Safety Assessment of Soy-Derived Ingredients as Used in Cosmetics

Status: Draft Report for Panel Review

Release Date: May 10, 2019 Panel Meeting Date: June 6-7, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer.



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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Priya Cherian, Scientific Analyst/Writer

Date: May 10, 2019

Subject: Draft Report on Soy-Derived ingredients

Enclosed is a draft report on 28 soy-derived ingredients. This ingredient family comprises cosmetic ingredients that are derived from the soybean plant (*Glycine soja* and *Glycine max*).

The attached report (soy062019rep) includes the following unpublished data that were received from the Council:

- 1) Use concentration data (soy062019data1)
- 2) Product specifications of a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract (soy062019data2)
- 3) Method of manufacturing data on a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract (soy062019data2)
- 4) Specifications for organic constituents/impurities on a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract (soy062019data2)
- 5) Cellular viability assay on a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract (soy062019data2)
- 6) HRIPT on a leave-on formulation containing 0.3% Glycine Soja (Soybean) Germ Extract (soy062019data3)
- 7) 48-hour patch test and in vitro ocular irritation data on a 13% Glycine Soja (Soybean) Seedcake Extract (in water) tested at 4% (*soy062019data4*)

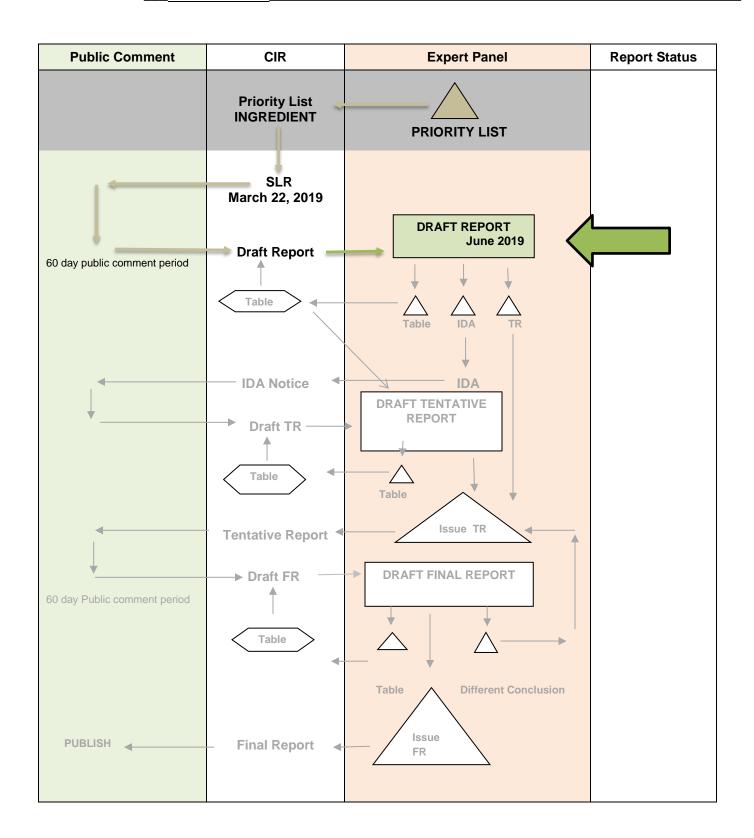
Also included in this package for your review are the CIR report history (*soy062019hist*), flow chart (*soy062019flow*), literature search strategy (*soy062019strat*), ingredient data profile (*soy062019prof*), and 2019 FDA VCRP data (*soy062019fda*). Comments provided by Council were received and addressed (*soy062019pcpc*).

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

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Soy-Derived Ingredients

MEETING ____June 2019



CIR History of:

Soy-Derived Ingredients

February 2019

A Scientific Literature Review (SLR) on the Soy-derived ingredients was issued on February 14, 2019. Unpublished data were received from the Council after announcement of the SLR.

March 2019

The following unpublished data were received from council:

- -specifications of a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract
- -list of limitations on possible allergens of a trade name mixture containing Glycine (Soja) Phytoplacenta Extract
- -method of manufacturing information on a trade name mixture containing Glycine (Soja) Phytoplacenta Extract
- -cell viability assay on a trade name mixture containing Glycine (Soja) Phytoplacenta Extract

April 2019

- -unpublished data was received from council regarding an HRIPT on a leave-on product containing 0.3% Glycine Soja (Soybean) Germ Extract
- -unpublished data received from Council regarding a 48-hour patch test and an in vitro ocular irritation assay on a mixture consisting of water and Glycine Soja (Soybean) Seedcake Extract (13%)
- -Draft report was revised to include the unpublished data from Council

June 2019

-Panel reviews the Draft Report

					Soy-I	Derive											Quote Priya (ian											
						Toxi kine		Acı	ute T	ox		peat se T		DA	RT	Gen	otox	Ca	rci	Dermal Irritation				erma sitiza			Ocu Irrita		Clini Stud	
	Reported Use	GRAS	Method of Mfg	Constituents	Impurities	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
Glycine Max (Soybean) Callus Culture																														
Glycine Max (Soybean) Callus Culture Extract																														
Glycine Max (Soybean) Callus Extract Glycine Max (Soybean) Fiber																														
Glycine Max (Soybean) Flower/Leaf/Stem Juice																														
Glycine Max (Soybean) Leaf Cell Extract			X																											
Glycine Max (Soybean) Phytoplacenta Conditioned Media																														
Glycine Max (Soybean) Phytoplacenta Extract	X				X																									
Glycine Max (Soybean) Pulp			X	X																										
Glycine Max (Soybean) Seed Extract Glycine Max (Soybean) Seedcake	X																					Х					Х			
Extract Glycine Max (Soybean) Seedcoat Extract			X	X					X			X																		
Glycine Max (Soybean) Seed Powder																														
Glycine Max (Soybean) Sprout Extract			X																			X					X			
Glycine Soja (Soybean) Extract	X		X	X			X					X										X								X
Glycine Soja (Soybean) Fiber	T 7		T 7									37																		
Glycine Soja (Soybean) Flour Glycine Soja (Soybean) Germ Extract	X		X	X								X													X					
Glycine Soja (Soybean) Germ Extract	Λ			Λ																					Λ					
Glycine Soja (Soybean) Lipids	X																													
Glycine Soja (Soybean)	21																													
Phytoplacenta Extract			X																											
Glycine Soja (Soybean) Seed	X																													
Glycine Soja (Soybean) Seedcake Extract																													_	
Glycine Soja (Soybean) Seed Extract	X																													
Glycine Soja (Soybean) Seed Powder																														

1

Glycine Soja (Soybean) Seed Water										
Gylcine Soja (Soybean) Sprout										
Extract										

^{* &}quot;X" indicates that data were available in a category for the ingredient

[Soy-Derived Ingredients]

Ingredient	CAS#	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Glycine Max (Soybean) Callus Culture		X	X				X													
Glycine Max (Soybean) Callus Culture Extract		X					X													
Glycine Max (Soybean) Callus Extract		X	X				X													
Glycine Max (Soybean) Fiber		X	X	X			X													
Glycine Max (Soybean) Flower/Leaf/Ste m juice		X					X													
Glycine Max (Soybean) Leaf Cell Extract		X					X													
Glycine Max (Soybean) Leaf Extract		X		X			X													
Glycine Max (Soybean) Phytoplacenta Conditioned Media		X					X													
Glycine Max (Soybean) Phytoplacenta Extract		X					X													
Glycine Max (Soybean) Pulp		X	X				X													
Glycine Max (Soybean) Seedcake Extract		X					X													
Glycine Max (Soybean) Seedcoat Extract		X		X			X													
Glycine Max (Soybean) Seed Powder		X					X													
Glycine Max (Soybean) Sprout Extract		X	X	X			X													

Ingredient	CAS#	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ЕСНА	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Glycine Soja (Soybean) Extract		X		X			X													
Glycine Soja (Soybean) Fiber		X					X													
Glycine Soja (Soybean) Flour	68513-95-1	X		X			X													
Glycine Soja (Soybean) Germ Extract		X					X													
Glycine Soja (Soybean) Hull		X					X													
Glycine Soja (Soybean) Lipids		X					X													
Glycine Soja (Soybean) Phytoplacenta Extract		X					X													
Glycine Soja (Soybean) Seed		X					X													
Glycine Soja (Soybean) Seedcake Extract		X					X													
Glycine Soja (Soybean) Seed Extract		X					X													
Glycine Soja (Soybean) Seed Powder		X					X													
Glycine Soja (Soybean) Seed Water		X					X													
Glycine Soja (Soybean) Sprout Extract		X					X													

X = useful hits were found

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- additional terms will be used as appropriate

Key Words: dermal, irritation, sensitization, inhalation, metabolism, toxicity

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary search results are reviewed to identify relevant documents

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;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- 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
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) http://www.ntis.gov/
- NTP (National Toxicology Program) http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency REACH dossiers) http://echa.europa.eu/information-on-chemicals;;jessionid=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/
- IUCLID (International Uniform Chemical Information Database) https://iuclid6.echa.europa.eu/search
- 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
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.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

Botanical Websites, if applicable

- Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- European Medicines Agency Herbal Medicines http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

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INTRODUCTION

This is a safety assessment of the following 28 soy-derived ingredients as used in cosmetic formulations:

Glycine Max (Soybean) Callus Culture
Glycine Max (Soybean) Callus Culture Extract
Glycine Max (Soybean) Callus Extract
Glycine Max (Soybean) Callus Extract
Glycine Soja (Soybean) Fiber
Glycine Max (Soybean) Fiber
Glycine Soja (Soybean) Germ Extract

Glycine Max (Soybean) Flower/Leaf/Stem Juice Glycine Soja (Soybean) Hull

Glycine Max (Soybean) Leaf Cell Extract
Glycine Soja (Soybean) Lipids
Glycine Max (Soybean) Lipids

Glycine Max (Soybean) Leaf Extract Glycine Soja (Soybean) Phytoplacenta Extract

Glycine Max (Soybean) Phytoplacenta Conditioned Media Glycine Soja (Soybean) Seed

Glycine Max (Soybean) Sprout Extract

Glycine Max (Soybean) Phytoplacenta Extract
Glycine Max (Soybean) Pulp
Glycine Max (Soybean) Seed Extract
Glycine Soja (Soybean) Seed Powder
Glycine Max (Soybean) Seed Cake Extract
Glycine Soja (Soybean) Seed Water

Glycine Max (Soybean) Seedcoat Extract
Glycine Max (Soybean) Seed Powder

Glycine Max (Soybean) Seed Powder

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the majority of these ingredients are reported to function as antioxidants, skin protectants, skin-conditioning agents – miscellaneous, and hair-conditioning agents; several other functions are also reported (Table 1).

Several soy-derived ingredients such as Glycine Soja (Soybean) Oil, Glycine Soja (Soybean) Sterols, Glycine Soja (Soybean) Peptide, Glycine Soja (Soybean) Polypeptide, and Glycine Soja (Soybean) Protein, have been reviewed by the Cosmetic Ingredient Review (CIR), and were considered safe as used in cosmetics in the present practices of use and concentration described in the safety assessment. The full reports on these ingredients can be accessed on the CIR website (https://www.cir-safety.org/ingredients); therefore, data on these ingredients will not be included in this report.

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

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (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.

Botanicals, such as soy-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, CIR is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex mixture.

It is often not known how the substance being tested in a study compares to the cosmetic ingredient. In the report text, if it is known that the material being tested is a cosmetic ingredient, the INCI naming convention will be used (i.e., the names of cosmetic ingredients are capitalized, without italics (e.g., Glycine Max (Soybean) Leaf Extract)). If it is not known that the test substance is the same as the cosmetic ingredient, the taxonomic naming conventions (i.e. with genus and species name italicized (e.g., a *Glycine max* leaf extract) or generic terminology (e.g., soybean extract) will be used.

CHEMISTRY

Definition

All ingredients reviewed in this report are derived from the soybean plant (*Glycine max*). *Glycine max* is the domesticated version of its wild progenitor *Glycine soja*. According to the *Dictionary*, *Glycine max* is the accepted scientific name for *Glycine soja*. The definitions of the soy-derived ingredients included in this review are provided in Table 1.

Plant Identification

Soybeans (*Glycine max* and *Glycine soja*) are a species of legume native to East Asia, from where they have spread to Europe and the Americas.³ Soybean plant height varies greatly, ranging from 0.2 to 2 m. The leaves of the plant are trifoliate, and fall before seeds mature. The fruit is a hairy pod containing 2-4 seeds. Soybeans of both subgenera (*Glycine*

max and *Glycine soja*) are found in various colors. Typical soybeans are different shades of yellow, brown, green, or black.⁴ Compositions of soybeans may vary depending on the seed coat color. Details regarding this variation in composition dependent on color, are described in the Composition section of this report.

According to one study, differences in plant morphological characteristics are attributed between the two subgenera *Glycine max* and *Glycine soja*. The wild soybean, *Glycine soja*, grows in the form of creepers with many lateral branches. These plants flower later than the cultivated soybean and produce small black seeds. *Glycine max* produces large yellow seeds, with a fragile pod. In addition, differences at the genomic level between *Glycine max* and *Glycine soja* have been reported. However, such delineation between these species names is far from ubiquitous and these differences are not expected to affect their role in cosmetics; therefore, the generic terms "soy" and "soybean" are used throughout much of this report.

Method of Manufacture

The methods below are general to the processing of soy products, and it is unknown if they apply to cosmetic ingredient manufacture.

Glycine Max (Soybean) Leaf Extract

The production of a soy leaf extract involved leaf washing, grinding, freeze-drying, and extraction using a 30-fold volume of 80% ethanol for 4 hours at room temperature. The extracted solution was collected, and a vacuum evaporator was used to remove the ethanol solvent in the supernatant. The amount of extract yielded was $22.3 \pm 1.3\%$ on a dry weight basis.

Glycine Max (Soybean) Pulp

To produce a black soybean pulp, black soybeans were soaked in water in a 3:1 ratio for 8 hours. Pulp was obtained after grinding and removing the milk with a muslin cloth, and then freeze-dried.

Glycine Max (Soybean) Seedcoat Extract

In order to make a black soybean seedcoat extract, the black soybean seedcoat was extracted with acidic water and ethanol, purified using absorbent resin, and powdered by spray-drying.⁷

Glycine Max (Soybean) Seed Extract

To obtain a soybean powder, soybean seeds were washed with water, then dried. The dried samples were ground to obtain the powdered form. To produce methanolic and hydroalcoholic extracts of seed powder, samples were extracted separately with methanol (100% and 50% aqueous, respectively) by cold maceration. Methanolic samples were extracted three times with 280 mL methanol for 3 hours in an electrical shaker at 40° C. The extracts were then filtered and evaporated. Hydroalcoholic extracts were produced in a similar manner, using alcohol and water as the extraction agents.

Another method to produce seed powder extract involves successive extraction with solvents in increasing order of their polarity (hexane, chloroform, ethyl acetate, ethanol, and water). First, powder materials are passed through a sieve. The sieved powder is then separated via a Soxhlet extractor for 16 hours. The extract is then evaporated to dryness in a rotary vacuum evaporator at 40° C. In order to prepare an ethanolic extract of the black soybean, black bean seeds were dried and ground. The resulting powder was placed into an Erlenmeyer flask and suspended in 500 mL of 99% ethanol. The extract was then filtered and dried using a rotary evaporator. Glycine Soja (Soybean) Extract

An n-hexane soybean extract was produced by extracting soybeans (25 g) twice at room temperature by shaking for 48 hours with 500 mL n-hexane. The combined n-hexane extracts were then dried in a vacuum desiccator under reduced pressure and concentrated using a rotavapor at 40 °C. According to the same study, similar procedures are used in order to prepare ethyl acetate and ethanol soybean extracts.

Glycine Max (Soybean) Sprout Extract

According to one study, the production of black soybean sprout extract begins with soaking of the beans in deionized water. ¹¹ The beans are then germinated, harvested, dried, crushed, sonicated, filtered, and centrifuged to separate the components and collect the supernatant.

Glycine Max (Soybean) Flour

Soybean flour has been reported to be produced by mechanically removing the hull of the soybean, followed by extraction of the oil with hexane. ¹² The residual hexane is either removed by indirect heating followed by steam sparging in a desolventizer toaster or by direct contact with superheated hexane in a flash desolventizer. The desolventized soy is then heat-processed, ground, and isolated to the desired particle-size distribution according to product specifications.

Glycine Soja (Soybean) Phytoplacenta Extract

A trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract was prepared by processing (mechanical grinding/milling) the soybeans, filtration, aqueous extraction, addition of phenoxyethanol, methylparaben, and tetrasodium EDTA, and refiltration.¹³ Quality control is performed during the process.

Composition

Powder Extract

Soybeans contain many phytochemicals, such as phenolic acids, flavonoids, isoflavonoids, saponins, phytosterols, and sphingolipids. ¹⁴ In order to determine the composition of 24 different soybeans, soybean seeds were ground to a powder and extracted with 80% methanol. The results of this study can be viewed in Table 2. The majorities of the extracts were made up of carbohydrates (30.16 g/100 g), fats (19.94 g/100 g), and proteins (36.49 g/100 g). The isoflavonoids present in soybeans and soybean extracts have shown capacity to bind estrogen receptors and to elicit estrogen-like effects. ¹⁵ In addition, these isoflavones have shown anti-carcinogenic potential. Genotoxicity has also been observed in cells treated with these isoflavones, however, these effects are inconsistent, and are only prevalent in in vitro studies.

Germ Extract

The isoflavone content of dry soybean germ extracts, extracted from ethanol (60 - 70%), methanol (80%), or ethanol (60%), were evaluated. ¹⁵ The isoflavone content of each of these extracts were reported to be 40%, 26%, and 30%, respectively.

Soybean Extract

The composition of a black soybean ethanolic extract was studied using thin layer chromatography (TLC). Flavanoids, alkaloids, saponins, tannins, triterpenoids, and glycosides were found. In a different study, the anthocyanins, saponins, and isoflavones of a black soybean extract were examined. Approximately 1.3 g anthocyanins (as tannins) were present per 100 g. Isoflavones were found in the following amounts: daidzin (25 mg/100 g), daidzein (92 mg/100 g), genistin (22 mg/100 g), genistein (51 mg/100 g), and glycitin (16 mg/100 g). In soybeans, isoflavones are strongly associated with proteins. These isoflavones can be dissociated from soy-proteins using alcohol extraction which significantly diminishes the amount of bound-isoflavones.

According to high-performance liquid chromatography (HPLC), an n-hexane soy extract contained a total isoflavone concentration of 27 mg/25 g extract. Among these isoflavones were 40% daidzin, 56% genistin, 2% daidzein, and 2% genistein. An ethyl acetate soy extract and ethanolic soy extract contained total isoflavone concentrations of 48 mg/25 g and 52 mg/25 g, respectively. In a different study, a black soybean extract contained 32.5 mg gallic acid equivalents/g (gallic acid used as sample phenolic compound), 5.7% protein, 80.4 g glucose/100 g, and 5.1% lipid. The total phenolic acid content was 6652.2 μ g/g, including gallic acid, protocatechuic acid, caffeic acid, chlorogenic acid, *m*-coumaric acid, ferulic acid, and sinapic acid. The total phytochemical content was 11,776.5 μ g/g, including daidzein, genistein, glycitein, daidzin, genistin, glycitin, acetylganistin, acetylganistin, acetylganistin, and malonylganistin, and malonylgycitin. Flavanols included epigallocatechin (3003.8 μ g/g), epicatechin (635.8 μ g/g), and epicatechin gallate (735.5 μ g/g), and anthocyanins included cyanidin-3-*O*-glucoside (921.4 μ g/g), peonidin-3-*O*-glucoside (113.6 μ g/g), dephinidin-3-*O*-glucoside (50.9 μ g/g), petunidin-3-*O*-glucoside (40.7 μ g/g), and pelargonidin-3-*O*-glucoside (38.8 μ g/g).

Seedcoat (Hull)

Thirty-nine samples of soybean hulls from feed mills and soy processors throughout the US were collected to examine their chemical composition. ¹⁹ The mean values of nutrients and amino acids found in these samples can be seen in Table 3. Samples predominantly consisted of crude fiber, acid detergent fiber, neutral detergent fiber, and nitrogen-free extract. Soybeans vary in composition based on color and country of origin. Black soybeans have unique properties owing to its black hull. ²⁰ The black hull contains polyphenols, such as anthocyanins, procyanidins, and catechins. According to another study, the chemical composition of soybean hulls is dependent upon the efficiency of the dehulling process. ²¹ The soybean hulls may contain variable amounts of cellulose (29 - 51%), hemicelluloses (10 - 25%), lignin (1 - 4%), pectins (4 - 8%), proteins (11 - 15%), and minor extractives.

Soybean Flour

A comparison of the composition of soybeans differing in seed coat color was examined.⁴ Soybeans of a light yellow, dark yellow, brown, and black color were ground to a flour and analyzed for isoflavone content and other chemical composition. Flours were defatted using n-hexane as a solvent for lipid extraction. Lipid, protein, ash, crude fiber, and carbohydrate content were similar among all tested samples. The average amount of lipids, protein, ash, crude fiber, and carbohydrates were 19.05, 37.8, 4.2, 6.3, and 24.7 g/100 g, respectively. Isoflavone content was determined by HPLC. Soybean flour extracted from soybeans with a light yellow seed coat showed the highest isoflavone content (415.98 mg/100 g), while soybean flour extracted from soybeans with a dark yellow seed coat showed the lowest isoflavone content (220.88 mg/100 g). All samples showed significantly different levels of isoflavone glycosides. Malonyl genistin, for

example, was discovered in amounts of 74.98, 95.23, 138.57, and 116.29 mg/100 g, in dark yellow, brown, light yellow, and black soybean samples, respectively.

<u>Pulp</u>

HPLC was used to determine the isoflavone content of a black soybean pulp.⁷ The amounts of daidzin, daidzein, genistin, and genistein in the black soybean pulp were determined to be 2.85, 0.27, 1.85, and 0.51 mg/100 g, respectively. *Sprout*

The variation of isoflavone content in 17 different types of yellow and green soybean sprouts was studied using HPLC. Yellow soybean sprouts were produced in a dark room. For green soybeans sprouts, seeds were germinated in the dark and then transferred to a box under a yellow light source. Sprouts were separated into cotyledons, hypocotyls, and roots. The average isoflavone concentration in the cotyledon, hypocotyl, and root of the green sprouts was 2167, 1169, and 2399 μ g/g, respectively. The average isoflavone concentration in the cotyledon, hypocotyl, and root of the yellow sprouts was 2538, 1132, and 2852 μ g/g, respectively.

Leaf Extract/Seed Extract

The phytochemical content of ethanolic leaf and seed extracts were evaluated. The total phenol, flavonoid, beta carotene, and lycopene content in the ethanolic leaf extract was 1092, 877, 40, and 0.69 mg/100 g extract, respectively. The total phenol, flavonoid, beta carotene, lycopene, and ascorbic acid content in the ethanolic seed extract was 938, 274, 11, 10, and 1.3 mg/100 g extract, respectively. In a different study, the phytochemical content of a methanolic soybean leaf extract was studied via various chromatographic procedures. Among the 16 phytochemicals found were 6 isoflavones (4,5,7-trihydroxyisoflavone-7-O- β -D-glucopyranoside, 7-dihydroxy-6-methoxyisoflavone, 4,7-dihydroxyisoflavone, and 3',4',5-trihydroxyflavone-7-O- β -D-glucopyranoside, 4',5,7-tetrahydroxyflavone), 2 pterocarpans (coumestrol and glyceofuran), 2 phytosterols (soyasapogenol B and stigmasterol), 2 phenolic compounds (4-hydroxybenzoic acid and methyl-4-hydroxybenzoate) and 1 sugar alcohol (D-mannitol).

Impurities

Glycine Soja (Soybean) Phytoplacenta Extract

Product specifications for a trade name mixture consisting of water (78.93%), Glycine Soja (Soybean) Phytoplacenta Extract (20%), phenoxyethanol (0.90%), methylparaben (0.15%), and tetrasodium EDTA (0.02%), include the following parameters: < 20 ppm heavy metals, < 10 ppm lead, < 2 ppm arsenic, and < 1 ppm cadmium. These specifications have also included a number of organic constituents/impurities, which can be found in Table 4. In addition, this trade name mixture did not exceed current US Environmental Protection Agency (EPA) pesticide specifications.

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

In some cases, VCRP data were submitted under a non-INCI name. For example, Glycine Soja (Soybean) Flour is an INCI name, but *Glycine max* (soybean) flour, is not. VCRP data were available for *Glycine max* (soybean) flour, but not for Glycine Soja (Soybean) Flour; therefore, these data are reported for Glycine Soja (Soybean) Flour, as these names are believed to be synonymous because, according to the *Dictionary*, the accepted scientific name for *Glycine soja* is *Glycine max*.

According to 2019 VCRP data, Glycine Max (Soybean) Seed Extract is reported to be used in 395 formulations, 273 of which are leave-on formulations, and *Glycine max* (soybean) flour (synonymous with Glycine Soja (Soybean) Flour) is reported to be used in 66 formulations (Table 5). All other in-use ingredients are reported to be used in 51 formulations or less. The results of the 2016 concentration of use survey conducted by the Council indicate Glycine Soja (Soybean) Seed Extract has the highest concentration of use; it is used at up to 2% in face and neck products. Ingredients that are not reported to be in use, according to VCRP and Council survey data, are listed in Table 6.

Incidental ingestion of these soy-derived ingredients is possible as Glycine Max (Soybean) Seed Extract, Glycine Soja (Soybean) Lipids, and Glycine Soja (Soybean) Seed Extract are used in lipstick formulations at up to 0.65%. In addition, some soy-derived ingredients are used in in products applied near the eye (e.g. in eyeshadows at a maximum concentration of up to 0.09% Glycine Soja (Soybean) Lipids).

Additionally, some of the soy-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Glycine Soja (Soybean) Seed Extract is reported to be used at a concentration of 0.000001% in hair spray formulations. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 μ m, with propellant sprays yielding a greater fraction of droplets/particles < 10 μ m compared with pump sprays. Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. In addition, Glycine Max (Soybean) Seed Extract and Glycine (Max) Soybean Lipids are reported to be used in face powders, and could possibly be inhaled; concentration of use data were not reported for these uses. 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. $^{32-34}$

The soy-derived ingredients are not restricted from use in any way under the rules governing cosmetic products in the European Union. 35

Non-Cosmetic

Food

Soy has been a common staple in Asian diets for thousands of years, and is also currently present in modern Western diets. Soybeans can be processed to be used in or as food products such as soy milk, soy sauce, soy curds, tofu, miso, cheese, candies, ice cream, baked goods, and oil.³⁶ In addition, soy can be found in infant formulas. Soybeans and soybean constituents are commonly used as food fortifiers as their protein content is high. Soybean hulls are commonly used in poultry and swine feeding.¹⁹ In addition, the FDA requires allergen labeling when major allergens are included in food; these allergens include soybeans.³⁷

Industrial

Soybean meal and soybean proteins are used in the manufacture of synthetic fiber, adhesives, varnishes, paints, and pesticides. ^{14,36} In addition, soybeans are used for biodiesel fuel, upholstery, candles, ink, crayons, lubricants, and hydraulic fluid. ³⁸ Soybean hulls are used in the treatment of wastewater. ²¹

Medicine

Soybean germ extract has been reported to be used in herbal medication for the treatment of menopausal symptoms. Soy products are also taken as supplements to alleviate high blood pressure/cholesterol, and to increase bone health. None of the ingredients included in this report are used in US FDA-approved medical preparations; however, soybean oil is used in an FDA-approved, intravenous medication, used to provide a source of calories and essential fatty acids for patients requiring parenteral nutrition when oral or enteral nutrition is not possible or insufficient. It is also used as an inactive ingredient in FDA-approved oral and topical treatments for acne, hypoparathyroidism, vitamin D deficiency, hypocalcemia, and hypophosphatemia.

TOXICOKINETIC STUDIES

When rats were given a single oral dose of a soybean extract containing 74 µmol genistein and 77 µmol daidzein/kg as conjugates, the urinary excretion of daidzein and genistein was 17.9% and 11.9%, respectively, over a 48-hour post-dose period. No other details regarding this study were provided. In a human study, 11 German post-menopausal women were given a bolus dose of a commercial soy extract. Sulphoglucuronides were the major metabolites of daidzein and genistein in the plasma, and 7-*O*-glucuronides were the predominant metabolites in the urine.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

No acute oral, dermal, or inhalation toxicity studies were discovered in the published literature regarding these soyderived ingredients, and no unpublished data were submitted. However, a study regarding the oral toxicity of a soybean hull extract was found and is summarized below.

Oral

Nine male and nine female Sprague-Dawley rats, as well as 42 male and 44 female C57BL/6 mice were given a single oral dose of black soybean hull extract (2.5 g/kg bw) via gavage. Control animals were given purified water. Rats were observed for 14 days, and mice were observed for 15 days for signs of morbidity or mortality. No deaths, significant decreases in body weight, or gross pathological abnormalities were observed in either species. The LD_{50} was reported to be greater than 2.5 g/kg bw in rats and mice.

Short-Term Toxicity Studies

No short-term dermal or inhalation studies were discovered in the published literature, and no unpublished data were submitted.

Oral

Glycine Soja (Soybean) Extract

The potential toxicity of a hot water extract of black soybeans was studied. Sprague-Dawley IGS rats (6/sex/group) were given 0, 0.5, 1.5, or 5% black soybean extract in the diet for 28 days. No deaths or abnormalities regarding the general conditions of the animals were reported throughout the study. At week 4, a statistically significant increase in urinary potassium values were found in females receiving 5% black soybean extract compared to controls. No treatment-related hematological adverse effects were observed. Platelet count levels were significantly lower in all dosed males, however, changes were minimal and values were within historical control data. Significant elevation of mean corpuscular volumes and reticulocytes levels were noted in the highest dosed males, however, these changes were also minimal and values were within historical control data. A statistically significant increase in alkaline phosphatase enzymes was found in male rats given 1.5% black soybean extract; however, these changes were not dose-dependent. A statistically significant lowering of relative epididymis weights were found in all extract-dosed males. In addition, a statistically significant but non-dose-dependent elevation of relative heart weight was found in females given 0.5% black soybean extract.

Subchronic Toxicity Studies

No subchronic dermal or inhalation studies were discovered in the published literature, and no unpublished data were submitted.

Oral

Glycine Soja (Soybean) Extract

The systemic toxicity of aqueous and ethanolic soybean extracts was studied in F344 rats (40 rats/sex). The grinded extract was mixed into the diet for 13 weeks at doses of 0, 1.25, 2.5, and 5%. The composition of the extract was 94% saponins and 6% isoflavones. Neither mortality nor deterioration in general conditions were observed during the course of the study. Results given in this study did not specify which solvent was used when stating extract-induced effects. Statistically significant body weight reductions were noted in males treated with 5% soybean extract, and in all treated females. Statistically significant decreases in red blood cell count, hematocrit levels, and an increase in mean corpuscular volume were detected in 5% males. This effect was not seen in females. Statistically significant, but minimal increases in total protein, albumin, calcium, and aspartate aminotransferase were found in males treated with 2.5% or higher. In females, significant increases of potassium and decreases in chloride were observed in the 5% group. Males in the 5% group displayed a decrease in absolute heart and spleen weights. Dose-dependent decreases in absolute brain weights were observed in male rats dosed with 2.5% and higher. A statistically significant increase in absolute liver weight was observed, in a dose-dependent manner, in all treated animals. Relative kidney weights were also increased in the highest dosed groups of both sexes. Females in the high-dose group displayed a statistically significant decrease in absolute lung weight. Dosedependent decreases in the absolute weights of the heart and spleen were observed in females at 2.5% and 5%. Soybeanextract related effects were noted in the prostate, vagina, and ovaries. Male rats in the 5% group displayed epithelial atrophy in the ventral prostate, accompanied by cytoplasmic vacuolation and decreases of the luminal secretory fluid. In female rats treated with 2.5% and above, increased incidences of mucification and atrophy of the vaginal epithelium, as well as increased atretic follicles, were observed.

Glycine Soja (Soybean) Fiber

Soluble soybean fiber (SSF) was given in the diet to Sprague-Dawley CD rats (20/sex/group) at concentrations of 2, 3, and 4%, for three months. A separate group was given an untreated diet, and served as the control. The SSF was extracted from the fibrous residue in the production process of soy protein. The estimated amount of fiber in the SSF was approximately 72 - 77%. There were no test article related deaths during the study. In both sexes, weight gain in all dose groups during weeks 2 - 7 was low compared to the controls; however this effect was not dose-related. By the end of the period, weight gain differences were minimal in dosed groups versus control animals. Decreased food consumption was noted in males (weeks 2 - 5; all dose levels) and in females (weeks 2 - 4; all dose levels). This was followed by a period of increased food intake in both males (weeks 8 - 10; all dose levels) and females (weeks 8 - 11; all dose levels). In all treated males, an increased erythrocyte and decreased reticulocyte count was noted, however, these effects were not dose-dependent. In females, there was a slight, but dose-related increase in the hematocrit and erythrocyte counts of animals of the 3 and 4% dose groups. A reduction in spleen weight was noted in all dosed animals, however this effect was not dose-dependent, and no other histopathological adverse effects were found relating to this matter.

Chronic Toxicity Studies

No chronic dermal or inhalation studies were discovered in the published literature, and no unpublished data were submitted.

Oral

Glycine Max (Soybean) Seedcoat Extract

Thirty-three male and 35 female C57BL/6 mice were randomly divided into three groups and fed a diet supplemented with 0, 2, or 5% of a black soybean seedcoat extract (acidic water and ethanol used as the extraction agent) for 26 weeks. The mean intake of the extract in males and females was 1468.9 and 2621 mg/kg bw/d in the 2% group, and 5074.1 and 7619.9 mg/kg bw/d, respectively, in the 5% group. A significant reduction in body weights was noted in 5% males compared to 2% males and control males. At week 26, the abdominal fat of 5% males was 40% lower than that of controls. This effect was not seen in females. The white blood cell count in 5% males and red blood cell count, hemoglobin, and hematocrit levels in 5% females were significantly increased compared to control animals. Triglyceride and chloride levels in 5% males were significantly decreased. In female animals, triglyceride and blood urea nitrogen levels were decreased in the 5% group. In 5% males, an increase in the relative weights of the kidney, spleen, and brain was apparent. In the same dosing group, a decrease in the relative weight of the spleen was noted. In 5% females, absolute weights of the heart, liver, and kidney were decreased. No significant changes in final body weights were noted in any dosed females. In animals dosed with both 2% and 5% soybean seedcoat extract, in the duodenum, slight pigment accumulation in histiocytes of the lamina propria was found. Slight accumulation of pigment in Kupffer cells of the liver was apparent in 5% males and females.

Glycine Soja (Soybean) Flour

Sixty male Wistar rats were divided into three groups and given diets containing 19.1, 42.1, or 79.7% raw soy flour. 44 Each of the three groups was subdivided into two groups, one of which was fed ad libitum, and the other a single 4-hour meal per day. Two weeks after the start of the experiment, 5 rats per group were subjected to an injection of azaserine (0.5 mg/100 g bw), dissolved in 0.5 mL sterile saline. Injections were given once a week for 20 weeks. Rats were given their respective diets for up to 12 months. Azaserine injections had no effect on food intake or body weight. A significant decrease in food intake and body weight was noted in animals receiving increased levels of raw soy flour in the diet (P < 0.01). Animals fed one meal per day containing 19.1% raw soy flour reached 85% of the body weight of their ad libitum-fed counterparts. Animals fed diets containing 42.1% and 79.7% raw soy flour reached 76 and 62% of the body weight of the ad libitum-fed rats, respectively. Pancreas weights increased as the level of raw soy flour in the diet increased. Approximately 45% of all animals used in the experiment died prior to study termination. In rats fed 19.1% raw soy flour, 25% of rats fed ad libitum were alive at the end of the experiment, while 75% of rats fed only once per day survived until study termination. In rats fed 42.1% raw soy flour, 80% of the meal-fed animals survived vs. 62.5% in the ad libitum group. Carcinogenic effects observed in this study can be found in the Tumor Promotion section of this report.

Male albino mice (n = 216) were separated into 3 groups and fed diets of either raw soy flour, heated soy flour, or casein for up to 18 months. The soy flour diet consisted of soy flour (42.1%), glucose (15%), non-nutritive fiber (5%), corn oil (5.5%), lard (2.5%), DL-methionine (0.1%), choline chloride (0.2%), vitamin mix (2%), mineral mix (5%), and dextrin (22.6%). Animals were also given an injection of either azaserine (10 mg/kg/bw) or 0.9% sodium chloride. Growth of mice was significantly lower (P < 0.01) in mice given raw soy flour compared to mice given heated soy flour or casein. The injections with azeserine and sodium chloride did not seem to have an effect.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

No DART studies were discovered in the published literature regarding these soy-derived ingredients, and no unpublished data were submitted. However, a study analyzing the reproductive effects of orally ingested soybean was found and included below.

The potential reproductive toxicity of the soybean was tested in 20 male and 60 female rats. ⁴⁶ The rats were treated with processed soybean meal at 0, 100, 200 and 300 mg/kg bw for 65 days. The test substance was administrated via diet. No statistically significant effect of soybean meal on the weight of the testes and epididymis was observed. Sperm viability and sperm count were significantly reduced in a dose-dependent manner. In addition, sperm head abnormality was significantly increased in a dose-dependent manner. Rats in the control group displayed seminiferous tubules at various stages of development. Rats in the 100 mg/kg bw group had testicular tissues with compacted interstitial spaces, mild hemorrhaging along the Sertoli's cells, and slight degeneration of the spermatids. Rats treated with 200 mg/kg bw displayed similar effects, and rats treated with 300 mg/kg bw displayed adverse effects such as testicular tissues with inflammation of interstitial cells, severe hemorrhaging along the Sertoli's cells, and excessive degeneration of spermatids, and necrosis. The conception rate of female rats sired by males in the treated groups was reduced in a dose-dependent manner when compared to controls. No other effects regarding treated female rats were observed.

GENOTOXICITY

No genotoxicity studies were discovered in the published literature, and no unpublished data were submitted.

CARCINOGENICITY STUDIES

No carcinogenicity studies were discovered in the published literature, and no unpublished data were submitted.

TUMOR-PROMOTION STUDIES

Glycine Soja (Soybean) Flour

Sixty male Wistar rats were divided into three groups and given diets containing 19.1, 42.1, or 79.7% raw soy flour. ⁴⁴ Each of the three groups was subdivided into two groups, one of which was fed ad libitum, and the other one 4-hour meal per day. Two weeks after the start of the experiment, 5 rats per group were subjected to an injection of azaserine (0.5 mg/100 g bw), dissolved in 0.5 mL sterile saline. Injections were given once a week for 20 weeks. Rats were given their respective diets for up to 12 months. Twenty-seven rats died prior to the end of the study. Among these animals, pancreatic nodules were observed in 1/11, 3/7, and 6/9 rats given 19.1, 42.1, 79.7% raw soy flour, respectively. In rats that were sacrificed after 10-12 months, in the absence of azaserine injections, the incidence of nodules was low and unaffected by the feeding regime. Animals that received azaserine injections had a much higher incidence of nodules, which increased with the level of raw soy flour in the diet. No nodules were found in any other organ examined. Other toxic effects observed during this study can be seen in the Chronic Toxicity Studies section of this report.

ANTI-TUMORIGENICITY STUDIES

Glycine Soja (Soybean) Flour

In a 15-month study, 54 Syrian Golden male hamsters were divided into four groups and given raw soy flour, heated soy flour, raw soy flour/co-administered injection with N-nitrosobis(2-oxopropyl)amine (BOP), or heated soy flour / injected with BOP. BOP injections were given at a level of 10 mg/kg bw on days 7 and 14. Animals not given a BOP injection received an injection of 0.9% sodium chloride. The soy flour composition is the same as was used in the experiment above. Animals fed raw soy flour displayed a slower growth rate (P < 0.01) than those fed heated soy flour. At 7 - 8 months, animals injected with BOP lost weight at a significantly (P < 0.05) faster rate than animals injected with saline. No significant difference was found in the weights of the pancreas in any of the groups by the end of the study. In groups that did not receive BOP, tumor incidence was quite low; however, in groups that did receive BOP, tumor incidence was increased. Seven out of 8 surviving animals that were given heated soy flour and BOP injections had pancreatic adenomas, and 5 had pancreatic adenocarcinomas. One out of 11 surviving BOP-injected animals given raw soy flour had a pancreatic adenoma, and no adenocarcinomas.

OTHER RELEVANT STUDIES

Effect on Cancer Cell Proliferation

Glycine Soja (Soybean) Extract

The potential anti-proliferative effect of an ethanolic extract of the black soybean on A549 lung cancer cells was studied. The black soy ethanol extract was dissolved in 10% dimethyl sulfoxide (DMSO) at a concentration of 10 mg/mL. The extract was used to prepare final diluted concentrations of 6.25, 12.5, 50, 100, 200, 400, and 800 μ g/mL. Cancer cells were cultured for 1 week before exposure to the test substance. The cells were then subjected to 100 μ L of each dilution of the test substance as stated above. Each experiment was performed three times, and results were averaged. After incubation for 48 hours, cell viability was measured using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The extract exhibited cytotoxic activity in a concentration-dependent manner in A549 cells. Percent inhibition of A549 lung cancer cells by the soy ethanol extract was 5.2, 4.4, 20.6, 37, 52.8, 60.8, 68.7, and 83.8% when tested at concentrations of 6.25, 12.5, 50, 100, 200, 400, and 800 μ g/mL, respectively.

The effect of black soybean extract on the suppression of the proliferation of human gastric cancer (AGS) cells was studied. For this study, the soybean extract was obtained by extracting black soybean with acidified aqueous acetone. AGS cells were plated at a density of 5 x 10³ cells/well in 96-well plates. The effect of the extract on the growth of AGS cells was investigated using an MTT assay. After incubation (24 hours), the extract was added to the plates in concentrations of 1 - 5 mg/mL, and incubated for another 48 hours. The extract inhibited growth of AGS cells in a dose-dependent manner. When a concentration of 3 mg/mL extract was used on the AGS cells, cell viability was significantly decreased compared to control

cells (p < 0.05). Approximately 65.7, 38.8, and 22.5% cells survived after treatment with 3, 4, and 5 mg/mL of black soybean extract. The same procedure was performed on normal rat fibroblast cells. No cytotoxicity was observed when black soybean extract was used on these cells.

Glycine Max (Soybean) Leaf Extract

The anti-proliferative effects of an ethanolic extract of soybean leaves (SLE) were studied in both human colon cancer cells (HCT116) and human lung cancer cells (H1299). The treatment of the HCT116 cells with SLE at concentrations of 125, 250, and 500 μ g/mL for 72 hours resulted in a significant inhibition of growth (by 34-89%). When HCT116 cells were treated with the same concentrations of SLE for 96 hours, growth inhibition increased (by 62-87%). Treatment of H129 cells with SLE (125, 250, and 500 μ g/mL) inhibited growth by 45 - 85%. In both types of cancer cells, the growth inhibitory effects of SLE increased with increasing concentrations of SLE, showing a significant dose-response relationship. In addition to inhibition of growth, the effect of SLE on adhesion and migration of the human cancer cells was also studied. When H1299 cells were treated with SLE at 500 μ g/mL, a significant inhibition of migration was noted. Treatment of HCT116 and H1299 cells with SLE also inhibited cell adhesion to fibronectin by 21 - 31% (at 125 - 500 μ g/mL) and 14% (at 500 μ g/mL), respectively.

Epidermal Hyperplasia Inhibition

Glycine Soja (Soybean) Extract

The possible inhibition of retinoid-induced epidermal hyperplasia was studied in 7 human skin organ cultures. ⁴⁷ Cultures of human skin were incubated with 1 μ g/mL of 14-all *trans* retinoic acid (14-all *trans* RA) for 8 days. A soy extract was prepared by mixing 250 mg of soy powder in 2 mL of a basal medium. A DMSO extract was also prepared by dissolving 250 mg of soy powder in 1 mL of solvent. All of the soy dissolved in the DMSO, and this solution was used as a control. Hyperplasia-induced organ cultures were treated with soy extracts at 4, 20, or 40 μ g/mL. In the presence of 40 μ g/mL soy extract, retinoid-induced hyperplasia was reduced by 41% relative to the retinoid response in the absence of soy. Sixteen percent inhibition was observed at 4 μ g/mL, and 32% inhibition was observed at 20 μ g/mL.

Effects on Pigmentation

Glycine Soja (Soybean) Sprout Extract

An aqueous extract of black soybean sprouts was examined for whitening capacity. Whitening capacity was measured via the measurement of tyrosinase-inhibition. Tyrosinase inhibition capacity of the extract, when used at 40 mg/mL, reached 98%. Inhibition capacity reached 60-95% after treatment with 4 mg/mL of the extract, and 40% after treatment with 2 mg/mL of the extract.

Estrogenic Activity

Methanol extracts were prepared from soybeans and analyzed by measuring the MCF-7 (breast cancer cell line) cell proliferation in response to various concentrations of the extract $(0.1-100\,\mu\text{g/mL})$. Soybean extract $(0.1\,\mu\text{g/mL})$ caused an increase in proliferation to approximately 35% of what would be expected from estradiol; while at 100 $\mu\text{g/mL}$, proliferation was increased to 90%. In order to determine whether the induced cell proliferation was mediated via an estrogen receptor (ER)-dependent mechanism, the soybean extract $(100\,\mu\text{g/mL})$ was tested in combination with the pure estrogen antagonist, 7α -[9-[(4,4,5,5,5-pentafluoropentyl)-sulfinyl]nonyl] estra-1,3,5(10)-triene-3,17 β -diol (ICI 182,780). Testing of the soybean extract in combination with ICI 182,780 resulted in decreased activity. A reporter gene assay was also performed using human embryonic kidney cells (HEK 293 cells) in order to determine whether the effects of the extracts were mediated via ER α and/or ER β . Preferential agonist activity toward ER β was observed. For ER β transcriptional activation, the maximal value obtained at $100\,\mu\text{g/mL}$ was 79.7%, compared to 53.2% for ER α transcriptional activation.

A study was performed to analyze the effects of orally administered soybean extract, obtained using different extraction methods, on the skin of 64 Sprague-Dawley female rats (8/group). The specific soy extracts were administered via gavage each day for one month. Animals in group A were untreated, and animals in group B received carboxymethyl cellulose (0.5%); this solution was also used to dilute the extracts for administration to the experimental animals. Group C received an n-hexane soy extract at a dose of 100 mg/kg and group D received the same extract at a dose of 200 mg/kg. Groups E and F received ethyl-acetate soy extracts at doses of 100 and 200 mg/kg, respectively, and groups G and H received an ethanolic soy extract at 100 and 200 mg/kg, respectively. (Details about the preparation of these extracts can be seen in the Method of Manufacturing section of this report.) A statistically significant reduction in the number of estrogen receptor-positive cells (per 10 high-power fields) and an increase in the collagen layer thickness were observed (p < 0.05%) in all groups treated with a soy extract. The thickness of the collagen layer of the rats in group F (1154.93 μ M) was significantly higher than that of the rats in group A (864.32 μ M). The number of estrogen receptor-positive cells in group D (2.37) was significantly reduced compared to that of group A (6.87), B (8.25), and C (4.75). The number of estrogen receptors in all soy extracted –treated groups were decreased compared to that of the controls.

Cytotoxicity

Glycine Max (Soybean) Callus Culture

A trade name mixture containing water (100% w/w), Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%), was tested for cytotoxicity. The product showed a half maximal inhibitory concentration (IC $_{50}$) greater than 5 μ L/mL on human keratinocytes with an 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. No other details regarding this study were provided.

Glycine Soja (Soybean) Phytoplacenta Extract

The cytotoxic potential of a trade name mixture consisting of water (78.93%), Glycine Soja (Soybean) Phytoplacenta Extract (20%), phenoxyethanol (0.90%), methylparaben (0.15%), and tetrasodium EDTA (0.02%) was studied. Human dermal fibroblasts were treated with this trade name mixture at concentrations of 0.01, 0.1, and 1% and incubated for 24 hours. The test substance did not appear to have an effect on cellular viability.

Immunotoxicity

BALB/c mice were dorsally shaved and epicutaneously exposed to a crude soybean extract (50 mg/mL) containing 0.5% sodium dodecyl sulfate in distilled water (n = 9) or distilled water alone (n = 8). Each week, the skin of the animals was shaved and stripped 10 times using adhesive tape. Mice were also intraperitoneally injected with a mixture of midazolam, butorphanol, and medetomidine to control pain. Three times a week for 5 weeks, 50 μ L samples were applied epidermally. Various specific immunoglobulin E (IgEs) secreted in response to 7S globulin (Gly m 5), 11S globulin (Gly m 6), profilin (Gly m 3), and PR-10 starvation-associated message 22 (Gly m 4) were measured using enzyme-linked immunosorbent assays or immunoblots. Percutaneous exposure to the soybean extract caused a systemic secretion of soybean-specific IgEs. Of the soy proteins, both 7S and 11S globulins were allergenic in 67% of tested mice. Of the 3 subunits of 7S globulin, it was determined that the β subunit is especially prone to eliciting secretion of soybean-specific IgEs following percutaneous exposure.

DERMAL IRRITATION AND SENSITIZATION

Irritation

Glycine Soja (Soybean) Extract

Patches containing a cosmetic water-in-oil emulsion incorporating 4% soybean extract were applied to a 5 cm x 4 cm area on the forearms of 11 subjects. ⁵² One gram of base emulsion and emulsion with soy were used to treat sites. Following application of the test substance, a surgical dressing was used to cover the marked area. It was not stated whether or not the dressing used was occlusive. After 48 hours, the dressing was removed and forearms were washed with physiological saline. Irritation was not observed in any of the subjects.

Glycine Soja (Soybean) Seedcake Extract

The irritation potential of a mixture containing water and Glycine Soja (Soybean) Seedcake Extract (13%) was studied in 10 subjects.⁵³ The test material was applied to the skin at a concentration of 5% and covered with an occlusive patch for 48 hours. No irritation was observed.

Glycine Max (Soybean) Sprout Extract

The irritation potential of a black soybean sprout extract (4 or 40 mg/mL) was studied in 30 subjects (15/sex). Extracts were applied on the arm, under a patch, for 24 hours. It was not stated whether or not the dressing used was occlusive. No other details regarding this study were provided. No signs of irritation were observed in any subject.

Sensitization

In Vitro

Glycine Max (Soybean) Callus Culture

The sensitizing potential of a trade name mixture containing water (100% w/w), Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%), was tested. ⁴⁹ The product did not affect the investigated markers expression (CD80 and CD86) immunocompetent cells (monocyte cell line THP-1. Therefore, the test substance did not show any stimulating potential on the immune cellular response mediated by monocyte/macrophage.

In Vivo

Glycine Soja (Soybean) Germ Extract

A human repeated insult patch test (HRIPT) was completed with 108 subjects.⁵⁴ The test substance used was a leave-on skin care preparation containing 0.3% Glycine Soja (Soybean) Germ Extract. The undiluted test substance was placed on the skin under an occlusive patch 3 times a week for a total of 9 applications during the induction period. After a 2-week rest period, challenge patches were applied to previously untreated sites. After 24 hours, patches were removed and the test sites were evaluated. The test material was non-sensitizing and non-irritating.

OCULAR IRRITATION STUDIES

In Vitro

Glycine Max (Soybean) Sprout Extract

The ocular irritation potential of black soybean sprout extract (40 mg/mL and 4 mg/mL) was studied using a chicken chorioallantoic membrane (CAM) assay. Sodium dodecyl sulfate (0.4% and 4%) was used as a positive control, and 0.9% saline was used as a negative control. Similar results were observed in both the negative control group and groups treated with the soybean sprout extract. The test substance was considered to be non-irritating. No other details regarding this study were provided.

Glycine Soja (Soybean) Seedcake Extract

A neutral red release assay (which assesses the cytotoxicity of the test substance) was performed to evaluate the ocular irritation potential of a mixture containing water and Glycine Soja (Soybean) Seedcake Extract (13%). Rabbit cornea fibroblasts were exposed to the test substance at concentrations of 5 - 50%. The IC₅₀ (i.e., the concentration causing 50% mortality) was greater than 50%. (The percent mortality observed at the dilution of 50% was less than 20%.) Thus, the cytotoxicity of the test substance was considered to be negligible, and the mixture non-irritating to the eye.

CLINICAL STUDIES

Case Reports

A 55-year-old woman with a 5-month history of reacting to a facial cosmetic cream developed erythema and swelling of the face after using a night cream containing soybean extract. Patch tests were performed using different dilutions of soybean extract, the night cream itself, components of the night cream, and standard cosmetic/facial ingredients. The following allergens were tested: para-phenylenediamine (1% in petrolatum (pet.)), fragrance mix (8% pet.), cocamidopropyl betaine (1% pet.), night cream, ceramide 3 and soybean extract (2% pet.), ceramide 3 (5%), ceramide 3 (2%), and three different dilutions of soybean extract (1, 10, and 20%). When the soybean extract dilutions were applied under occlusive patches to the forearm and read at 30 minutes, slight erythema was observed at the 20% dilution. Palpable erythema was observed after 36 hours at the 10 and 20% dilution. Patch tests using both concentrations of ceramide 3 were negative, however, the patch test using ceramide 3 and soybean extract (2%), yielded positive results. Positive results were obtained for all dilutions of the soybean extract on days 2 and 7. Para-phenylenediamine and cocamidopropyl betaine resulted in positive results on day 4, and the fragrance mix yielded positive results on day 2 and 4. The patient reported previous consumption of soybeans without adverse reactions and was subjected to an allergen-specific IgE test to soybean, which was negative.

A 30-year-old female esthetician with atopic dermatitis and severe hand eczema developed anaphylactic symptoms (systemic urticaria, dyspnea, and hypotension) after consuming soy products. Prior to working as an esthetician, she did not experience hand eczema or soy food allergies. Beginning at the age of 23, she began to touch cosmetic lotions frequently at the work place. Several months later, she noticed eczema on her fingers. At 28 years old, she experiences severe symptoms such as systemic urticaria and dyspnea after consumption of soy products. Examinations revealed the following: a total serum immunoglobulin (IgE) level of 3280 international units (IU)/mL, thymus and activation-regulated chemokine level of 715 pg/mL, and lactase dehydrogenase levels of 274 units (U)/L. Specific IgE antibodies were detected for soy (19.3 U_A/mL), Japanese cedar (4.72 U_A/mL) and Japanese white birch (1.24 U_A/mL). Skin pricks test were preformed using soy extract (10 mg/mL), the cosmetic lotion containing soy extract used by the patient, and commercially available soy milk. All tests yielded positive results. Skin prick tests performed on three healthy volunteers using the same cosmetic lotion yielded negative results.

Occupational Exposure

The allergenicity to soybean hull in subjects exposed to different levels of soybean dust inhalation (SDI) in Argentina was studied.⁵⁷ Exposure to SDI was defined as follows: (1) direct = occupational, (2) indirect = proximity to soybean fields or grain elevators, and (3) urban = urbanized areas without a known source of SDI. Two different types of

groups were studied. Group 1 consisted of 365 patients who were clinically diagnosed with asthma or allergic rhinitis. Group 2 consisted of 50 healthy subjects. All participants were given a standard questionnaire, and were subjected to a prick skin test (ST) with common allergens and a soybean hull extract. In addition, specific IgE and immunoglobin G4p (IgG4) secreted in response to soybean hulls were measured in the sera of 51 patients from group 1 with a positive ST to soybean hull, and in all subjects from group 2. From group 1, 15.3% of subjects had a positive ST to soybean hulls. No subjects from group 2 had a positive ST. Of those with a positive ST to soybean hulls, 38.7, 20.3, and 8.2% of the affected subjects were associated with direct, indirect, and urban exposures, respectively. The percentage of positive soybean hull-specific IgE secretion in groups 1 and 2 were 39.2% and 10%, respectively, and for IgG4 were 27.4% and 12%, in groups 1 and 2, respectively. IgG4 levels in group 1 were significantly higher in subjects with direct exposure compared to subjects with indirect or urban exposure.

In a different study, effects in workers from three soybean-processing plants in South Africa were evaluated using a respiratory questionnaire and estimation of atopy.⁵⁸ A total of 144 employees completed the questionnaire, and 136 gave blood samples for analysis of specific IgE levels. The processes in all three worksites were based on similar milling techniques. Soybeans arrive at the processing mill, are off-loaded, and stored. The beans are then de-hulled, subjected to cooking, milled, and bagged. According to the questionnaire, 38 individuals reported either an upper or lower work-related respiratory symptom. Among these individuals, eight employees reported upper respiratory symptoms in the absence of any lower respiratory symptoms. Twenty-two employees reported lower-respiratory symptoms only (cough, wheezing, or chest tightness). The remaining eight employees reported both upper and lower respiratory symptoms. Cough and chest tightness were the most commonly reported symptoms, followed by nasal irritation and wheezing. Altogether, 33.1% (45/136) of workers were atopic, and 14% (19/136) of workers exhibited sensitization to soybean allergens.

SUMMARY

The safety of 28 soy-derived ingredients as used in cosmetics is reviewed in this CIR safety assessment. All ingredients reviewed in this report are derived from the soybean plant (*Glycine max* or *Glycine soja*). According to the *Dictionary*, most of these ingredients are reported to function as antioxidants, skin protectants, skin-conditioning agents – miscellaneous, and hair-conditioning agents; however, other functions are also reported. Soybeans and ingredients made from soybeans are commonly used in foods. Because daily exposure via ingestion would result in much greater systemic exposure than what is expected from cosmetic use, potential for effects from topical exposure is the focus of this report.

Soybeans contain many phytochemicals, such as phenolic acids, flavonoids, isoflavanoids, saponins, phytosterols, and sphingolipids. These phytochemicals vary based on geographic location, specific plant parts, and color of the bean/plant.

According to 2019 VCRP survey data, Glycine Soja (Soybean) Seed Extract is reported to be used in 395 formulations, 273 of which are leave-on formulations, and Glycine Soja (Soybean) Flour is reported to be used in 66 formulations. The results of the concentration of use survey conducted by the Council indicate Glycine Soja (Soybean) Lipids has the highest concentration of use in a leave-on formulation; it is used at up to 0.65% in lipsticks. Additionally, inhalation of Glycine Soja (Soybean) Seed Extract is possible, as it was reported to be used at 0.000001% in hair sprays.

When rats were given a single oral dose of a soybean extract containing 74 μ mol genistein and 77 μ mol daidzein/kg as conjugates, the urinary excretion of daidzein and genistein was 17.9% and 11.9%, respectively, over a 48-hour post-dose period. When humans were given a bolus dose of a commercial soy extract, sulphoglucuronides were the major metabolites of daidzein and genistein the in the plasma, and 7-O-glucuronidse were the predominant metabolites in the urine.

When 18 Sprague-Dawley rats and 86 C57BL/6 mice were given a single oral dose of black soybean hull extract (2.5 g/kg/bw) via gavage, the LD₅₀ was reported to be greater than 2.5 g/kg bw in both species. In a different study, Sprague-Dawley IGS rats (6/sex/group) were given up to 5% black soybean extract in the diet for 28 days. No deaths were reported throughout the study, however a statistically significant increase in phosphatase enzymes was found in male rats given 1.5% black soybean extract. In addition, a statistically significant but non-dose-dependent elevation of relative heart weight was found in females given 0.5% black soybean extract. In a different study, SSF was given to Sprague-Dawley CD rats (20/sex/group) at concentrations up to 4% for three months. A slight, but dose-related increase in the hematocrit and erythrocyte count at the 3 and 4% level was noted. In a 13-week toxicity study, the systemic toxicity of aqueous and ethanolic soybean extracts (up to 5%) was studied in F344 rats (40 rats/sex). Statistically significant body weight reductions were noted in males treated with 5% soybean extract, and in all treated females. Statistically significant, but minimal increases in total protein, albumin, calcium, and aspartate aminotransferase were found in males treated with 2.5% or higher. Dose-dependent, statistically significant changes in organ weights compared to control animals were also noted. In a different study, 33 male and 35 female C57BL/6 mice were given up to 5% black soybean seedcoat extract in the diet for 26 weeks. Significant body weight reduction was noted in high-dosed males. Significant reductions in triglyceride, hemoglobin, and hematocrit levels were noted in high-dosed females. Relative weights of the kidney, spleen, and brain were increased in high-dosed males. In animals dosed with both 2% and 5% soybean seedcoat extract, in the duodenum, slight pigment accumulation in histiocytes of the lamina propria was found. Slight accumulation of pigment in Kupffer cells of the liver was apparent in 5% males and females.

A chronic toxicity study was performed on 60 male Wistar rats given up to 79.7% raw soy flour ad libitum or as a single meal per day. Azaserine injections were also given to select animals. Approximately 45% of all animals died prior to the termination of the experiment. Pancreas weights increased as the level of raw soy flour in the diet increased.

The reproductive toxicity of the soybean was tested in 20 male and 60 female rats. Rats were given processed soybean meal at up to 300 mg/kg bw for 65 days. Rats in the 100 mg/kg/bw group had testicular tissues with compacted interstitial spaces, mild hemorrhaging along the Sertoli's cells, and slight degeneration of the spermatids. Rats treated with 200 mg/kg/bw displayed similar effects, and rats treated with 300 mg/kg /bw displayed adverse effects such as testicular tissues with inflammation of interstitial cells, severe hemorrhaging along the Sertoli's cells, and excessive degeneration of spermatids, and necrosis. The conception rate of female rats sired by males in the control and treated groups were reduced in a dose-dependent manner. No other effects regarding treated female rats were observed.

Wistar rats were given up to raw soy flour in the diet. Injections of azaserine were also given to select rats. Animals that received azaserine injections had a much higher incidence of nodules, which increased with the level of raw soy flour in the diet. In a study involving male albino mice, mice given raw soy flour in comparison to heated soy flower or casein displayed a significant decrease in growth. In a different study involving Syrian gold male hamsters, animals were given raw or heated soy flour alone, or raw or heated soy flower with a BOP injection. Groups that did not receive BOP had a low tumor incidence. All but one animal displayed either pancreatic adenomas or adenocarcinomas when given heated soy flour and a BOP injection, while only one out of 11 animals given BOP injections and raw soy flour displayed a pancreatic adenoma.

Studies were performed in order to analyze the effects of soy-derived extracts on cancer cell proliferation. An ethanolic soybean extract inhibited cytotoxic activity in A549 cells in a concentration-dependent manner. The potential of a soybean extract to inhibit the proliferation of cancer cells was also studied on AGS cells. Approximately 65.7, 38.8, and 22.5% cells survived after treatment with 3, 4, and 5 mg/mL of black soybean extract. The same procedure was performed on normal rat fibroblast cells. No cytotoxicity was observed when black soybean extract was used on these cells. In a different assay, HCT116 and H1299 cells were exposed to an ethanolic extract of soybean leaves. In both types of cancer cells, the growth inhibitory effects of SLE increased with increasing concentrations of SLE, showing a significant doseresponse relationship. In addition to inhibition of growth, the effect of SLE on adhesion and migration of the human cancer cells was also studied.

The possible inhibition of retinoid-induced epidermal hyperplasia was studied in 7 human skin organ cultures. In the presence of a 40 μ g/mL soy extract, retinoid-induced hyperplasia was reduced by 41% relative to the retinoid response in the absence of soy.

An aqueous extract of black soybean sprouts was examined for whitening capacity via the measurement of tyrosinase-inhibition. Tyrosinase inhibition capacity of the extract, when used at 40 mg/mL, reached 98%.

A methanolic soybean extract ($0.1~\mu g/mL$) caused an increase of cell proliferation to approximately 35%, while at $100~\mu g/mL$, proliferation was increased to 90%. Testing of the soybean extract in combination with ICI 182,780 resulted in decreased proliferation (below 0%). A reported gene assay was also performed using human embryonic kidney cells (HEK 293 cells) in order to determine whether the effects of the extracts were mediated via ER α and/or ER β . Preferential agonist activity toward ER β was observed. For ER β transcriptional activation, the maximal value obtained at $100~\mu g/mL$ was 79.7%, compared to 53.2% for ER α transcriptional activation. A study was performed to analyze the effects of orally administrated soybean extract obtained using different extraction methods on the skin of 64 Sprague-Dawley female rats (8/group). The number of estrogen receptors in all soy extract—treated groups were decreased compared to that of the controls.

A percutaneous immunotoxicity study was performed on BALB/c mice. Mice were dermally exposed (after tape stripping 10x) to crude soybean extract (50 mg/mL, 3 times a week). Exposure to the soybean extract resulted in an increase of circulatory soybean-specific IgEs. Of the soy proteins, both 7S and 11S globulins were allergens in 67% of tested mice.

A trade name mixture containing water (100% q.b. to 100% w/w), Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%) and a trade name mixture consisting of water (78.93%), Glycine Soja (Soybean) Phytoplacenta Extract (20%), phenoxyethanol (0.90%), methylparaben (0.15%), and Tetrasodium EDTA (0.02%) displayed no cytotoxic potential in cytotoxicity assays.

A 48-hour patch test was performed on 11 subjects using a cosmetic formulation containing 4% soybean extract. No irritation was observed. No irritation was observed when a 48-hour patch test was performed using a mixture containing water and Glycine Soja (Soybean) Seedcake Extract (13%) at a concentration of 5%. A 24-hour patch test performed on 30 subjects using 4 or 40 mg/mL black soybean sprout extract yielded negative results. No sensitizing potential was observed in a trade name mixture containing water (100% w/w), Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%). No sensitization or irritation was observed when an HRIPT was completed with 108 subjects using a leave-on formulation containing 0.3% Glycine (Soja) Soybean Germ Extract.

A CAM assay was performed using a soybean sprout extract revealed no potential irritation. A trade name mixture containing 87.5% Glycine Soja (Soybean) Seed Extract was considered to be non-irritating to the eyes. In a different study, a

mixture consisting of water and Glycine Soja (Soybean) Seedcake Extract was considered non-irritating when tested on rabbit cornea fibroblasts.

According to a case study, a 55-year-old woman with a 5-month history of reacting to a facial cosmetic cream developed erythema and swelling of the face after using a night cream containing soybean extract. Patch tests were performed using different dilutions of soybean extract, the night cream itself, components of the night cream, and standard cosmetic/facial ingredients. Positive results were obtained for all dilutions of the soybean extract on days 2 and 7. In a different case study, a 30-year-old female esthetician with atopic dermatitis and severe hand eczema developed anaphylactic symptoms after consuming soy products. Skin pricks test were preformed using soy extract (10 mg/mL), the cosmetic lotion containing soy extract used by the patient, and commercially available soy milk. All tests yielded positive results.

Allergenicity to soybean hull was studied in an occupational exposure study. Positive skin prick tests to soybean hull were reported for 38.7, 20.3, and 8.2% in subjects with direct (occupational), indirect (proximity to soybean fields or grain elevators), or urban (no known source of soy dust inhalation) exposures, respectively. Another occupational study was performed, assessing soybean-processing plant workers in South Africa. In 38/144 individuals that reported either an upper or lower work-related respiratory symptom, eight employees reported upper respiratory symptoms in the absence of any lower respiratory symptoms, 22 reported lower-respiratory symptoms only (cough, wheezing, or chest tightness), and the remaining eight employees reported both upper and lower respiratory symptoms.

To be formulated.

CONCLUSION

To be determined.

TABLES

Table 1. INCI names, definitions, and functions of the soy-derived ingredients in this safety assessment¹

Ingredient Glycine Max (Soybean) Callus Culture	Definition Glycine Max (Soybean) Callus Culture is a suspension of the cultured	Function Antioxidants; Humectants;
Orycline Wax (Soybean) Canus Culture	callus cells of Glycine max.	Skin Protectants; Skin- Conditioning Agents -
		Miscellaneous
Glycine Max (Soybean) Callus Culture Extract	Glycine Max (Soybean) Callus Culture Extract is the extract of a culture of the callus of <i>Glycine max</i> .	Antifungal Agents; Antioxidants; Hair
		Conditioning Agents; Skin- Conditioning Agents - Humectant
Glycine Max (Soybean) Callus Extract	Glycine Max (Soybean) Callus Extract is the extract of the callus of <i>Glycine max</i> grown in culture.	Antimicrobial Agents; Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin-
		Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Fiber	Glycine Max (Soybean) Fiber is the fiber obtained from the pulp of the soybean, <i>Glycine max</i> .	Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Flower/Leaf/Stem Juice	Glycine Max (Soybean) Flower/Leaf/Stem Juice is the juice expressed from the flowers, leaves and stems of <i>Glycine max</i> .	Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Leaf Cell Extract	Glycine Max (Soybean) Leaf Cell Extract is the extract of a culture of the leaf cells of <i>Glycine max</i> .	Antioxidants; Skin Protectants
Glycine Max (Soybean) Leaf Extract	Glycine Max (Soybean) Leaf Extract is the extract of the leaves of <i>Glycine max</i> .	Antioxidants; Skin Protectants; Skin- Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Phytoplacenta Conditioned Media	Glycine Max (Soybean) Phytoplacenta Conditioned Media is the growth media removed from cultures of the phytoplacenta of <i>Glycine max</i> after several days of growth.	Antimicrobial Agents; Hair Conditioning Agents; Skin Protectants; Skin- Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Phytoplacenta Extract	Glycine Max (Soybean) Phytoplacenta Extract is the extract of the phytoplacenta cells directly isolated from the plant <i>Glycine max</i> or grown in culture.	Antimicrobial Agents; Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin- Conditioning Agents - Humectant
Glycine Max (Soybean) Pulp	Glycine Max (Soybean) Pulp is the pulp of Glycine max.	Skin-Conditioning Agents - Humectant
Glycine Max (Soybean) Seedcake Extract	Glycine Max (Soybean) Seedcake Extract is the extract of the seedcake of <i>Glycine max</i> .	Skin-Conditioning Agents - Emollient
Glycine Max (Soybean) Seedcoat Extract	Glycine Max (Soybean) Seedcoat Extract is the extract of the seedcoat of <i>Glycine max</i> .	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Seed Powder	Glycine Max (Soybean) Seed Powder is the powder obtained from the dried, ground seeds of <i>Glycine max</i> .	Exfoliants; Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Sprout Extract	Glycine Max (Soybean) Sprout Extract is the extract of the sprout of the soybean, Glycine max.	Body and Hand Preparations (Excluding Shaving Preparations); Face and Neck Preparations (Excluding Shaving Preparations); Moisturizing Preparations; Shampoos (Non-coloring); Skin Care Preparations, Misc.
Glycine Soja (Soybean) Extract	Glycine Soja (Soybean) Extract is the extract of the whole plant, Glycine soja. The accepted scientific name for Glycine soja is Glycine max.	Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Fiber	Glycine Soja (Soybean) Fiber is the fiber obtained from the pulp of the soybean, <i>Glycine soja</i> . The accepted scientific name for <i>Glycine soja</i> is <i>Glycine max</i> .	Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Flour 68513-95-1	Glycine Soja (Soybean) Flour is the powder prepared from the fine grinding of the soybean, <i>Glycine max</i> . The accepted scientific name for <i>Glycine soja</i> is <i>Glycine max</i> .	Abrasives; Bulking Agents; Viscosity Increasing Agents - Aqueous
Glycine Soja (Soybean) Germ Extract	Glycine Soja (Soybean) Germ Extract is the extract of the germ of <i>Glycine soja</i> . The accepted scientific name for <i>Glycine soja</i> is <i>Glycine max</i> .	Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Hull	Glycine Soja (Soybean) Hull is the outer covering of the soybean, Glycine soja The accepted scientific name for Glycine soja is Glycine max.	Exfoliants; Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Lipids	Glycine Soja (Soybean) Lipids is the alcohol soluble fraction of the gummy portion obtained during the refining of Glycine Soja (Soybean) Oil. It is a blend consisting predominantly of phospholipids, sterols and triglycerides. The accepted scientific name for <i>Glycine soja</i> is <i>Glycine max</i> .	Hair Conditioning Agents; Skin-Conditioning Agents - Occlusive

Table 1. INCI names, definitions, and functions of the soy-derived ingredients in this safety assessment¹

Ingredient	Definition	Function
Glycine Soja (Soybean) Phytoplacenta	Glycine Soja (Soybean) Phytoplacenta Extract is the extract of the	Hair Conditioning Agents;
Extract	phytoplacenta cells directly isolated from the plant Glycine soja or grown	Skin-Conditioning Agents -
	in culture. The accepted scientific name for Glycine soja is Glycine max.	Miscellaneous
Glycine Soja (Soybean) Seed	Glycine Soja (Soybean) Seed is the bean of Glycine soja. The accepted	Not Reported
	scientific name for Glycine soja is Glycine max.	
Glycine Soja (Soybean) Seedcake	Glycine Soja (Soybean) Seedcake Extract is the extract of the seedcake of	Skin Protectants
Extract	Glycine soja. The accepted scientific name for Glycine soja is Glycine	
	max.	
Glycine Soja (Soybean) Seed Extract	Glycine Soja (Soybean) Seed Extract is the extract of the seeds of Glycine	Skin-Conditioning Agents -
	soja. The accepted scientific name for Glycine soja is Glycine max.	Miscellaneous
Glycine Soja (Soybean) Seed Powder	Glycine Soja (Soybean) Seed Powder is the powder obtained from the	Abrasives; Bulking Agents;
	dried, ground seeds of Glycine soja. The accepted scientific name for	Skin-Conditioning Agents -
	Glycine soja is Glycine max.	Miscellaneous
Glycine Soja (Soybean) Seed Water	Glycine Soja (Soybean) Seed Water is an aqueous solution of the steam	Skin-Conditioning Agents -
	distillate obtained from the seeds of Glycine soja. The accepted scientific	Humectant
	name for Glycine soja is Glycine max.	
Glycine Soja (Soybean) Sprout Extract	Glycine Soja (Soybean) Sprout Extract is the extract of the young shoots	Skin-Conditioning Agents -
	of the soybean, <i>Glycine soja</i> . The accepted scientific name for <i>Glycine soja</i> is <i>Glycine max</i> .	Miscellaneous

Table 2. Average constituents in 24 soybean seed extracts (g/100 g)¹⁴

Carbohydrates	30.16	Alanine	1.915
Sugars	7.33	Aspartic acid	5.112
Fat	19.94	Glutamic acid	7.874
Protein	36.49	Glycine	1.880
Tryptophan	0.591	Proline	2.379
Threonine	1.766	Serine	2.375
Isoleucine	1.971	Water	8.54
Leucine	3.309	Calcium	0.277
Lysine	2.706	Iron	0.0175
Methionine	0.547	Magnesium	0.280
Phenylalanine	2.122	Phosphorus	0.704
Tyrosine	1.539	Potassium	1.797
Valine	2.029	Sodium	0.002
Arginine	3.153	Zinc	0.00489
Histidine	1.097		

Table 3. Mean nutrient and amino acid values for 38 samples of soybean hulls (%)¹⁹

Moisture	8.18
Crude fiber	33.32
Nitrogen-free extract	39.18
Ash	4.87
Calcium	0.52
Phosphorous	0.15
Lysine	0.86
Methionine	0.16
Threonine	0.48
Tryptophan	0.15
Arginine	0.65
Histidine	0.31
Leucine	0.82
Isoleucine	0.48
Phenylalanine	0.54
Valine	0.55

Table 4. Specifications for organic constituents/impurities of a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract⁵⁹

Allergen	ppm
Alpha-IsoMethyl Ionone	< 0.02
Amyl Cinnamal	< 0.10
Anise Alcohol	< 0.00
Benzyl Alcohol	< 0.01
Benzyl Benzoate	< 0.09
Benzyl Cinnamate	< 0.30
Benzyl Salicylate	< 0.06
Butylphenyl Methylpropional	< 0.50
Cinnamal	< 0.01
Cinnamyl Alcohol	< 0.30
Citral	< 1.00
Citronellol	< 0.00
Coumarin	< 0.00
Eugenol	< 0.70
Farnesol	< 0.04
Farnesol	< 0.04
Geraniol	< 0.08
Hexyl Cinnamal	< 0.40
Hydroxycitronellal	< 1.00
Hydroxymethylpentyl 3-Cylcohexene	< 0.30
carboxaldehyde	
Isoeugenol	< 0.06
Limonene	< 0.05
Linalool	< 0.00
Methyl 2-Octynoate	< 0.20
Evernia prunastri	< 0.02
Evernia furfuracea	< 0.00
Amylcinnamyl Alcohol	< 1.00

	# of Uses	Conc of Use (%)	# of Uses	Conc of Use (%)	# of Uses	Conc of Use (%)
	Glycine Max	(Soybean) Seed Extract	•	oybean) Phytoplacenta Extract		(Soybean) Extract (also ne Max) Soybean Extract in VCRP)
Totals*	395	0.0066 - 1	16	NR	11	NR
Duration of Use						
Leave-On	273	0.0066 – 1	13	NR	9^d	NR
Rinse-Off	121	0.0066	3	NR	2^d	NR
Diluted for (Bath) Use	1	NR	NR	NR	NR	NR
Exposure Type					•	
Eye Area	35	0.0066	1	NR	NR	NR
Incidental Ingestion	22	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	6; 93 ^a ; 70 ^b	NR	1; 6 ^a ; 3 ^b	NR	2 ^a ; 4 ^b	NR
Incidental Inhalation-Powder	5; 70 ^b	0.0066^{c}	2 ^b ; 3 ^c	NR	4 ^b	NR
Dermal Contact	235	0.0066 - 1	14	NR	9	NR
Deodorant (underarm)	1 ^a	NR	NR	NR	NR	NR
Hair - Non-Coloring	137	NR	2	NR	2	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	28	NR	NR	NR	NR	NR
Baby Products	NR	NR	3	NR	NR	NR

	Glycine Soja (Soybean) Flour		Glycine Soja (Soybean) Germ Extract	Glycine Soja (Soybean) Lipids (also			
	(also listed as G	Slycine Max (Soybean)	(also listed as	Glycine Max (Soybean)	listed as Glycine	Max (Soybean) Lipids		
	Flou	r in VCRP)	Germ I	Extract in VCRP)	iı	n VCRP)		
Totals*	66	0.0001	47	0.00002 - 0.45	51	0.086 - 0.65		
Duration of Use								
Leave-On	64	0.0001	40	0.0002 - 0.45	41	0.086 - 0.65		
Rinse-Off	2	NR	7	0.00002 - 0.00014	10	NR		
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR		
Exposure Type								
Eye Area	1	NR	6^{d}	0.01	6	0.09		
Incidental Ingestion	NR	NR	NR	NR	2	0.65		
Incidental Inhalation-Spray	60°; 1°	NR	8 ^a ; 16 ^b	NR	20°; 7 ^b	NR		
Incidental Inhalation-Powder	1 ^b	0.0001°	16 ^b	$0.005 - 0.45^{c}$	1	NR		
Dermal Contact	64	0.0001	47	0.00002 - 0.45	43	0.09		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	2	NR	NR	0.00014 - 0.11	5	NR		
Hair-Coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	NR	1	NR		
Mucous Membrane	1	NR	1	NR	2	NR		
Baby Products	NR	NR	NR	NR	NR	NR		

Due j 110 due to	- 1-1	- 1-1	- 1-1	- 1-1
	Glycine Soja (Soybean) Seed (also listed as Glycine Max (Soybean) Seed in VCRP)		Glycine Soja (Soybean) Seed Extract	
Totals*	1	NR	NR	0.000001 - 2
Duration of Use				_
Leave-On	NR	NR	NR	0.000001 - 2
Rinse-Off	1	NR	NR	0.00008 - 0.7
Diluted for (Bath) Use	NR	NR	NR	0.0004
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.0001
Incidental Inhalation-Spray	NR	NR	NR	$0.000001; 0.005^{a}$
Incidental Inhalation-Powder	NR	NR	NR	$0.002 - 2^{c}$
Dermal Contact	1 ^d	NR	NR	0.0004 - 2
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.000001 - 0.01
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	0.001
Mucous Membrane	NR	NR	NR	0.0001 - 0.0004
Baby Products	NR	NR	NR	NR

NR = Not Reported

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

^a It is possible these products <u>may</u> be sprays, but it is not specified whether the reported uses are sprays.
^b Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^c It is possible these products <u>may</u> be powders, but it is not specified whether the reported uses are powders.

Table 6. Soy-Derived Ingredients not reported to be in use

Glycine Max (Soybean) Callus Culture

Glycine Max (Soybean) Callus Culture Extract

Glycine Max (Soybean) Callus Extract

Glycine Max (Soybean) Fiber Glycine Max (Soybean) Flower/Leaf/Stem Juice

Glycine Max (Soybean) Leaf Cell Extract

Glycine Max (Soybean) Leaf Extract

Glycine Max (Soybean) Phytoplacenta Conditioned Media

Glycine Max (Soybean) Pulp

Glycine Max (Soybean) Seedcake Extract

Glycine Max (Soybean) Seedcoat Extract

Glycine Max (Soybean) Seed Powder

Glycine Max (Soybean) Sprout Extract

Glycine Soja (Soybean) Fiber

Glycine Soja (Soybean) Hull

Glycine Soja (Soybean) Phytoplacenta Extract

Glycine Soja (Soybean) Seedcake Extract

Glycine Soja (Soybean) Seed Powder

Glycine Soja (Soybean) Seed Water

Glycine Soja (Soybean) Sprout Extract

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2019 Frequency of use data

 05F - Shampoos (non-coloring) 07C - Foundations 12C - Face and Neck (exc shave) 12F - Moisturizing 12J - Other Skin Care Preps 	GLYCINE MAX (SOYBEAN) EXTRACT	2 1 4 2 2
 01A - Baby Shampoos 01B - Baby Lotions, Oils, Powders, and Creams 03D - Eye Lotion 05B - Hair Spray (aerosol fixatives) 12A - Cleansing 12C - Face and Neck (exc shave) 12F - Moisturizing 12G - Night 	GLYCINE MAX (SOYBEAN) PHYTOPLACENTA EXTRACT	1 2 1 1 2 3 5 1
12H - Paste Masks (mud packs)	GLYCINE MAX (SOYBEAN) SEED	1
 02D - Other Bath Preparations 03C - Eye Shadow 03D - Eye Lotion 03F - Mascara 03G - Other Eye Makeup Preparations 05A - Hair Conditioner 05B - Hair Spray (aerosol fixatives) 	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1 13 13 1 8 40 6

05C - Hair Straighteners	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
05D - Permanent Waves	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
05F - Shampoos (non-coloring)	GLYCINE MAX (SOYBEAN) SEED EXTRACT	42
05G - Tonics, Dressings, and Other Hair Grooming Aids	GLYCINE MAX (SOYBEAN) SEED EXTRACT	31
05I - Other Hair Preparations	GLYCINE MAX (SOYBEAN) SEED EXTRACT	14
07A - Blushers (all types)	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
07B - Face Powders	GLYCINE MAX (SOYBEAN) SEED EXTRACT	5
07C - Foundations	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
07E - Lipstick	GLYCINE MAX (SOYBEAN) SEED EXTRACT	22
07I - Other Makeup Preparations	GLYCINE MAX (SOYBEAN) SEED EXTRACT	5
10A - Bath Soaps and Detergents	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
10B - Deodorants (underarm)	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
10E - Other Personal Cleanliness Products	GLYCINE MAX (SOYBEAN) SEED EXTRACT	3
11A - Aftershave Lotion	GLYCINE MAX (SOYBEAN) SEED EXTRACT	3
11E - Shaving Cream	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
11G - Other Shaving Preparation Products	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
12A - Cleansing	GLYCINE MAX (SOYBEAN) SEED EXTRACT	17
12B - Depilatories	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
12C - Face and Neck (exc shave)	GLYCINE MAX (SOYBEAN) SEED EXTRACT	56
12D - Body and Hand (exc shave)	GLYCINE MAX (SOYBEAN) SEED EXTRACT	14
12F - Moisturizing	GLYCINE MAX (SOYBEAN) SEED EXTRACT	42
12G - Night	GLYCINE MAX (SOYBEAN) SEED EXTRACT	16
12H - Paste Masks (mud packs)	GLYCINE MAX (SOYBEAN) SEED EXTRACT	9
12I - Skin Fresheners	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
12J - Other Skin Care Preps	GLYCINE MAX (SOYBEAN) SEED EXTRACT	16
13A - Suntan Gels, Creams, and Liquids	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
03C - Eye Shadow	GLYCINE MAX (SOYBEAN) FLOUR	1
05A - Hair Conditioner	GLYCINE MAX (SOYBEAN) FLOUR	1

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 05G - Tonics, Dressings, and Other Hair Grooming Aids 07A - Blushers (all types) 10A - Bath Soaps and Detergents 12D - Body and Hand (exc shave) 12F - Moisturizing 12G - Night 12J - Other Skin Care Preps 	GLYCINE MAX (SOYBEAN) FLOUR	1 1 1 1 58 1 1
03A - Eyebrow Pencil	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
03D - Eye Lotion	GLYCINE MAX (SOYBEAN) GERM EXTRACT	2
03G - Other Eye Makeup Preparations	GLYCINE MAX (SOYBEAN) GERM EXTRACT	3
07C - Foundations	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
07I - Other Makeup Preparations	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
10A - Bath Soaps and Detergents	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
12A - Cleansing	GLYCINE MAX (SOYBEAN) GERM EXTRACT	5
12C - Face and Neck (exc shave)	GLYCINE MAX (SOYBEAN) GERM EXTRACT	9
12D - Body and Hand (exc shave)	GLYCINE MAX (SOYBEAN) GERM EXTRACT	7
12F - Moisturizing	GLYCINE MAX (SOYBEAN) GERM EXTRACT	6
12G - Night	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
12H - Paste Masks (mud packs)	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
12J - Other Skin Care Preps	GLYCINE MAX (SOYBEAN) GERM EXTRACT	8
13B - Indoor Tanning Preparations	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
03D - Eye Lotion	GLYCINE MAX (SOYBEAN) LIPIDS	4
03G - Other Eye Makeup Preparations	GLYCINE MAX (SOYBEAN) LIPIDS	2
05A - Hair Conditioner	GLYCINE MAX (SOYBEAN) LIPIDS	1
05F - Shampoos (non-coloring)	GLYCINE MAX (SOYBEAN) LIPIDS	4
07B - Face Powders	GLYCINE MAX (SOYBEAN) LIPIDS	1

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07C - Foundations	GLYCINE MAX (SOYBEAN) LIPIDS	1
07E - Lipstick	GLYCINE MAX (SOYBEAN) LIPIDS	2
07I - Other Makeup Preparations	GLYCINE MAX (SOYBEAN) LIPIDS	2
08G - Other Manicuring Preparations	GLYCINE MAX (SOYBEAN) LIPIDS	1
11E - Shaving Cream	GLYCINE MAX (SOYBEAN) LIPIDS	1
12A - Cleansing	GLYCINE MAX (SOYBEAN) LIPIDS	3
12C - Face and Neck (exc shave)	GLYCINE MAX (SOYBEAN) LIPIDS	6
12D - Body and Hand (exc shave)	GLYCINE MAX (SOYBEAN) LIPIDS	1
12F - Moisturizing	GLYCINE MAX (SOYBEAN) LIPIDS	18
12G - Night	GLYCINE MAX (SOYBEAN) LIPIDS	2
12H - Paste Masks (mud packs)	GLYCINE MAX (SOYBEAN) LIPIDS	1
12J - Other Skin Care Preps	GLYCINE MAX (SOYBEAN) LIPIDS	1

2018 Frequency of Use Data

05F - Shampoos (non-coloring)	999004241	GLYCINE MAX (SOYBEAN) EXTRACT	2
07C - Foundations	999004241	GLYCINE MAX (SOYBEAN) EXTRACT	1
12C - Face and Neck (exc shave)	999004241	GLYCINE MAX (SOYBEAN) EXTRACT	5
12F - Moisturizing	999004241	GLYCINE MAX (SOYBEAN) EXTRACT	2
12J - Other Skin Care Preps	999004241	GLYCINE MAX (SOYBEAN) EXTRACT	2
03C - Eye Shadow	68513951	GLYCINE MAX (SOYBEAN) FLOUR	8
05A - Hair Conditioner	68513951	GLYCINE MAX (SOYBEAN) FLOUR	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	68513951	GLYCINE MAX (SOYBEAN) FLOUR	1
07A - Blushers (all types)	68513951	GLYCINE MAX (SOYBEAN) FLOUR	6
10A - Bath Soaps and Detergents	68513951	GLYCINE MAX (SOYBEAN) FLOUR	1
12D - Body and Hand (exc shave)	68513951	GLYCINE MAX (SOYBEAN) FLOUR	1
12F - Moisturizing	68513951	GLYCINE MAX (SOYBEAN) FLOUR	37
12J - Other Skin Care Preps	68513951	GLYCINE MAX (SOYBEAN) FLOUR	1
03A - Eyebrow Pencil	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1

03D - Eye Lotion	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	2
03G - Other Eye Makeup Preparations	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	3
07C - Foundations	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
07I - Other Makeup Preparations	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
10A - Bath Soaps and Detergents	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
12A - Cleansing	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	4
12C - Face and Neck (exc shave)	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	9
12D - Body and Hand (exc shave)	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	7
12F - Moisturizing	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	5
12G - Night	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
12J - Other Skin Care Preps	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	8
13B - Indoor Tanning Preparations	999002353	GLYCINE MAX (SOYBEAN) GERM EXTRACT	1
03D - Eye Lotion	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	4
03G - Other Eye Makeup Preparations	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	1
05A - Hair Conditioner	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	1
05F - Shampoos (non-coloring)	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	4
07B - Face Powders	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	1
07C - Foundations	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	1
07E - Lipstick	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	2
07I - Other Makeup Preparations	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	1
08G - Other Manicuring Preparations	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	1
11E - Shaving Cream	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	1
12A - Cleansing	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	3
12C - Face and Neck (exc shave)	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	5
12D - Body and Hand (exc shave)	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	1
12F - Moisturizing	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	16
12G - Night	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	2
12H - Paste Masks (mud packs)	977169893	GLYCINE MAX (SOYBEAN) LIPIDS	2
		GLYCINE MAX (SOYBEAN) PHYTOPLACENTA	
01A - Baby Shampoos	999004319		1
01B - Baby Lotions, Oils, Powders, and Creams	999004319	GLYCINE MAX (SOYBEAN) PHYTOPLACENTA	2

		EXTRACT	
		GLYCINE MAX (SOYBEAN) PHYTOPLACENTA	
03D - Eye Lotion	999004319	EXTRACT	1
		GLYCINE MAX (SOYBEAN) PHYTOPLACENTA	
05B - Hair Spray (aerosol fixatives)	999004319	EXTRACT	1
		GLYCINE MAX (SOYBEAN) PHYTOPLACENTA	
12A - Cleansing	999004319	EXTRACT	1
		GLYCINE MAX (SOYBEAN) PHYTOPLACENTA	
12C - Face and Neck (exc shave)	999004319	EXTRACT	2
405 44 1 1 1 1	000004040	GLYCINE MAX (SOYBEAN) PHYTOPLACENTA	_
12F - Moisturizing	999004319	EXTRACT	5
12G - Night	999004319	GLYCINE MAX (SOYBEAN) PHYTOPLACENTA EXTRACT	1
-			_
12H - Paste Masks (mud packs)	999004696	GLYCINE MAX (SOYBEAN) SEED	1
02D - Other Bath Preparations	977013209	,	1
03C - Eye Shadow	977013209	,	13
03D - Eye Lotion	977013209	,	13
03F - Mascara	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
03G - Other Eye Makeup Preparations	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	8
05A - Hair Conditioner	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	45
05B - Hair Spray (aerosol fixatives)	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	6
05C - Hair Straighteners	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
05D - Permanent Waves	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
05F - Shampoos (non-coloring)	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	48
05G - Tonics, Dressings, and Other Hair Grooming Aids	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	30
05I - Other Hair Preparations	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	13
07A - Blushers (all types)	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	7
07B - Face Powders	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	6
07C - Foundations	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
07E - Lipstick	977013209		21
07I - Other Makeup Preparations	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	5
10A - Bath Soaps and Detergents	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	3

Distributed for Comment Only -- Do Not Cite or Quote

10B - Deodorants (underarm)	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
10E - Other Personal Cleanliness Products	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	3
11A - Aftershave Lotion	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	3
11E - Shaving Cream	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2
11G - Other Shaving Preparation Products	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
12A - Cleansing	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	16
12B - Depilatories	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
12C - Face and Neck (exc shave)	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	52
12D - Body and Hand (exc shave)	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	13
12F - Moisturizing	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	39
12G - Night	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	16
12H - Paste Masks (mud packs)	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	15
12I - Skin Fresheners	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	1
12J - Other Skin Care Preps	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	17
13A - Suntan Gels, Creams, and Liquids	977013209	GLYCINE MAX (SOYBEAN) SEED EXTRACT	2

Concentration of Use by FDA Product Category – Soy-Derived Ingredients*

Glycine Max (Soybean) Seed Extract Glycine Max (Soybean) Sprout Extract Glycine Max (Soybean) Callus Culture Glycine Soja (Soybean) Extract Glycine Max (Soybean) Callus Culture Extract Glycine Soja (Soybean) Fiber Glycine Max (Soybean) Callus Extract Glycine Soja (Soybean) Flour Glycine Max (Soybean) Fiber Glycine Soja (Soybean) Germ Extract Glycine Max (Soybean) Flower/Leaf/Stem Juice Glycine Soja (Soybean) Hull Glycine Max (Soybean) Leaf Cell Extract Glycine Soja (Soybean) Lipids Glycine Max (Soybean) Leaf Extract Glycine Soja (Soybean) Phytoplacenta Extract Glycine Max (Soybean) Phytoplacenta Glycine Soja (Soybean) Seed Conditioned Media Glycine Soja (Soybean) Seedcake Extract Glycine Max (Soybean) Phytoplacenta Extract Glycine Soja (Soybean) Seed Extract Glycine Max (Soybean) Pulp Glycine Soja (Soybean) Seed Powder Glycine Max (Soybean) Seedcake Extract Glycine Soja (Soybean) Seed Water Glycine Max (Soybean) Seedcoat Extract Glycine Soja (Soybean) Sprout Extract

Glycine Max (Soybean) Seed Powder

Ingredient	FDA Product Category	Maximum
	5 1	Concentration of Use
Glycine Max (Soybean) Seed Extract	Eye lotions	0.0066%
Glycine Max (Soybean) Seed Extract	Skin cleansing (cold creams, cleansing	0.0066%
	lotions, liquids and pads)	
Glycine Max (Soybean) Seed Extract	Face and neck products	
	Not spray	0.0066%
Glycine Max (Soybean) Seed Extract	Moisturizing products	
	Not spray	1%
Glycine Max (Soybean) Seed Extract	Night products	
	Not spray	0.0066%
Glycine Max (Soybean) Seed Extract	Paste masks and mud packs	0.0066%
Glycine Max (Soybean) Seed Extract	Other skin care preparations	0.03%
Glycine Soja (Soybean) Flour	Body and hand products	
	Not spray	0.0001%
Glycine Soja (Soybean) Germ Extract	Other eye makeup preparations	0.01%
Glycine Soja (Soybean) Germ Extract	Shampoos (noncoloring)	0.00014%
Glycine Soja (Soybean) Germ Extract	Tonics, dressings and other hair	
	grooming aids	
	Not spray	0.11%
Glycine Soja (Soybean) Germ Extract	Skin cleansing (cold creams, cleansing	0.00002%
	lotions, liquids and pads)	
Glycine Soja (Soybean) Germ Extract	Face and neck products	
	Not spray	0.005-0.45%
Glycine Soja (Soybean) Germ Extract	Moisturizing products	
	Not spray	0.00002%
Glycine Soja (Soybean) Germ Extract	Paste masks and mud packs	0.00002%
Glycine Soja (Soybean) Germ Extract	Other skin care preparations	0.00002-0.3%

	1	
Glycine Soja (Soybean) Lipids	Eye shadows	0.09%
Glycine Soja (Soybean) Lipids	Lipstick	0.65%
Glycine Soja (Soybean) Lipids	Body and hand products	
	Not spray or powder	0.086%
Glycine Soja (Soybean) Seed Extract	Bath oils, tablets and salts	0.0004%
Glycine Soja (Soybean) Seed Extract	Hair conditioners	0.000096-0.01%
Glycine Soja (Soybean) Seed Extract	Hair sprays	
	Aerosol	0.000001%
Glycine Soja (Soybean) Seed Extract	Shampoos (noncoloring)	0.00008-0.001%
Glycine Soja (Soybean) Seed Extract	Tonics, dressings and other hair	0.005%
	grooming aids	
	Not spray	0.000006%
Glycine Soja (Soybean) Seed Extract	Lipstick	0.0001%
Glycine Soja (Soybean) Seed Extract	Makeup fixatives	0.00075%
Glycine Soja (Soybean) Seed Extract	Nail creams and lotions	0.001%
Glycine Soja (Soybean) Seed Extract	Skin cleansing (cold creams, cleansing	0.0004-0.7%
	lotions, liquids and pads)	
Glycine Soja (Soybean) Seed Extract	Depilatories	0.001%
Glycine Soja (Soybean) Seed Extract	Face and neck products	
	Not spray	0.002-2%
Glycine Soja (Soybean) Seed Extract	Other skin care preparations	0.2%

^{*}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 2016 Table prepared December 14, 2016



Memorandum

TO:

Bart Heldreth, Ph.D.

Executive Director - Cosmetic Ingredient Review (CIR)

FROM:

Carol Eisenmann, Ph.D.

Personal Care Products Council

DATE:

March 29, 2019

SUBJECT:

Glycine Soja (Soybean) Phytoplacenta Extract

Active Concepts. 2017. Product specification AC Soy Phytoplacenta Extract (Water and Glycine Soja (Soybean) Phytoplacenta Extract).

Active Concepts. 2017. Compositional breakdown AC Soy Phytoplacenta Extract (Water and Glycine Soja (Soybean) Phytoplacenta Extract).

Active Concepts. 2015. Manufacturing flow chart AC Soy Phytoplacenta Extract (Water and Glycine Soja (Soybean) Phytoplacenta Extract).

Active Concepts. 2013. Cellular viability assay analysis AC Soy Phytoplacenta Extract (Water and Glycine Soja (Soybean) Phytoplacenta Extract).



Product Specification

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Product Name:

AC Soy Phytoplacenta Extract

Code Number:

20426

CAS #'s:

7732-18-5 & 84776-91-0

EINECS #'s:

231-791-2 & N/A

INCI Name:

Water & Glycine Soja (Soybean) Phytoplacenta Extract

Specification	Parameter
Appearance	Clear to Hazy Viscous Liquid
Color	4 Gardner Maximum
Odor	Characteristic
pH (25°C)	3.5 – 5.5
Non-Volatile Matter (1g, 105°C, 1hr)	3.5 – 5.5%
Identification (Protein)	Positive
Methyl Paraben	Positive
Heavy Metals	< 20 ppm
Lead	< 10 ppm
Arsenic	< 2 ppm
Cadmium	< 1 ppm
Microbial Content Yeast & Mold Gram Negative Bacteria	< 100 CFU/g; No pathogens < 100 CFU/g 0 CFU/g

May Sediment upon Standing; Mix Well Prior to Use

^{**}Note: Product may change appearance if exposed to cold temperatures during shipment or storage. If this happens, please gently warm to 45-50°C and mix until normal appearance is restored.



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AC Soy Phytoplacenta Extract Code: 20426

Water and Glycine Soja (seybean)

Compositional Breakdown:

Phytoplacenta Extract

Ingredient

%

Water	78.93
Glycine Soja (Soybean) Phytoplacenta Extract	20.00
Phenoxyethanol	0.90
Methylparaben	0.15
Tetrasodium EDTA	0.02



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This is to certify that AC Soy Phytoplacenta Extract does not contain allergen levels exceeding the following (Gas Chromatography-Mass Spectrometer Coupled):

ALI	ERGENS Dir 2003 15 CEE	
INCI NAME	CAS NUMBER	Limit (ppm)
Alpha-IsoMethyl Ionone	127-51-5	< 0.02
Amyl Cinnamal	122-40-7	< 0.10
Anise Alcohol	105-13-5	< 0.00
Benzyl Alcohol	100-51-6	< 0.01
Benzyl Benzoate	120-51-4	< 0.09
Benzyl Cinnamate	103-41-3	< 0.30
Benzyl Salicylate	118-58-1	< 0.06
Butylphenyl Methylpropional	80-54-6	< 0.50
Cinnamal	104-55-2	< 0.01
Cinnamyl Alcohol	104-54-1	< 0.30
Citral	5392-40-5	< 1.00
Citronellol	106-22-9	< 1.00
Coumarin	91-64-5	< 0.00
Eugenol	97-53-0	< 0.70
Farnesol	4602-84-0	< 0.04
Geraniol	106-24-1	< 0.08
Hexyl Cinnamal	101-86-0	< 0.40
Hydroxycitronellal	107-75-5	< 1.00
Hydroxymethylpentyl 3-Cyclohexene carboxaldehyde	31906-04-4	< 0.30
Isoeugenol	97-54-1	< 0.06
Limonene	5989-27-5	< 0.05
Linalool	78-70-6	< 0.00
Methyl 2 Octynoate	111-12-6	< 0.20
Evernia prunastri	90028-68-5	< 0.02
Evernia furfuracea	90028-67-4	< 0.00
Amylcinnamyl Alcohol	101-85-9	< 1.00



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This is to certify that AC Soy Phytoplacenta Extract does not contain pesticide levels exceeding the following (Reverse Phase High Performance Liquid Chromatography-Mass Spectrometer Coupled):

EPA Pesticide Levels		
INCI NAME	LIMIT (mg/kg)	
Alachlor	< 0.02	
Aldrin and Dieldrin	< 0 .05	
Azinphos-methyl	< 1. 00	
Bromopropylate	< 3.0 0	
Chlordane(cis and trans)	< 0.05	
Chlorfenvinphos	< 0.50	
Chlorpyrifos	< 0.20	
Chlorpyrifos-methyl	< 0.10	
Cypermethrin	< 1.00	
DDT	< 1.00	
Deltamethrin	< 0.50	
Diazinon	< 0.50	
Dichlorvos	< 1.00	
Dithiocarbamates	< 2.00	
Endosulfan	< 3.00	
Endrin	< 0.05	
Ethion	< 2.00	
Fenitrothion	< 0.50	
Fenvalerate	< 1.50	
Fonofos	< 0.05	
Heptachlor	< 0.05	
Hexachlorobenzene	< 0.10	
Hexachiorocyclohexane	< 0.30	
Lindane	< 0.60	
Malathion	< 1.00	
Methidathion	< 0.20	
Parathion	< 0.50	
Parathion-methyl	< 0.20	

This information is presented in good faith but is not warranted as to accuracy of results. Also, freedom from patent infringement is not implied.

This information is offered solely for your investigation, verification, and consideration.



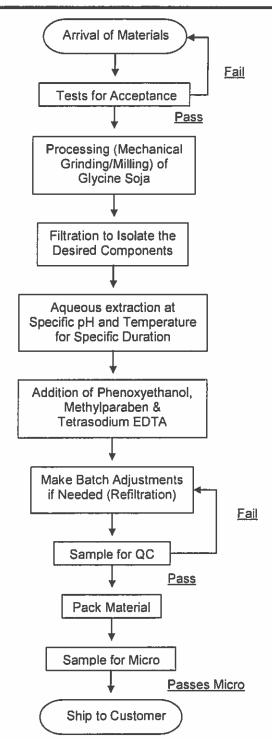
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G	
Permethrin	< 1.00
Phosalone	< 0.10
Piperonyl butoxide	< 3.00
Pirimiphos-methyl	< 4.00
Pyrethrins	< 3.00
Quintozene(sum of 3 items)	< 1.00



20426-AC Soy Phytoplacenta Extract - Manufacturing Flow Chart

info@activeconceptsllc.com · Phone: +1-704-276-7100 · Fax: +1-704-276-7101 Extract



Information contained in this technical literature is believed to be accurate and is offered in good faith for the benefit of the customer. The company, however, cannot assume any liability or risk involved in the use of its chemical products since the conditions of use are beyond our control. Statements concerning the possible use of our products are not intended as recommendations to use our products in the infringement of any patent. We make no warranty of any kind, expressed or implied, other than that the material conforms to the applicable standard specification.



Cellular Viability Assay Analysis

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Tradename: AC Soy Phytoplacenta Extract Water and Glycine Soja (Soybean)
Phytoplacenta Extract

Code: 20426

CAS #: 7732-18-5 & 84776-91-0

Test Request Form #: 474

Sponsor: Active Concepts, LLC; 107 Technology Drive Lincolnton, NC 28092

Study Director: Erica Segura

Principle Investigator: Meghan Darley

Test Performed:

Cellular Viability Assay

Introduction

The cellular viability assay is useful for quantitatively measuring cell-mediated cytotoxicity, cell proliferation and mitochondrial metabolic activity. Increased metabolism in a cell indicates ample cellular respiration and adenosine triphosphate (ATP) production. ATP is the molecular energy of cells and is required in basic cell function and signal transduction. A decrease is ATP levels indicates cytotoxicity and decreased cell function while an increase in ATP levels indicates healthy cells.

The cellular viability assay was conducted to assess the ability of AC Soy Phytopiacenta Extract to increase cellular metabolic activity in cultured dermal fibroblasts.

Assay Principle

The assay utilizes a nonfluorescent dye, resazurin, which is converted to a fluorescent dye, resorufin, in response to chemical reduction of growth medium from cell growth and by respiring mitochondria. Healthy cells that are in a proliferative state will be able to easily convert resazurin into resorufin without harming the cells. This method is a more sensitive assay than other commonly used mitochondrial reductase dyes such as MTT. An increase in the signal generated by resazurin-conversion is indicative of a proliferative cellular state.



Cellular Viability Assay Analysis

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Materials

A. Kit: PrestoBlue™ Cell Viability Reagent (Invitrogen, A13261)

B. Incubation Conditions: 37°C at 5% CO₂ and 95% relative humidity (RH)

C. Equipment: Forma humidified incubator; ESCO biosafety laminar flow hood; Light

microscope; Pipettes

D. Cell Line: Normal Human Dermal Fibroblasts (NHDF) (Lonza; CC-2511)

E. Media/Buffers: Dulbecco's Modified Eagle Medium (DMEM); Penicillin-Streptomycin

(50U- 50mg/mL); Fetal Bovine Serum (FBS); Phosphate Buffered

Saline (PBS)

F. Culture Plate: Falcon flat bottom 96-well tissue culture treated plates

G. Reagents: PrestoBlue™ reagent (10X)

H. Other: Sterile disposable pipette tips

Methods

Human dermal fibroblasts were seeded into 96-well tissue culture plates and allowed to grow to confluency in complete DMEM. A 10-fold serial dilution was performed resulting in **AC Soy Phytoplacenta Extract** concentrations on 1%, 0.1%, and 0.01% in complete DMEM and incubated with fibroblasts for 24 hours.

Ten microliters of viability reagent was added to 90µL of cell culture media in culture wells.



Cellular Viability Assay Analysis

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Results

The data obtained from this study met criteria for a valid assay and the controls performed as anticipated.

AC Soy Phytoplacenta Extract did not exhibited significant effects on cellular metabolism compared to the control.

Cellular metabolism results are expressed as a percentage of the control.

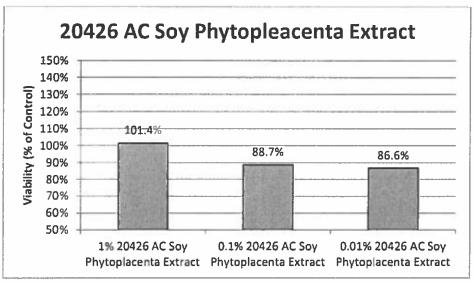


Figure 1: Cellular Metabolism of AC Soy Phytoplacenta Extract-treated fibroblasts expressed in terms of percent of control.

Discussion

As shown in figure 1, AC Soy Phytoplacenta Extract exhibited comparable results by increasing cell metabolism. An increase in fluorescent signal indicates an increase in cellular metabolism and viability. AC Soy Phytoplacenta Extract does not appear to have significant negative effects on cellular metabolism and can safely be used in cosmetic materials.



Memorandum

TO:

Bart Heldreth, Ph.D.

Executive Director - Cosmetic Ingredient Review (CIR)

FROM:

Carol Eisenmann, Ph.D.

Personal Care Products Council

DATE:

April 11, 2019

SUBJECT:

Glycine Soja (Soybean) Germ Extract

Clinical Research Laboratories, Inc. 2010. Repeated insult patch test (other skin care preparation (leave-on) containing 0.3% Glycine Soja (Soybean) Germ Extract).



Final Report	
Repeated Insult Patch Test Other skin care preparation (leave-on) Containin	
CLIENT:	9 ره
ATTENTION:) Ger.
TEST MATERIAL:	
CRL STUDY NUMBER: CRL96509-2 AUTHORIZED SIGNATURES:	
Bruce E. Kanengiser, M.D. President/Medical Director Executive Vice President/COO	
George J. Neumaier, M.D. Diplomate American Board of Dermatology	
REPORT DATE: Jánuary 4, 2010	



Good Clinical Practice Quality Assurance Audit Statement

Clinical Study Number: CRL96509-2

Start Date: November 9, 2009

Completion Date: December 18, 2009

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

Signature of OA Auditor

Date

Final Report
Client:
Study Number: CRL96509-2
Page 3 of 13

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc. 371 Hoes Lane Piscataway, New Jersey 08854 732-981-1616

TEST MATERIAL

The following test material was provided by and was received by Clinical Research Laboratories, Inc. on October 12, 2009:

Test Material	Test Condition	Patch Type
	Test as Received	Occlusive*

The test material was coded with the following CRL identification number:

CRL96509-2

STUDY DATES

This study was initiated on November 9, 2009 and was completed on December 18, 2009.

^{*} Occlusive Strip with Flexcon® (Brady Medical, Mesquite TX)

Final Report
Client:
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PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix 1). Subjects who met the following criteria were impaneled:

- Male and female panelists between the ages of 18 and 70;
- Subjects who have completed a Panelist Profile/Medical History;
- Subjects who are in general good health as determined by a Panelist Profile/Medical History;
- Subjects who do not exhibit any skin diseases that might be confused with a skin reaction from the test material;
- Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;
- Subjects willing to sign an Informed Consent Form in conformance with 21 CFR Part 50: "Protection of Human Subjects";
- Subjects who have completed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164:
- Females who are not pregnant or lactating;
- Subjects who demonstrate dependability and intelligence in following directions;
- Subjects who are not currently using any systemic or topical corticosteroids, antiinflammatory drugs or antihistamines;
- Subjects who do not exhibit skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

Final Report
Client:
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Page 5 of 13

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

- 0 No visible skin reaction
- ± Barely perceptible erythema
- I+ Mild erythema
- 2+ Well defined erythema
- 3+ Erythema and edema
- 4+ Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

Final Report
Client:
Study Number: CRL96509-2
Page 6 of 13

RESULTS

This study was initiated with 112 subjects. Four subjects discontinued study participation for reasons unrelated to the test material. A total of 108 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 108 subjects and under the conditions of this study, the test material identified as did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

Final Report Client: Study Number: CRL96509-2 Page 7 of 13

TABLE I
Summary of Dermal Scores

	Γest Ma	aterial:	B 100									·
Subject				Indu	ction S	cores				Chal	lenge S	cores
Number	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	1+	#	±	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0_
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0_
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23		Discontinued										
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

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TABLE I (Continued)

Те	st Mate	erial:	ahini.	HAR								
Subject				Indu	ction S	cores			-2	Chal	lenge S	cores
Number	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	X	0*
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0 _
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	Discontinued							1		
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0

^{*}The 96 hour reading occurred on Saturday, December 19 when Clinical Research Laboratories, Inc. was closed. X = Subject Absent

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TABLE I (Continued)

Te	st Mate	erial:	hristan Maranti				W 55.5	1				
Subject	-XT1			Indu	ction S	cores				Chal	lenge S	cores
Number	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0				Di	scontin	ued			
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0_	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	00	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0 _
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0

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TABLE I (Continued)

Te	st Mat	erial:	Nas									
Subject				Indu	ction S	cores				Chal	lenge S	cores
Number	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0				Di	scontinu	ıed			
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	. 0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

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TABLE I (Continued)

Te	st Mate	erial:										-	
Subject			TEN,	Induction Scores							Challenge Scores		
Number	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour	
101	0	0	0	0	0	0	0	0	0	0	0	0	
102	0	0	0	0	0	0	0	0	0	0	0	0	
103	0	0	0	0	0	0	0	0	0	0	0	0	
104	0	0	0	0	0	0	0	0	0	0	0	0	
105	0	0	0	0	0	0	0	0	0	0	0	0	
106	0	0	0	0	0	0	0	0	0	0	0	0	
107	0	0	0	0	0	0	0	0	0	0	0	0	
108	0	0	0	0	0	0	0	0	0	±	0	0	
109	0	0	0	0	0	0	0	0	0	0	0	0	
110	0	0	0	0	0	0	0	0	0	0	0	0	
111	0	0	0	0	0	0	0	0	0	0	0	0	
112	0	0	0	0	0	0	0	0	0	0	0	0	

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Appendix I Subject Demographics

Subject Number	Subject Initials	CRL ID#	Age	Sex
1	JB	14759	58	F
2	MR	15390	48	F
3	RJ	26063	47	F
4	DG	16950	51	F
5	KS	23456	51	F
6	FR	25686	32	М
7	MM	24933	39	F
8	NG	25711	36	M
9	SR	02417	62	F
10	RA	20421	52	F
11	SK	18539	58	F
12	RM	21100	56	М
13	EN	14911	56	F
14	DL	03280	39	F
15	DG	16132	57	F
16	RH	25758	60	M
17	EL	26069	48	F
18	СН	24373	45	F
19	AJ	23767	60	М
20	CJ	24059	46	F
21	KS	25876	42	F
22	EJ	24955	48	М
23	LL	10549	33	F
24	KL	16938	53	F
25	KM	26029	49	F
26	BW	06687	62	F
27	JН	23464	63	F
28	LW	06688	64	M

Subject Number	Subject Initials	CRL ID#	Age	Sex
29	MC	25806	34	F
30	RB	21755	28	F
31	DB	21823	60	F
32	PS	24548	25	F
33	ВН	26055	53	F
34	YP	11690	53	F
35	ED	20237	50	F
36	CM	19646	51	F
37	GO	14807	49	F
38	BP	22742	55	M
39	AG	26080	56	M
40	SS	24983	37	F
41	JV	26071	43	M
42	LK	26057	49	F
43	DB	26075	40	F
44	Ml	14669	65	F
45	CL	14668	65	F_
46	MC	17245	36	F
47	AC	26058	35	F
48	KP	22765	21	F
49	CD	25061	40	F
50	AC	23736	40	F
51	CM	23078	38	F
52	PR	00278	48	F
53	HG	23938	36	M
54	MV	15003	61	F
55	PP	21196	21	F
56	DG	22064	54	M

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Appendix I (Continued)

Subject Demographics

Subject Number	Subject Initials	CRL ID#	Age	Sex
57	ΑI	21944	56	F
58	LN	14920	53	F
59	SP	25963	66	F
60	RP	25964	34	F
6I	LP	23082	46	F
62	SP	26003	31	F
63	PG	13984	48	F
64	UP	26008	52	F
65	HP	26009	59	M
66	BS	25765	63	F
67	GK	26082	51	М
68	SR	25994	44	F
69	ER	25999	46	M
70	EJ	17508	60	F
71	CC	25487	61	F
72	WO	26031	37	F
73	RC	25488	61	M
74	FA	21228	45	М
75	RM	26013	32	М
76	CS	19650	65	F
77	RM	24917	59	F
78	CG	20751	47	F
79	AJ	23193	47	F
80	BF	25674	65	F
81	NA	24910	38	F
82	WP	03329	42	F
83	JL	17689	42	F
84	JW	16392	43	F

Subject	Subject	CRL	A	C
Number	Initials	ID#	Age	Sex
85	JP	17665	36	F
86	BL	25002	58	M
87	DF	13552	32	F
88	MW	25001	48	F
89	AG	23159	44	F
90	WM	23824	51	F
91	BU	15599	63	F
92	DL	00674	49	F
93	EC	04349	62	F
94	SC	23733	34	F
95	GM	19064	36	F
96	MP	15018	31	F
97	SD	05604	20	F
98	AM	06580	39	F
99	DD	18786	51	F
100	SL	24903	52	F
101	GO	22764	59	F_
102	KP	20301	24	F
103	JK	15698	52	F_
104	IA	17837	43	F
105	GT	20882	57	M
106	RD	21017	48	М
107	LF	02384	47	F
108	CF	09391	19	F
109	JS	03048	44	F_
110	RA	23557	38	F
111	SB	26043	38	M
112	JS	23457	22	F



Memorandum

TO: Bart Heldreth, Ph.D.

Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.

Personal Care Products Council

DATE: April 19, 2019

Glycine Soja (Soybean) Seedcake Extract SUBJECT:

Anonymous. 2019. Summary information Glycine Soja (Seedcake) Extract.

April 2019

Summary Information Glycine Soja (Soybean) Seedcake Extract

Composition: Water and Glycine Soja (Soybean) Seedcake Extract (13% maximum)

Maximum recommended use in cosmetic products: 4%

Safety Information:

Cutaneous tolerance after a single application of an occlusive bandage for 48 hours:

The objective is to assess on 10 volunteers the irritant potential of the studied cosmetic product (at 5%) after its unique application, maintained for 48 hours in contact with the skin, with the help of an occlusive patch.

In conclusion, the product can be considered as non-irritant after an application of 48 consecutive hours on 10 volunteers and after dermatology analysis of skin reactions.

<u>Determination of irritant potential by direct application on a monolayer of Rabbit cornea Fibroblasts – Method of Neutral Red Release</u>

The study was conducted according to the official method for evaluating irritant potential: appendix VI of the JO N°302 of Dec. 30, 1999.

The principal is based on assessing the cytotoxicity of the product tested by identifying the concentration causing 50% mortality (IC50%) using the technique of neutral red neutral release.

The irritant potential of the product towards rabbit cornea fibroblasts was determined at concentrations of 5 to 50%. The IC50 is higher than 50%. The percent mortality observed at the dilution of 50% is less than 20%. The cytotoxicity of the product is thus negligible.

Memorandum

TO:

Bart Heldreth, Ph.D.

Executive Director - Cosmetic Ingredient Review (CIR)

FROM:

Alexandra Kowcz, MS, MBA

Industry Liaison to the CIR Expert Panel

DATE:

April 23, 2019

SUBJECT:

Scientific Literature Review: Safety Assessment of Soy-Derived Ingredients as

Used in Cosmetics (release date March 22, 2019)

The Personal Care Products Council has no suppliers listed for Glycine Max (Soybean) Flower/Leaf/Stem Juice.

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Soy-Derived Ingredients as Used in Cosmetics.

Key Issue

The conclusions of the CIR reports on other soy-derived ingredients should be stated somewhere in this report.

Additional Considerations

Definition - Please correct: "Glycine soja is the accepted scientific name for Glycine max" -Glycine max is the current accepted scientific name for the commercially grown soybean.

Method of Manufacture, Glycine Max (Soybean) Leaf Extract - It would be helpful to include the yield of the extract provided in reference 6 (22.3 \pm 1.3% on a dry weight basis).

Method of Manufacture, Glycine Max (Soybean) Seed Powder Extract - As plant parts are often ground up before extraction, the ingredient described in this section would be named as a seed extract (there are no INCI names "powder extract"). The heading should be changed to "Glycine Max (Soybean) Seed Extract, and the first paragraph should be deleted.

Method of Manufacture, Glycine Soja (Soybean) Extract - As the title of reference 11 says "Glycine max", this study should be presented under the subheading, Glycine Max (Soybean) Seed Extract.

Method of Manufacture, Glycine Soja (Soybean) Flour - Since Glycine max is the commercially grown soybean, please change this heading to Glycine Max.

Composition, Germ Extract - Please provide a reference(s) for the information in this section.

Composition, Soybean extract - Please correct: "isflavones"

Composition, Seedcoat (Hull) Extract - The information described in this section concerns

- soybean flour not a seedcoat (or hull) extract. The heading needs to be corrected.
- Cosmetic Use Please state the concentrations of Glycine Max (Soybean) Seed Extract and Glycine Max (Soybean) Lipids in lipstick.
- Non-Cosmetic Use, Food It would be helpful to state that the US FDA requires the presence of soy to be on the label of food because it is a considered a food allergen (see the CIR report on soy proteins as an example).
- Non-Cosmetic Use, Medicine The EMEA assessment report (reference 14) states the isoflavone content (10-30%) of the extracts they consider to be herbal medication. This should be stated in the CIR report. The FDA inactives database https://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm would be a better reference to discuss the use of soy in medical preparations. Soybean oil is used in more than just the intravenous medication mentioned in the CIR report and other soy derived ingredients are used as inactive ingredients in medical preparations.
- Short-Term, Oral As *Glycine max* is the commercially grown soybean, it is not clear why the heading is Glycine Soja.
- Subchronic, Oral, Flour The material studied in reference 39 was soluble soybean fiber (the trade name stated in the study SOYAFIBE-S has been assigned the INCl name Glycine Max (Soybean) Fiber). Therefore, it is not clear why the subheading is "Glycine Soja (Soybean) Flour".
- Subchronic, Oral, Soybean Extract The subheading should be changed from "Soja" to "Max".

 Although which solvent was used to prepare the extract that was tested may not be stated, reference 40 does provide the composition of the extract that was tested. It consisted of 94% saponins and 6% isoflavones. The composition should be stated in the CIR report.
- Chronic, Seedcoat Extract Reference 19 also stated the mg/kg doses associated with the dietary concentrations of black seedcoat extract. The doses, in addition to the dietary concentrations should be stated in the CIR report. The description of reference 19 states: "A significant reduction in body weights was noted in 5% males compared to 2% males and control males." and "The final body weight of males in the 5% group was significantly lower than that of control males and 2% males." Is it necessary to discuss male body weight effects twice in the same paragraph?
- Chronic, Flour The subheading should be changed from "Soja" to "Max". This section says that the carcinogenic effects are found in the Carcinogenicity section, but they are actually in the anti-carcinogenicity section (soybean flour did not reduce pancreatic tumors in azaserine treated rats).
- Anti-Carcinogenicity The subheading should be changed from "Soja" to "Max".
- Estrogen Activity What were the "different extraction methods" (or composition if stated) used to prepare the soy extracts studied in reference 11?
- Cytotoxicity Please correct"100% q.b. to 100% w/w" (the first 100% should be deleted).
- Immunotoxicity Reference 47 should be moved to the Sensitization section. Rather than stating that the mice were treated with midazolam, butorphanol and medetomidine, the CIR report should state that the mice were medicated by iv injection to control pain.
- Irritation The subheading should be changed from "Soja" to "Max". Reference 48 states that 1 g of base emulsion and emulsion with the soy were used to treat the sites. "The amount of test substance applied was not noted" should be deleted.
- Sensitization Reference 46 summarizes a study of a callus culture in monocyte cells (no effect

- on markers of sensitization). This information should be presented in the Sensitization section.
- Clinical Studies It is not clear why the 12 week study of the product containing a soybean extract (reference 48) is not presented in the Clinical Studies section.
- Summary Rather than stating that "These ingredients are commonly used in food..." it should state that soybeans and ingredients made from soybeans are commonly used in food.
 - Please state the route of exposure and species for the study of 2% and 5% soybean seedcoat extract.
- Table 2 If available, the standard deviation (or other measure of variability) should be added to Table 2. The numbers less than 1 should all be presented with a 0 in front of the decimal point, e.g., 0.704 (not .704).
- Reference 41 Please correct: "Regine"