Safety Assessment of Phytosteryl Glutamates as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (i.e., February 11, 2023) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to the Cosmetic Ingredient Review (CIR) will be discussed in open meetings, will be available for review by any interested party, and may be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.

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ABBREVIATIONS

CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	US Consumer Product Safety Commission
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook*
FDA	Food and Drug Administration
HRIPT	human repeated insult patch test
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
NR	not reported
t_{50}	duration of exposure resulting in a 50% decrease in MTT conversion
US	United States
VCRP	Voluntary Cosmetic Registration Program
WHO	World Health Organization

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 3 phytosteryl glutamates as used in cosmetics. All of these ingredients are reported to function as skin conditioning agents in cosmetics. The Panel reviewed the available data to determine the safety of these ingredients. The Panel concluded that the available data are insufficient to make a determination of safety under the intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of the following 3 phytosteryl glutamates as used in cosmetics is reviewed in this safety assessment.

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate
Phytosteryl/Behenyl/Octyldodecyl/Isostearyl Lauroyl Glutamate
Phytosteryl/Octyldodecyl Lauroyl Glutamate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all 3 phytosteryl glutamates are reported to function in cosmetics as skin conditioning agents, and Phytosteryl/Behenyl/Octyldodecyl/Isostearyl Lauroyl Glutamate is also reported to function as a hair conditioning agent (Table 1).[1] These ingredients are being reviewed together as they are all mixed esters of phytosterols, octyldodecanol (and other respective fatty alcohols), and lauroyl glutamic acid. The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of several phytosterols and lauroyl glutamic acid. The phytosterols ingredient group were considered safe as used in the present practices of use and concentration (as described in that safety assessment).[2] Lauroyl glutamic acid was reviewed as part of the safety assessment of amino acid alkyl amides.[3] At the time of the assessment lauroyl glutamic acid was not in current use, but the Panel concluded it would be considered safe if used in product categories and at concentrations comparable to others in the group (as described in the safety assessment). The full reports on these ingredients can be accessed 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. The published data in this document were identified by conducting an exhaustive search of the world's literature. A list 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 available 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 may be provided by the cosmetics industry, as well as by other interested parties.

CHEMISTRY

Definition and Structure

Each of these ingredients comprise 2 core chemical structural residues, phytosterols and lauroyl glutamate. These ingredients also comprise certain fatty alkyl chains. The "/"in the names of these ingredients signifies mixtures. For example, Phytosteryl/Octyldodecyl Lauroyl Glutamate is a mixture of phytosteryl lauroyl glutamate and octyldodecyl lauroyl glutamate. The term "phytosteryl" also signifies a mixture, specifically of steroidal constituents derived from plants (i.e., "phyto"). The most common phytosterols (β-sitosterol, stigmasterol, avenasterol, campesterol, and campestanol) are illustrated in Figure 1, as is an example of connectivity with lauroyl glutamate.

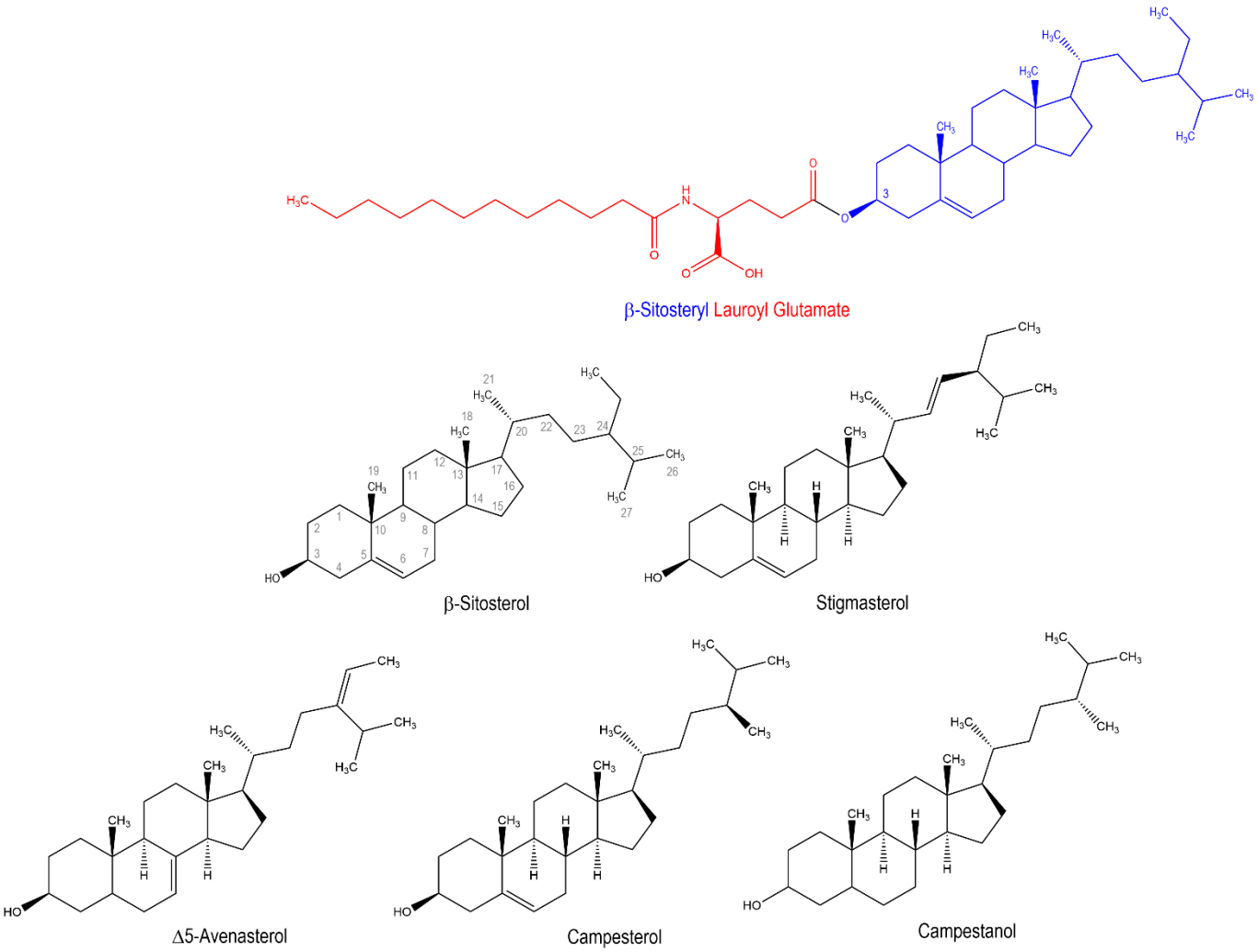

Figure 1. Phytosterols and phytosteryl connectivity

All such connectivities are the result of esterification via the 3-position alcohol functional group of one or more phytosterols. The connectivity of various fatty alkyl chains with lauroyl glutamate is similarly the result of esterification (e.g., octyldodecyl lauroyl glutamate (Figure 2)).

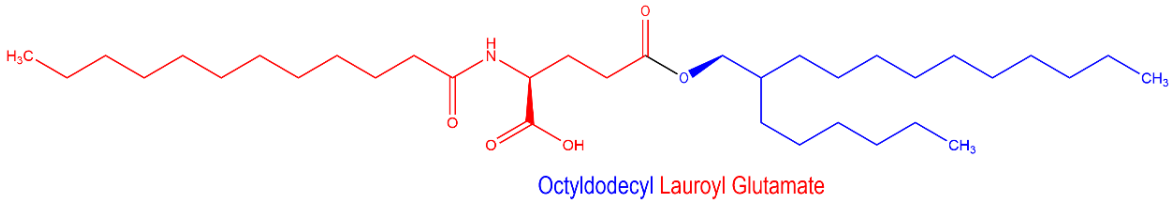

Figure 2. Octyldodecyl Lauroyl Glutamate

Accordingly, Phytosteryl/Octyldodecyl Lauroyl Glutamate is a mixture potentially comprising all of the above instances of esterified lauroyl glutamate. Likewise, Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate and Phytosteryl/Behenyl/ Octyldodecyl/Isostearyl Lauroyl Glutamate comprise similar such mixtures.

The definitions and reported functions of the phytosteryl glutamates included in this safety assessment are presented in Table 1.[1] The only ingredient with a CAS No. in this safety assessment is Phytosteryl/Octyldodecyl Lauroyl Glutamate (220465-88-33).

Chemical Properties

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate is a white solid.[4] Results of gel permeation chromatography of Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate in tetrahydrofuran are found in Table 2. The standard was polystyrene.

Method of Manufacture

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate

A method of manufacture of Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate involves the synthesis, cooling, washing, and drying of the ingredient.[4] This is followed by quality control and packing.

Impurities

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate

In an arsenic and lead analysis of Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate where the detection limit was 1 μg/g for arsenic and 2 μg/g for lead, neither arsenic nor lead was detected.[4] The loss on drying of Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate (105°C, for 1 h) is 0.1%.

USE

Cosmetic

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

According to 2022 FDA VCRP data, Phytosteryl/Octyldodecyl Lauroyl Glutamate has the greatest frequency of use; it is reported to be used in 325 cosmetic products, 311 of which are leave-on products and over a third of which are in lipstick formulations (Table 3).[5] The results of the concentration of use survey conducted by the Council in 2021 indicate that Phytosteryl/Behenyl/Octyldodecyl/Isostearyl Lauroyl Glutamate has the highest concentration of use; it is used at maximum use concentrations up to 25.6% in leave-on products (rouges).[6] The maximum concentration of use reported for Phytosteryl/Octyldodecyl Lauroyl Glutamate is very similar; it is reported to be used at up to 25% in rouges and in lipsticks.

Cosmetic products containing phytosteryl glutamates may incidentally come in contact with the eyes (e.g., Phytosteryl/Octyldodecyl Lauroyl Glutamate at concentrations up to 12% in eye shadow), and all 3 of these ingredients are used in products that are reported to be used in formulations that could be incidentally ingested and that come in contact with mucous membranes (e.g., Phytosteryl/Octyldodecyl Lauroyl Glutamate at concentrations up to 25% in lipstick). Use in baby products is also reported (e.g., Phytosteryl/Octyldodecyl Lauroyl Glutamate is used at up to 0.3% in baby lotions, oils, and creams).

Some of these ingredients are used in cosmetic products that could possibly be inhaled; for example, Phytosteryl/Octyldodecyl Lauroyl Glutamate is reported to be used in hairsprays (concentration not reported), aerosol deodorant (up to 0.1%), and in face powders at concentrations up to 5%. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

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

The phytosteryl glutamates reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[7]

TOXICOKINETIC STUDIES

Data on toxicokinetic effects of phytosteryl glutamate ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Data on the acute toxicity of the phytosteryl glutamate ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

Short-Term Toxicity Studies

Oral

Phytosteryl/Octyldodecyl Lauroyl Glutamate

In a short-term oral toxicity study, a daily dose of Phytosteryl/Octydodecyl Lauroyl Glutamate was administered by gavage to SPF-bred Wistar rats of both sexes at dose levels of 50, 200, or 1000 mg/kg for 28 d.[8] During the experiment, clinical signs, outside cage observation, food consumption, and body weights were recorded. Functional observational battery, locomotor activity, and grip strength were performed during week 4. After the dosing period, blood samples were drawn for hematology and blood chemistry profile. Histological examinations were performed on organs and tissues. No test substance-related clinical signs were noted, along with no changes in functional observational battery, grip strength, locomotor activity, food consumption, and body weight. Changes in hematology or clinical chemistry parameters were also not reported. There were no reported experimental effects on organ weights; macroscopic and microscopic examination found no changes in experimental animals.

Subchronic and Chronic Toxicity Studies

Data on the subchronic and chronic toxicity of the phytosteryl glutamates reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of phytosteryl glutamates reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

In Vitro

Phytosteryl Octyldodecyl Lauroyl Glutamate

The mutagenicity of Phytosteryl/Octyldodecyl Lauroyl Glutamate was examined in a reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 and *Escherichia coli* strain WP2 uvr A.[9] Doses of 33, 100, 333, 1000, 2500, and 5000 µg/plate were tested. The assay was performed in two independent experiments with and without liver microsomal activation. The test was performed in triplicate. The vehicle and positive controls produced appropriate responses. The test article did not cause a positive increase in the number of revertants per plate in any of the tester strains either in the presence or absence of metabolic activation. Under the conditions of the assay, Phytosteryl/Octyldodecyl Lauroyl Glutamate was not mutagenic.

An in vitro assay was performed to assess the potential of Phytosteryl/Octyldodecyl Lauroyl Glutamate in 0.5% acetone to induce structural chromosome aberrations in Chinese hamsters V79 cells in two parallel cell cultures.[10] In both independent experiments, no biologically relevant increase in the number of cells carrying structural chromosomal aberrations were observed after treatment with the test substance ranging in concentration from 2.5 µg/ml to 2500 µg/ml, with and without S9 liver activation. One instance of increase in 1250 µg/ml concentration in the absence of S9 was noted, however this was not reproducible and was not considered biologically relevant. Thus, the test substance was considered to be non-clastogenic.

OTHER RELEVANT STUDIES

Because skin irritation is a sign of dermatitis (skin inflammation), data on anti-inflammatory activity may be useful in evaluating the safety of Rosa Centifolia Flower Extract in the absence of skin irritation data.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal irritation and sensitization studies are described in Table 4, and summarized below.

According to summary data, an in vitro cell viability assay was performed, using EpiSkin™ reconstituted human epidermis. The test substance, a product containing 1% Phytosteryl/Octyldodecyl Lauroyl Glutamate, was predicted to be non-

irritating.[11] In a 24-h patch test, in which an occlusive patch containing 15 µl of a product containing 100% Phytosteryl/ Behenyl/Octyldodecyl Lauroyl Glutamate cream was applied to 31 subjects, the test article was determined to be a non-irritant.[4] In a human cumulative irritation patch test with 25 subjects that took place over 7 d, a face cream containing 1% Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate was determined to be non-irritating.[12] A 7-d semi-occlusive cumulative irritation patch study with a face cream containing 1.5% Phytosteryl/Octyldodecyl Lauroyl Glutamate was performed with 38 subjects; no evidence of irritation was observed.[13]

In a direct peptide reactivity assay (DPRA), Phytosteryl/Octydodecyl Lauroyl Glutamate was prepared as a 100 mM stock solution and tested for cysteine and lysine depletion.[14] Both peptides showed minimal reactivity. In a human repeated insult patch test (HRIPT), a face cream containing 5% Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate (102 subjects, tested neat, occlusive patch) was not a sensitizer.[15] In another HRIPT, a mixture containing 5.99% Phytosteryl/Octyldodecyl Lauroyl Glutamate (219 subjects; tested neat, occlusive patch) was not an irritant or a sensitizer.[16]

OCULAR IRRITATION STUDIES

Phytosteryl/Behenyl/Octydodecyl Lauroyl Glutamate

A tissue equivalent assay, measuring the conversion of 3-[4,5,-dimethylthiazol-2-y1]-2,5-diphenyltetrazolium bromide (MTT) by EpiOcular™ cultures, was performed to test the potential ocular irritancy of a face cream containing 1% Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate.[17] Approximately 100 µl of each test article was administered undiluted and then incubated. A face cream containing 1% Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate did not reduce MTT in the absence of viable tissue; the t_{50} (duration of exposure resulting in a 50% decrease in MTT conversion) was > 24 h.

CLINICAL STUDIES

Phytosteryl/Octyldodecyl Lauroyl Glutamate

In a human in-use test, a product containing 0.49995% Phytosteryl/Octyldodecyl Lauroyl Glutamate was applied to the eye area and lashes by 30 female subjects to assess skin and eye acceptability.[18] A pea-sized amount was applied to the eye area each morning and evening, and the product was swiped along the lash line each evening. On day 1, before the first application. and on day 29, a clinical examination of the skin was performed by a dermatologist and of the eyes was performed by an ophthalmologist. No adverse clinical signs were observed by the dermatologist or the ophthalmologist after 28 d of use, and no skin or eye discomfort was reported by the subjects.

SUMMARY

The safety of 3 phytosteryl glutamates as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, Phytosteryl/Octyldodecyl Lauroyl Glutamate and Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate are reported to function in cosmetics as skin conditioning agents and Phytosteryl/Behenyl/Octyldodecyl/Isostearyl Lauroyl Glutamate is reported to function as a hair conditioning agent and skin conditioning agent.

According to 2022 FDA VCRP data, Phytosteryl/Octyldodecyl Lauroyl Glutamate has the greatest frequency of use; it is reported to be used in 325 cosmetic products, (311 leave-on products and 14 rinse-off products). The results of a concentration of use survey conducted by the Council in 2021 indicate Phytosteryl/Octyldodecyl Lauroyl Glutamate has the highest concentration of use; it is used at maximum use concentrations up to 25.6% in leave-on products. The maximum concentration of use reported for Phytosteryl/Octyldodecyl Lauroyl Glutamate is very similar; it is reported to be used at up to 25% in rouges and in lipsticks.

In a short-term oral toxicity study, Phytosteryl/Octyldodecyl Lauroyl Glutamate was administered by gavage to SPF-bred Wistar rats of both sexes at dose levels of 50, 200, or 1000 mg/kg for 28 d. No experimental substance-related clinical signs were noted, along with no changes in functional observational battery, grip strength, locomotor activity, food consumption, and body weight were noted. Changes in hematology or clinical chemistry parameters, organ weights, or macroscopic and microscopic findings were also not observed.

Phytosteryl/Octyldodecyl Lauroyl Glutamate was not mutagenic in a reverse mutation assay, with or without metabolic activation, when tested at up to 5000 µg/plate. It was also not genotoxic, with or without metabolic activation, in a chromosomal aberration when tested at up to 2500 µg/plate in Chinese hamster V79 cells.

An in vitro cell viability assay was performed, using EpiSkin™ reconstituted human epidermis. The test substance, a product containing 1% Phytosteryl Octyldodecyl Lauroyl Glutamate, was predicted to be non-irritating. In a 24-h patch test in which an occlusive patch containing 15 µl of a Phytosteryl/Behenyl/Octyldodecyl Lauroyl cream (concentration not stated) was applied to 31 subjects, the test article was determined to be a non-irritant. In a human cumulative irritation patch test with 25 subjects that took place over 7 d, a face cream containing 1% Phytosteryl/Behenyl/ Octyldodecyl Lauroyl Glutamate was determined to be non-irritating. A 7-d semi-occlusive cumulative irritation patch study with a face cream containing 1.5% Phytosteryl/Octyldodecyl Lauroyl Glutamate was performed with 38 subjects; no evidence of irritation was observed.

In a DPRA, Phytosteryl/Octyldodecyl Lauroyl Glutamate was prepared in a 100 mM stock solution and tested for cysteine and lysine depletion. Both peptides showed minimal reactivity. An HRIPT with a face cream containing 5%

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate (102 subjects, tested neat, occlusive patch) was not a sensitizer. In another HRIPT, Phytosteryl/Octyldodecyl Lauroyl Glutamate (5.999%, 219 subjects; tested neat, occlusive patch) was not an irritant or sensitizer.

A tissue equivalent assay measuring the conversion of MTT by EpiOcular™ cultures to test the potential ocular irritancy of a test article containing 1% Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate in a face cream was performed. Approximately 100µl of each test article was administered undiluted. A time range finding assay was performed with exposure times ranging from 1-16 h, and a definitive assay whereby three to five exposure times were treated in duplicate. In both cases the test articles did not reduce MTT in the absence of viable tissue

A human in-use test of a product containing 0.49995% Phytosteryl/Octyldodecyl Lauroyl Glutamate was performed on 30 female subjects. A pea-sized amount was applied to the eye area and lashes. On day 1, before the first application. and on day 29, a clinical examination of the skin was performed by a dermatologist and of the eyes was performed by an ophthalmologist. No adverse clinical signs were observed by the dermatologist or the ophthalmologist after 28 d of use, and no skin or eye discomfort was reported by the subjects.

DISCUSSION

This assessment reviews the safety of 3 phytosteryl glutamates. The Panel concluded that the available data are insufficient for determining the safety of these ingredients under the intended conditions of use. The Panel noted a lack of relevant safety data and determined that the data needs from the original Insufficient Data Announcement from the June 2022 Panel meeting remain unmet. In order to come to a conclusion of safety for these cosmetic ingredients, the following additional data are needed:

- method of manufacturing
- impurities
- 28-day-dermal toxicity
    - if positive, other toxicological endpoints (e.g., developmental, and reproductive toxicity, genotoxicity, carcinogenicity, etc.) may be needed
- sensitization and irritation data for Phytosteryl/Octyldodecyl Lauroyl Glutamate at maximum concentration of use
- ocular irritation, if available

The Panel expressed concern regarding heavy metals that may be present in these ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in these ingredients before blending into cosmetic formulations.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (for example, Phytosteryl/Octyldodecyl Lauroyl Glutamate is reported to be used in hairsprays (concentration not reported), aerosol deodorant (up to 0.1 %), and in face powders (at concentrations up to 5%)). 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.

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

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination that the following 3 phytosteryl glutamates are safe under the intended conditions of use in cosmetic formulations:

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate
Phytosteryl/Behenyl/Octyldodecyl/Isostearyl Lauroyl Glutamate
Phytosteryl/Octyldodecyl Lauroyl Glutamate

TABLES

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

Ingredient/CAS No.	Definition	Function(s)
Phytosteryl/Octyldodecyl Lauroyl Glutamate 220465-88-3	Phytosteryl/Octyldodecyl Lauroyl Glutamate is the mixed ester of phytosterol and octyldodecanol with lauroyl glutamic acid.	Skin-Conditioning Agents – Occlusive
Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate	Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate is the mixed ester of phytosterol, behenyl alcohol, and octyldodecanol with lauroyl glutamic acid.	Skin-Conditioning Agents – Occlusive
Phytosteryl/Behenyl/Octyldodecyl/ Isostearyl Lauroyl Glutamate	Phytosteryl/Behenyl/Octyldodecyl/Isostearyl Lauroyl Glutamate is the mixed ester of phytosterols, behenyl alcohol, octyldodecanol and isostearyl alcohol with lauroyl glutamic acid.	Hair Conditioning Agents; Skin-Conditioning Agents – Emollient

Table 2. Gel permeation chromatography of Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate [4]

Peak No.	No. Avg. Molecular Weight	Weight average molecular weight	Size average molecular weight	Molecular weight at the highest peak	Degree of dispersion	Area%
1	1,344	1,372	1,402	1,389	1.021	74.2
2	746	757	768	765	1.015	13.8
3	383	396	409	388	1.034	12.0

Table 3. Frequency (2022)[5] and concentration (2021)[3] of use according to duration and exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Phytosteryl/Octyldodecyl Lauroyl Glutamate		Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate		Phytosteryl/Behenyl/Octyldodecyl/ Isostearyl Lauroyl Glutamate	
Totals*	**325**	**0.005-25**	**25**	**NR**	**1**	**0.00028-25.6**
Duration of Use						
Leave-On	*311*	*0.01-25*	*25*	*NR*	*1*	*0.03-25.6*
Rinse-Off	*14*	*0.005-2*	*NR*	*NR*	*NR*	*0.00028-1*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	26	0.1-12	4	NR	NR	1-8.6
Incidental Ingestion	133	1-25	1	NR	1	0.1-7
Incidental Inhalation-Spray	1; 94[a]; 40[b]	0.1-2 [a]	4 [a];4 [b]	NR	NR	0.2 [a]
Incidental Inhalation-Powder	40[b]	5; 0.01-8[c]	4 [b]	NR	NR	1; 0.03-5[c]
Dermal Contact	178	0.005-25	24	NR	NR	0.00028-25.6
Deodorant (underarm)	NR	not spray: 0.1 spray: 0.1	NR	NR	NR	NR
Hair – Non-Coloring	13	0.1-2	NR	NR	NR	0.2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	133	0.005-25	1	NR	1	0.1-7
Baby Products	NR	0.3	NR	NR	NR	NR

NR = Not Reported

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

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

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

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

Table 4. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION					
In Vitro					
Mixture containing 1 % Phytosteryl/Octyldodecyl Lauroyl Glutamate	150 mg ± 5 mg, applied in duplicate	2 different lots of reconstructed human epidermis (EpiSkin™)	Epidermis was prepared; a negative and positive control were tested in triplicate. At the end of incubation an MTT test was performed. Samples were plated, biopsied, and the epidermis was separated from the collagen and transferred to tubes. Cell viability was then determined. Acceptability and expression of results followed	Mean viability greater than 50% is interpreted as being potentially non-irritant; in two samples the mean viability resulted in 81.1% and 72.4%, thus this mixture is considered potentially non-irritant.	[11]
Human					
Phytosteryl/Behenyl/ Octyldodecyl Lauroyl Glutamate cream (concentration not specified)	15 µl, applied as is.	31 subjects	24-h occlusive patch test. The test sample was applied to the backs of subjects and fixed with plaster. Reactions were scored after 30 min, and at 24 and 48 h after patch removal.	One subject had a 0.5 score after 30 min that resolved to 0 at 24 and 48 h after patch removal. Another subject had a score of 0.5 only at 48 h after patch removal. All other subjects had scores of 0 at all time points. This cream is considered a non-irritant on human skin.	[4]
Face cream containing 1% Phytosteryl/Behenyl/ Octyldodecyl Lauroyl Glutamate	0.2 ml, applied neat	25 subjects	Human cumulative irritation patch test. On study day 1, a semi-occlusive patch containing 0.2.ml of the test sample was applied to the backs of subjects for 23 (+/- 1) h. On study days 2-6, patches were removed and graded 30 min following patch removal using a 60-W daylight blue bulb. Patches were then reapplied to the same area on the subjects. On study day 7, patches were removed and graded.	On the last day of the study, 5 subjects exhibited elevated irritation grades (≥ 2). All elevated grades were resolved. Two adverse events occurred during the course of the study, but were related to study procedures (i.e., tape irritation), not the test study material. Based on the cumulative irritation index, no unexpected skin conditions were observed and the test material elicited skin responses similar to the negative irritant control.	[12]
Facial essence containing 1.5% Phytosteryl/Octyldodecyl Lauroyl Glutamate	0.2 ml, applied neat	38 subjects	A 7-d semi-occlusive cumulative irritation patch study was performed. Distilled water served as the negative control and 0.75% SLS served as a positive control. Prior to the first application, sites were wiped with 70% isopropyl alcohol. Two-tenths (0.2) ml of the test sample was applied with a 2cm x 2cm pad to the back and upper arm for 23 (± 1) h and then removed. After patch removal sites were evaluated, and the responses recorded. This was repeated daily for 7 d.	Under the conditions employed in the study, the subjects showed no evidence of irritation.	[13]
SENSITIZATION					
In Chemico					
Phytosteryl/Octyldodecyl Lauroyl Glutamate	acetonitrile		A DPRA measuring reactivity (percent depletion) of cysteine and lysine peptides was conducted on Phytosteryl/Octydodecyl Lauroyl Glutamate dissolved in acetonitrile. The positive control was in the appropriate range for both peptides cysteine 60.8%<mean<100%; Lysine: 40.2<mean<69.4%)	The percent peptide depletion value of cysteine was 1.8% and 0.1% for lysine. Depletion less than 14.9 is considered to have no, or minimal reactivity, and is predicted to be negative for dermal sensitization. The control had the expected results and was predicted to have minimal reactivity.	[14]
Human					
Face cream containing 5% Phytosteryl/Behenyl/ Octyldodecyl Lauroyl Glutamate	0.2 ml applied as neat	102 subjects	HRIPT evaluating sensitization potential. During induction product was placed on an occlusive patch (2 cm x 2 cm) no longer than 15 min prior to patch application. The induction phase consisted of nine 24-h applications made over 3 wk. After a 10–15-d non-treatment period, challenge patches were applied for 24 h to previously untreated sites. Reactions were scored at 48 h and 72 h after patch removal.	During induction, no reactions were reported, and none were observed for any of the subjects at challenge. Under the conditions employed in this study, there was no evidence of sensitization to the product.	[15]

Table 4. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Mixture containing 5.999% Phytosteryl/ Octyldodecyl Lauroyl Glutamate	0.2ml applied as supplied.	219 subjects	HRIPT evaluating sensitization potential. During induction, product was placed on an occlusive patch (2 cm x 2 cm), which was applied to the infrascapular area of the back (either to right or left of midline), or to the upper arm. Induction phase consisted of nine 24-h applications made over 4 consecutive weeks. After a 10-15 d non-treatment period, challenge patches were applied for 24 h to previously untreated sites. Reactions were scored at 48 h and 72 h after patch removal.	During induction, no reactions were reported, and none were observed for any of the subjects at challenge. Under the conditions employed in this study, there was no evidence of sensitization to the product.	[16]

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

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