	0	0	-	0	0	-	-
10	0	0	-	0	0	-	0	0	-	0	0	-	-
11	0	0	-	0	0	-	0	0	-	0	0	-	-
12	0	0	-	0	0	-	0	0	-	0	0	-	-
13	0	0	-	0	0	-	0	0	-	0	0	-	-
14	0	0	-	0	0	-	0	0	-	0	0	-	-
15	0	0	-	0	0	-	0	0	-	0	0	-	-
16	0	0	-	0	0	-	0	0	-	0	0	-	-
17	0	0	-	0	0	-	0	0	-	0	0	-	-
18	0	0	-	0	0	-	0	0	-	0	0	-	-
19	0	0	-	0	0	-	0	0	-	0	0	-	-
20	0	0	-	0	0	-	0	0	-	0	0	-	-
21	0	0	-	0	0	-	0	0	-	0	0	-	-
22	0	0	-	0	0	-	0	0	-	0	0	-	-
23	0	0	-	0	0	-	0	0	-	0	0	-	-
24	0	0	-	0	0	-	0	0	-	0	0	-	-
25	0	0	-	0	0	-	0	0	-	0	0	-	-
26	0	0	-	0	0	-	0	0	-	0	0	-	-
27	0	0	-	0	0	-	0	0	-	0	0	-	-
28	°	°	°	°	°	°	°	°	°	°	°	°	°
29	0	0	-	0	0	-	0	0	-	0	0	-	-
30	0	0	-	0	0	-	0	0	-	0	0	-	-
31	0	0	-	0	0	-	0	0	-	0	0	-	-
32	0	0	-	0	0	-	0	0	-	0	0	-	-
33	0	0	-	0	0	-	0	0	-	0	0	-	-
34	°	°	°	°	°	°	°	°	°	°	°	°	°
35	0	0	-	0	0	-	0	0	-	0	0	-	-
36	0	0	-	0	0	-	0	0	-	0	0	-	-
37	0	0	-	0	0	-	0	0	-	0	0	-	-
38	0	0	-	0	0	-	0	0	-	0	0	-	-
39	°	°	°	°	°	°	°	°	°	°	°	°	°
40	0	0	-	0	0	-	0	0	-	0	0	-	-
41	0	0	-	0	0	-	0	0	-	0	0	-	-
42	0	0	-	0	0	-	0	0	-	0	0	-	-
43	0	0	-	0	0	-	0	0	-	0	0	-	-
44	0	0	-	0	0	-	0	0	-	0	0	-	-
45	0	0	-	0	0	-	0	0	-	0	0	-	-
46	0	0	-	0	0	-	0	0	-	0	0	-	-
47	0	0	-	0	0	-	0	0	-	0	0	-	-
48	0	0	-	0	0	-	0	0	-	0	0	-	-
49	0	0	-	0	0	-	0	0	-	0	0	-	-
50	0	0	-	0	0	-	0	0	-	0	0	-	-
51	0	0	-	0	0	-	0	0	-	0	0	-	-
52	0	0	-	0	0	-	0	0	-	0	0	-	-
53	0	0	-	0	0	-	0	0	-	0	0	-	-
54	0	0	-	0	0	-	0	0	-	0	0	-	-
55	0	0	-	0	0	-	0	0	-	0	0	-	-
56	0	0	-	0	0	-	0	0	-	0	0	-	-
57	0	0	-	0	0	-	0	0	-	0	0	-	-
58	0	0	-	0	0	-	0	0	-	0	0	-	-
59	0	0	-	0	0	-	0	0	-	0	0	-	-
60	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE IV: CHALLENGE PHASE – CONTROL (cont')

ALLERGY [A] AND IRRITATION [E]

SUBJECT N°	IRRITATION REACTION (E: 0 to 4) and ICDRG SCORE (A: 0 to 3)												CONCLUSION + (sensitization) - (no sensitization)
	15 - 35 min						48h ± 4h						
	Induction Site			Virgin Site			Induction Site			Virgin Site			
	A	E	M	A	E	M	A	E	M	A	E	M	
61	0	0	-	0	0	-	0	0	-	0	0	-	-
62	0	0	-	0	0	-	0	0	-	0	0	-	-
63	0	0	-	0	0	-	0	0	-	0	0	-	-
64	0	0	-	0	0	-	0	0	-	0	0	-	-
65	0	0	-	0	0	-	0	0	-	0	0	-	-
66	0	0	-	0	0	-	0	0	-	0	0	-	-
67	0	0	-	0	0	-	0	0	-	0	0	-	-
68	0	0	-	0	0	-	0	0	-	0	0	-	-
69	0	0	-	0	0	-	0	0	-	0	0	-	-
70	0	0	-	0	0	-	0	0	-	0	0	-	-
71	0	0	-	0	0	-	0	0	-	0	0	-	-
72	0	0	-	0	0	-	0	0	-	0	0	-	-
73	0	0	-	0	0	-	0	0	-	0	0	-	-
74	0	0	-	0	0	-	0	0	-	0	0	-	-
75	0	0	-	0	0	-	0	0	-	0	0	-	-
76	0	0	-	0	0	-	0	0	-	0	0	-	-
77	0	0	-	0	0	-	0	0	-	0	0	-	-
78	0	0	-	0	0	-	0	0	-	0	0	-	-
79	0	0	-	0	0	-	0	0	-	0	0	-	-
80	0	0	-	0	0	-	0	0	-	0	0	-	-
81	0	0	-	0	0	-	0	0	-	0	0	-	-
82	0	0	-	0	0	-	0	0	-	0	0	-	-
83	0	0	-	0	0	-	0	0	-	0	0	-	-
84	0	0	-	0	0	-	0	0	-	0	0	-	-
85	0	0	-	0	0	-	0	0	-	0	0	-	-
86	0	0	-	0	0	-	0	0	-	0	0	-	-
87	0	0	-	0	0	-	0	0	-	0	0	-	-
88	0	0	-	0	0	-	0	0	-	0	0	-	-
89	0	0	-	0	0	-	0	0	-	0	0	-	-
90	0	0	-	0	0	-	0	0	-	0	0	-	-
91	0	0	-	0	0	-	0	0	-	0	0	-	-
92	0	0	-	0	0	-	0	0	-	0	0	-	-
93	0	0	-	0	0	-	0	0	-	0	0	-	-
94	0	0	-	0	0	-	0	0	-	0	0	-	-
95	0	0	-	0	0	-	0	0	-	0	0	-	-
96	0	0	-	0	0	-	0	0	-	0	0	-	-
97	0	0	-	0	0	-	0	0	-	0	0	-	-
98	0	0	-	0	0	-	0	0	-	0	0	-	-
99	0	0	-	0	0	-	0	0	-	0	0	-	-
100	0	0	-	0	0	-	0	0	-	0	0	-	-
101	0	0	-	0	0	-	0	0	-	0	0	-	-
102	0	0	-	0	0	-	0	0	-	0	0	-	-
103	0	0	-	0	0	-	0	0	-	0	0	-	-
104	0	0	-	0	0	-	0	0	-	0	0	-	-
105	0	0	-	0	0	-	0	0	-	0	0	-	-
106	0	0	-	0	0	-	0	0	-	0	0	-	-
107	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V: CHALLENGE PHASE – INVESTIGATIONAL PRODUCT (cont')

ALLERGY [A] AND IRRITATION [E]

SUBJECT N°	IRRITATION REACTION (E: 0 to 4) and ICDRG SCORE (A: 0 to 3)												CONCLUSION + (sensitization) - (no sensitization)
	15 - 35 min						48h ± 4h						
	Induction Site			Virgin Site			Induction Site			Virgin Site			
	A	E	M	A	E	M	A	E	M	A	E	M	
1	0	0	-	0	0	-	0	0	-	0	0	-	-
2	0	0	-	0	0	-	0	0	-	0	0	-	-
3	0	0	-	0	0	-	0	0	-	0	0	-	-
4	0	0	-	0	0	-	0	0	-	0	0	-	-
5	0	0	-	0	0	-	0	0	-	0	0	-	-
6	0	0	-	0	0	-	0	0	-	0	0	-	-
7	0	0	-	0	0	-	0	0	-	0	0	-	-
8	0	0	-	0	0	-	0	0	-	0	0	-	-
9	0	0	-	0	0	-	0	0	-	0	0	-	-
10	0	0	-	0	0	-	0	0	-	0	0	-	-
11	0	0	-	0	0	-	0	0	-	0	0	-	-
12	0	0	-	0	0	-	0	0	-	0	0	-	-
13	0	0	-	0	0	-	0	0	-	0	0	-	-
14	0	0	-	0	0	-	0	0	-	0	0	-	-
15	0	0	-	0	0	-	0	0	-	0	0	-	-
16	0	0	-	0	0	-	0	0	-	0	0	-	-
17	0	0	-	0	0	-	0	0	-	0	0	-	-
18	0	0	-	0	0	-	0	0	-	0	0	-	-
19	0	0	-	0	0	-	0	0	-	0	0	-	-
20	0	0	-	0	0	-	0	0	-	0	0	-	-
21	0	0	-	0	0	-	0	0	-	0	0	-	-
22	0	0	-	0	0	-	0	0	-	0	0	-	-
23	0	0	-	0	0	-	0	0	-	0	0	-	-
24	0	0	-	0	0	-	0	0	-	0	0	-	-
25	0	0	-	0	0	-	0	0	-	0	0	-	-
26	0	0	-	0	0	-	0	0	-	0	0	-	-
27	0	0	-	0	0	-	0	0	-	0	0	-	-
28	°	°	°	°	°	°	°	°	°	°	°	°	°
29	0	0	-	0	0	-	0	0	-	0	0	-	-
30	0	0	-	0	0	-	0	0	-	0	0	-	-
31	0	0	-	0	0	-	0	0	-	0	0	-	-
32	0	0	-	0	0	-	0	0	-	0	0	-	-
33	0	0	-	0	0	-	0	0	-	0	0	-	-
34	°	°	°	°	°	°	°	°	°	°	°	°	°
35	0	0	-	0	0	-	0	0	-	0	0	-	-
36	0	0	-	0	0	-	0	0	-	0	0	-	-
37	0	0	-	0	0	-	0	0	-	0	0	-	-
38	0	0	-	0	0	-	0	0	-	0	0	-	-
39	°	°	°	°	°	°	°	°	°	°	°	°	°
40	0	0	-	0	0	-	0	0	-	0	0	-	-
41	0	0	-	0	0	-	0	0	-	0	0	-	-
42	0	0	-	0	0	-	0	0	-	0	0	-	-
43	0	0	-	0	0	-	0	0	-	0	0	-	-
44	0	0	-	0	0	-	0	0	-	0	0	-	-
45	0	0	-	0	0	-	0	0	-	0	0	-	-
46	0	0	-	0	0	-	0	0	-	0	0	-	-
47	0	0	-	0	0	-	0	0	-	0	0	-	-
48	0	0	-	0	0	-	0	0	-	0	0	-	-
49	0	0	-	0	0	-	0	0	-	0	0	-	-
50	0	0	-	0	0	-	0	0	-	0	0	-	-
51	0	0	-	0	0	-	0	0	-	0	0	-	-
52	0	0	-	0	0	-	0	0	-	0	0	-	-
53	0	0	-	0	0	-	0	0	-	0	0	-	-
54	0	0	-	0	0	-	0	0	-	0	0	-	-
55	0	0	-	0	0	-	0	0	-	0	0	-	-
56	0	0	-	0	0	-	0	0	-	0	0	-	-
57	0	0	-	0	0	-	0	0	-	0	0	-	-
58	0	0	-	0	0	-	0	0	-	0	0	-	-
59	0	0	-	0	0	-	0	0	-	0	0	-	-
60	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V: CHALLENGE PHASE – INVESTIGATIONAL PRODUCT (cont')

ALLERGY [A] AND IRRITATION [E]

SUBJECT N°	IRRITATION REACTION (E: 0 to 4) and ICDRG SCORE (A: 0 to 3)												CONCLUSION + (sensitization) - (no sensitization)
	15 - 35 min						48h ± 4h						
	Induction Site			Virgin Site			Induction Site			Virgin Site			
	A	E	M	A	E	M	A	E	M	A	E	M	
61	0	0	-	0	0	-	0	0	-	0	0	-	-
62	0	0	-	0	0	-	0	0	-	0	0	-	-
63	0	0	-	0	0	-	0	0	-	0	0	-	-
64	0	0	-	0	0	-	0	0	-	0	0	-	-
65	0	0	-	0	0	-	0	0	-	0	0	-	-
66	0	0	-	0	0	-	0	0	-	0	0	-	-
67	0	0	-	0	0	-	0	0	-	0	0	-	-
68	0	0	-	0	0	-	0	0	-	0	0	-	-
69	0	0	-	0	0	-	0	0	-	0	0	-	-
70	0	0	-	0	0	-	0	0	-	0	0	-	-
71	0	0	-	0	0	-	0	0	-	0	0	-	-
72	0	0	-	0	0	-	0	0	-	0	0	-	-
73	0	0	-	0	0	-	0	0	-	0	0	-	-
74	0	0	-	0	0	-	0	0	-	0	0	-	-
75	0	0	-	0	0	-	0	0	-	0	0	-	-
76	0	0	-	0	0	-	0	0	-	0	0	-	-
77	0	0	-	0	0	-	0	0	-	0	0	-	-
78	0	0	-	0	0	-	0	0	-	0	0	-	-
79	0	0	-	0	0	-	0	0	-	0	0	-	-
80	0	0	-	0	0	-	0	0	-	0	0	-	-
81	0	0	-	0	0	-	0	0	-	0	0	-	-
82	0	0	-	0	0	-	0	0	-	0	0	-	-
83	0	0	-	0	0	-	0	0	-	0	0	-	-
84	0	0	-	0	0	-	0	0	-	0	0	-	-
85	0	0	-	0	0	-	0	0	-	0	0	-	-
86	0	0	-	0	0	-	0	0	-	0	0	-	-
87	0	0	-	0	0	-	0	0	-	0	0	-	-
88	0	0	-	0	0	-	0	0	-	0	0	-	-
89	0	0	-	0	0	-	0	0	-	0	0	-	-
90	0	0	-	0	0	-	0	0	-	0	0	-	-
91	0	0	-	0	0	-	0	0	-	0	0	-	-
92	0	0	-	0	0	-	0	0	-	0	0	-	-
93	0	0	-	0	0	-	0	0	-	0	0	-	-
94	0	0	-	0	0	-	0	0	-	0	0	-	-
95	0	0	-	0	0	-	0	0	-	0	0	-	-
96	0	0	-	0	0	-	0	0	-	0	0	-	-
97	0	0	-	0	0	-	0	0	-	0	0	-	-
98	0	0	-	0	0	-	0	0	-	0	0	-	-
99	0	0	-	0	0	-	0	0	-	0	0	-	-
100	0	0	-	0	0	-	0	0	-	0	0	-	-
101	0	0	-	0	0	-	0	0	-	0	0	-	-
102	0	0	-	0	0	-	0	0	-	0	0	-	-
103	0	0	-	0	0	-	0	0	-	0	0	-	-
104	0	0	-	0	0	-	0	0	-	0	0	-	-
105	0	0	-	0	0	-	0	0	-	0	0	-	-
106	0	0	-	0	0	-	0	0	-	0	0	-	-
107	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE VI: DISCONTINUATION(S) / EXIT(S) OF THE STUDY NOT LINKED TO THE INVESTIGATIONAL PRODUCT

SUBJECT(S) N°	REASON(S)
34	Consent withdrawal by the subject
39	Violation of the protocol
28	Non related adverse event

TABLE VII: RELATED ADVERSE EVENTS

Subjects N°	Description	Serious Y/N	Imputability	Severity	Action taken	Outcome
/	/	/	/	/	/	/

/ = Nothing to report.

Draft 2020 Priorities

Concentration of Use by FDA Product Category – Polyhydroxystearic Acid and Related Ingredients*

Polyhydroxystearic Acid
Poly(3-Hydroxyoctanoic Acid)
Polylactic Acid

Ingredient	Product Category	Maximum Concentration of Use
Polyhydroxystearic Acid	Other baby products	0.9%
Polyhydroxystearic Acid	Eyebrow pencils	0.4-0.72%
Polyhydroxystearic Acid	Eyeliners	0.4%
Polyhydroxystearic Acid	Eye lotions	0.12%
Polyhydroxystearic Acid	Mascaras	8%
Polyhydroxystearic Acid	Other eye makeup preparations	0.18%
Polyhydroxystearic Acid	Hair sprays Aerosol	 0.5%
Polyhydroxystearic Acid	Tonics, dressings, and other hair grooming aids	8%
Polyhydroxystearic Acid	Blushers (all types)	0.11-0.3%
Polyhydroxystearic Acid	Foundations	0.1-0.22%
Polyhydroxystearic Acid	Lipstick	0.4-14.2%
Polyhydroxystearic Acid	Other makeup preparations	0.25%
Polyhydroxystearic Acid	Face and neck products Not spray	 0.014-0.88%
Polyhydroxystearic Acid	Body and hand products Not spray	 0.1%
Polyhydroxystearic Acid	Moisturizing products Not spray	 0.15-10%
Polyhydroxystearic Acid	Other skin care preparations	0.49-1.5%
Polyhydroxystearic Acid	Other suntan preparations	0.2-0.3%
Polylactic Acid	Lipstick	0.084%
Polylactic Acid	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	5%
Polylactic Acid	Paste masks and mud packs	3.5%

*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 2021
Table prepared: July 6, 2021

2022 VCRP Data: Polyhydroxystearic Acid

Ingredient Name	Category Description	CPIS Count
Polyhydroxystearic Acid		
Total Uses: 265		
Other Baby Products	01C- Other Baby Products	2
Polyhydroxystearic acid	03A - Eyebrow Pencil	10
Polyhydroxystearic acid	03B - Eyeliner	26
Polyhydroxystearic acid	03C - Eye Shadow	14
Polyhydroxystearic acid	03D - Eye Lotion	1
Polyhydroxystearic acid	03F - Mascara	2
Polyhydroxystearic acid	03G - Other Eye Makeup Preparations	9
Polyhydroxystearic acid	05G - Tonics, Dressings, and Other Hair Grooming Aids	2
Polyhydroxystearic acid	05I - Other Hair Preparations	2
Polyhydroxystearic acid	06B - Hair Tints	5
Polyhydroxystearic acid	07A - Blushers (all types)	4
Polyhydroxystearic acid	07B - Face Powders	5
Polyhydroxystearic acid	07C - Foundations	6
Polyhydroxystearic acid	07D - Leg and Body Paints	1
Polyhydroxystearic acid	07E - Lipstick	116
Polyhydroxystearic acid	07F - Makeup Bases	6
Polyhydroxystearic acid	07H - Makeup Fixatives	1
Polyhydroxystearic acid	07I - Other Makeup Preparations	25
Polyhydroxystearic acid	12A- Cleansing	1
Polyhydroxystearic acid	12C - Face and Neck (exc shave)	9
Polyhydroxystearic acid	12F - Moisturizing	8
Polyhydroxystearic acid	12J - Other Skin Care Preps	10
Polylactic Acid		
Total Uses: 18		
Polylactic acid	03C- Eye Shadow	3
Polylactic acid	05A - Hair Conditioner	1
Polylactic acid	07E - Lipstick	1
Polylactic acid	10A - Bath Soaps and Detergents	1
Polylactic acid	12A - Cleansing	3
Polylactic acid	12C - Face and Neck (exc shave)	1
Polylactic acid	12F -Moisturizing	5
Polylactic acid	12J - Other Skin Care Preps	3