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

Status:	Tentative Report for Public Comment
Release Date:	October 7, 2022
Panel Meeting Date:	March 6-7, 2023

All interested persons are provided 60 days from the above release date (i.e., December 6, 2022) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to the Cosmetic Ingredient Review (CIR) will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651
cirinfo@cir-safety.org

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 repeated 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

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as used in cosmetic formulations. These ingredients are reported to function in cosmetics as a non-surfactant dispersing agent, a skin-conditioning agent, and an abrasive agent, respectively. The Panel reviewed the available data to determine the safety of these ingredients and concluded that these ingredients are safe in cosmetics in the present practices of use and concentrations described in this safety assessment.

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 the monomers, hydroxystearic acid and lactic acid. The safety of hydroxystearic acid was evaluated in 2 separate reviews. In 1999, the Panel published a final report with the conclusion that hydroxystearic acid is safe as a cosmetic ingredient in the present practices of use as described in the safety assessment.[2] Hydroxystearic acid was then included in the report evaluating the safety of fatty acids and fatty acid salts, and in 2019, the Panel concluded that hydroxystearic acid is safe in 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] For lactic acid, the Panel published a final report in 1998 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] The Panel reaffirmed this conclusion, as published in 2017.[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.

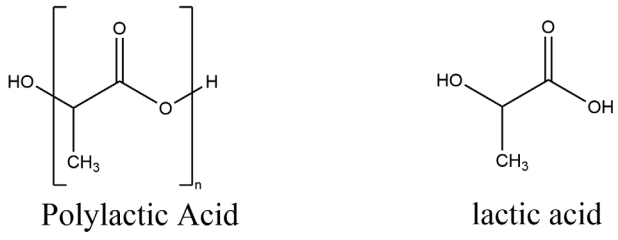


Figure 1. Polylactic Acid and lactic acid

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/ml, 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, and 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 dinitrofluorobenzene (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

This assessment reviews the safety of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid) and Polylactic Acid as used in cosmetic formulations. The Panel reviewed the available data and concluded that these 3 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

The Panel discussed that these are large molecules that are not likely to be absorbed. The Panel also noted that while the monomers used to make these ingredients are of different sizes and connectivities, the resulting polymers would be very similar in structural features. Additionally, the Panel considered their prior safety determinations of the corresponding monomers of these ingredients. These monomers would be the primary impurities and decomposition products of oligomers, including dimers and trimers, present in these polymers. In the Panel's prior assessments of these monomers, the safety of those ingredients was determined at higher concentrations than would be possible with the use of these polymers. Thus, it was determined that the safety profile of these polymeric ingredients would not differ from that of the monomers.

The Panel noted the lack of systemic toxicity data, including a lack of developmental and reproductive toxicity and carcinogenicity data. However, concerns regarding systemic toxicity of these ingredients were mitigated by the approved use in food contact materials, multiple FDA-approved uses of Polylactic Acid in medical devices, the existing 2019 ASTM

International standard for the use of amorphous Polylactic Acid in surgical implants, the very low likelihood of absorption, and the safety of the monomers used to manufacture these ingredients.

Negative dermal irritation and sensitization data included in this review reassured the Panel of the dermal safety of these ingredients. The Panel particularly noted that undiluted Polyhydroxystearic Acid was not irritating or sensitizing when tested in an occlusive HRIPT of 51 subjects, and that two separate products containing 3.45% Polyhydroxystearic Acid and 4% Polylactic Acid were neither irritating nor sensitizing when tested neat in HRIPTs using 107 and 104 subjects, respectively.

Furthermore, the Panel discussed the issue of incidental inhalation exposure resulting from these ingredients; for example, Polyhydroxystearic Acid is reported to be used at 0.5% in aerosol hair sprays. Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

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

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 3 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Polyhydroxystearic Acid
Polylactic Acid
Poly(3-Hydroxyoctanoic Acid)*

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

TABLES

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

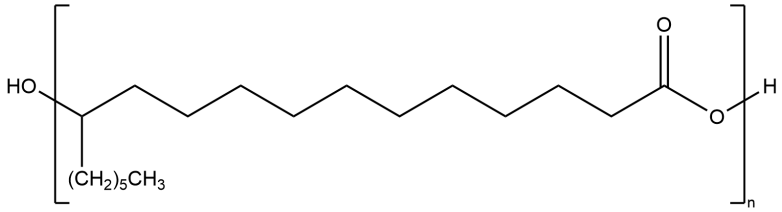
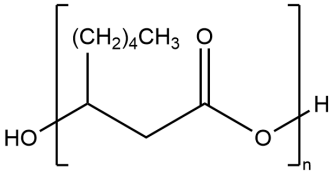
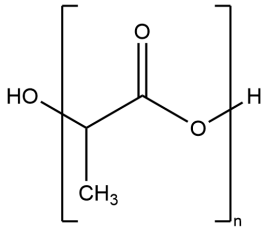
Ingredient	Definition	Function
Polyhydroxystearic Acid 27924-99-8 58128-22-6	Polyhydroxystearic Acid, defined as a polymer of hydroxystearic acid, generally conforms to the structure: 	Dispersing agents - nonsurfactant
Poly(3-Hydroxyoctanoic Acid)	Poly(3-Hydroxyoctanoic Acid) is the polymer of 3-hydroxyoctanoic 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

REFERENCES

1. Nikitakis J, Kowcz A. Web-Based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*). http://webdictionary.personalcarecouncil.org/jsp/IngredientSearchPage.jsp. Washington, D.C.: Personal Care Products Council. Last Updated: 2022. Accessed: 08/17/2022.

2. Andersen FA (ed.). Amended Final Report on the Safety Assessment of Hydroxystearic Acid. *Int J Toxicol.* 1999;18:1 - 10.

3. Burnett CL, Bergfeld WF, Belsito DV, et al. Safety Assessment of Fatty Acids & Fatty Acid Salts as Used in Cosmetics 2019. Available from CIR (https://www.cir-safety.org/ingredients).

4. Andersen FA (ed.). Final Report On the Safety Assessment of Glycolic Acid, Ammonium, Calcium, Potassium, and Sodium Glycolates, Methyl, Ethyl, Propyl, and Butyl Glycolates, and Lactic Acid, Ammonium, Calcium, Potassium, Sodium, and Tea-Lactates, Methyl, Ethyl, Isopropyl, and Butyl Lactates, and Lauryl, Myristyl, and Cetyl Lactates. *International Journal of Toxicology.* 1998;17(1 suppl):1-241.

5. Fiume M, Heldreth B. 40th Anniversary Overview and Rereview Summaries From 2011 to 2015. *Int J Toxicol.* 2017;36(5 suppl2):14S.

6. National Library of Medicine. PubChem : 12-Hydroxyoctadecanoic acid (Polyhydroxystearic Acid; CAS No. 27924-99-8). https://pubchem.ncbi.nlm.nih.gov/compound/12-Hydroxyoctadecanoic-acid#section=Chemical-and-Physical-Properties. Last Updated: 2022 Feb 12. Accessed: 11/15/2021.

7. Phoenix Chemical Inc. 2021. Pelemol® PHS-8 (INCI: Polyhydroxystearic Acid): Molecular weight information. (Unpublished data submitted by Personal Care Products Council on April 11, 2022.)

8. National Center for Biotechnology Information. PubChem Annotation Record for Polylactic acid, Source: Hazardous Substances Data Bank (HSDB). https://pubchem.ncbi.nlm.nih.gov/source/hsdb/8244. Last Updated: Accessed: 08/17/2022.

9. Phoenix Chemical Inc. 2022. Pelemol® PHS-8 (INCI: Polyhydroxystearic Acid). (Unpublished data submitted by Personal Care Products Council on April 11, 2022.)

10. Xiao L, Wang B, Yang G, Gauthier M. Poly(Lactic Acid)-based Biomaterials: Synthesis, Modification and Applications. In: Ghista D, ed. *Biomedical Science, Engineering, and Technology.* InTech; 2012:247-282.

11. Farah S, Anderson DG, Langer R. Physical and mechanical properties of PLA, and their functions in widespread applications — A comprehensive review. *Adv Drug Deliv Rev.* 2016;107:367-392.

12. Li G, Zhao M, Xu F, et al. Synthesis and biological application of polylactic acid. *Molecules.* 2020;25(21):5023.

13. Iñiguez-Franco F, Auras R, Burgess G, et al. Concurrent solvent induced crystallization and hydrolytic degradation of PLA by water-ethanol solutions. *Polymer.* 2016;99.

14. Elbahloul Y, Steinbüchel A. Large-scale production of Poly(3-Hydroxyoctanoic Acid) by *Pseudomonas putida* GPo1 and a simplified downstream process. *Appl Environ Microbiol.* 2009;75(3):643-651.

15. Balla E, Daniilidis V, Karlioti G, et al. Poly(lactic Acid): A versatile biobased polymer for the future with multifunctional properties—from monomer synthesis, polymerization techniques and molecular weight increase to PLA applications. *Polymers.* 2021;13(11):1822.

16. Inkinen S, Hakkarainen M, Albertsson AC, Södergård A. From lactic acid to poly(lactic acid) (PLA): characterization and analysis of PLA and its precursors. *Biomacromolecules.* 2011;12(3):523-532.

17. Abd Alsaheb RA, Aladdin A, Othman NZ, et al. Recent applications of polylactic acid in pharmaceutical and medical industries. *J Chem Pharm Res.* 2015;7(12):51-63.

18. Jem K, van der Pol J, de Vos S. Microbial lactic acid, its polymer, poly(lactic acid), and their industrial applications. In: Chen G-Q, ed. *Plastics from Bacteria: Natural Functions and Applications.* Vol 14. Berlin Heidelberg: Springer-Verlag; 2010.

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

20. Personal Care Products Council. 2021. Concentration of Use by FDA Product Category: Polyhydroxystearic Acid and Related Ingredients. (Unpublished data submitted by Personal Care Products Council on July 6, 2021.)

21. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated: 2020. Accessed: 2/5/2022.

22. European Food Safety Authority. Scientific opinion on the safety evaluation of the substance poly(12-hydroxystearic acid) stearate, CAS No. 58128-22-6 for use in food contact materials. Parma, Italy 2010. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2010.1520. Accessed February 10, 2022.

23. European Food Safety Authority. Scientific opinion on the safety evaluation of the substance glycolic acid for use in food contact materials. Parma, Italy 2010. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2010.1927. Accessed February 10, 2022.

24. Emami F, Mostafavi Yazdi SJ, Na DH. Poly(lactic acid)/poly(lactic-co-glycolic acid) particulate carriers for pulmonary drug delivery. *J Pharm Investig.* 2019;49:427-442.

25. Santoro M, Shah SR, Walker JL, Mikos AG. Poly(lactic acid) nanofibrous scaffolds for tissue engineering. *Adv Drug Deliv Rev.* 2016;107:206-212.

26. Alkahtani S, Alarifi S, Albasher G, et al. Poly lactic-co-glycolic acid- (PLGA-) loaded nanoformulation of cisplatin as a therapeutic approach for breast cancers. *Oxid Med Cell Longev.* 2021;2021:5834418.

27. Wang Y, Qiao X, Yang X, et al. The role of a drug-loaded poly (lactic co-glycolic acid) (PLGA) copolymer stent in the treatment of ovarian cancer. *Cancer Biol Med.* 2020;17(1):237-250.

28. Athanasiou KA, Niederauer GG, Agrawal CM. Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid/polyglycolic acid copolymers. *Biomaterials.* 1996;17(2):93-102.

29. Feng S, Li R, Wang Z. Experimental study on the biocompatibility and osteogenesis induction ability of PLLA/DDM scaffolds. *Odontology.* 2022.

30. Usami T, Takada N, Sakai H, et al. Treatment of patellar fractures using bioresorbable forged composites of raw particulate unsintered hydroxyapatite/poly-L-lactide cannulated screws and nonabsorbable sutures. *Injury.* 2021;52(6):1587-1591.

31. U.S. Food and Drug Administration (FDA). Devices@FDA. https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm. Last Updated: 2022. Accessed: March 4, 2022.

32. U.S. Food and Drug Administration (FDA). Product Classification. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/PCDSimpleSearch.cfm. Last Updated: 2022. Accessed: March 4, 2022.

33. Kulkarni R, Pani K, Neuman C, Leonard F. Polylactic Acid for surgical implants. *Arch Surg.* 1966;93(5):839-843.

34. Uzun N, Martins TD, Teixeira GM, et al. Poly(L-lactic acid) membranes: absence of genotoxic hazard and potential for drug delivery. *Toxicol Lett.* 2015;232(2):513-518.

35. Li RY, Liu ZG, Liu HQ, Chen L, Liu JF, Pan YH. Evaluation of biocompatibility and toxicity of biodegradable poly (DL-lactic acid) films. *Am J Transl Res.* 2015;7(8):1357-1370.

36. Göelzer J, Avelar R, Dolzan A, et al. Evaluation of tissue response and genotoxicity of poly(L/D-lactic acid) disks implanted in rat calvarium. *Histol Histopathol.* 2012;27(12):1551-1557.

37. AMA Laboratories. 2003. 50 Human subject repeat insult patch test skin irritation/sensitization evaluation (occlusive patch) Pelemol® PHS-8 (INCI: Polyhydroxystearic Acid). (Unpublished data submitted by Personal Care Products Council on April 11, 2022.)

38. Anonymous. 2021. Modified Marzulli-Maibach protocol - Human repeated insult patch test with challenge (product contains 3.45% Polyhydroxystearic Acid). (Unpublished data submitted by the Personal Care Products Council on April 15, 2022.)

39. Anonymous. 2014. Repeated insult patch test (RIPT) - Marzulli Maibach method (product contains 4% Polylactic Acid). (Unpublished data submitted by Personal Care Products Council on April 15. 2022.)

40. Lin J-Y, Lin C-Y. Injectable Poly-D, L-lactic acid in facial rejuvenation: three case reports. *J Cosmetol.* 2020;4(1):000120.