Safety Assessment of Soy Proteins and Peptides as Used in Cosmetics

Status:	Final Report
Release Date:	October 22, 2015
Panel Meeting Date:	September 21-22, 2015

The 2015 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 Director is Lillian J. Gill, D.P.A. This report was prepared by Christina Burnett, Senior Scientific Analyst/Writer, and Bart Heldreth, Ph.D., Chemist CIR.

Cosmetic Ingredient Review

1620 L Street, NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651 ◇ fax 202.331.0088 ◇ cirinfo@cir-safety.org

ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of soy proteins and peptides, which function in cosmetics primarily as hair conditioning agents and skin conditioning agents-miscellaneous. The Panel considered relevant data related to these ingredients. The Panel concluded that soy proteins and peptides are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

Soy protein and peptide ingredients function mainly as skin and hair conditioning agents in personal care products.[1] This report assesses the safety of the following 6 soy ingredients:

Glycine Max (Soybean) Polypeptide	Hydrolyzed Soy Protein
Glycine Soja (Soybean) Peptide	Hydrolyzed Soy Protein Extract
Glycine Soja (Soybean) Protein	Hydrolyzed Soymilk Protein

The safety of several hydrolyzed proteins as used in cosmetics has previously been reviewed by the Panel. The Panel concluded that hydrolyzed collagen, hydrolyzed corn protein, hydrolyzed rice protein, and hydrolyzed silk are safe for use in cosmetics.[2-6] Additionally, the Panel concluded that hydrolyzed wheat gluten and hydrolyzed wheat protein are safe for use in cosmetics when formulated to restrict peptides to a weight-average MW of 3500 Da or less.[7]

Soy proteins and peptides are used as food. The U.S. Food and Drug Administration (FDA) determined that the use of peptones as direct food substances is generally recognized as safe (GRAS) and that soybean protein is GRAS as an indirect food additive for substances migrating to food from paper and paperboard products. Because daily exposure from food use would result in much larger systemic exposures than from use in cosmetic products, the systemic toxicity potential of soy peptide ingredients via oral exposure is not addressed further in this report. The primary focus of the safety assessment is the review of safety based on topical exposure

Note: Ingredients with the name glycine soja (soybean) are undergoing a name change to glycine max (soybean) through the International Nomenclature of Cosmetic Ingredients (INCI) Committee of the Personal Care Products Council (Council). Both names refer to the same plant species.[8] This change represents the more commonly accepted nomenclature.

CHEMISTRY

Definition

The definitions of the soy peptide ingredients included in this report are provided in Table 1.

The soy protein and peptide derivatives form a broad category of materials which are prepared by extraction from soy and partial hydrolysis to yield cosmetic ingredients. Soy proteins and peptides can also be separated on the basis of molecular size. By removing oil at lower temperatures, soy protein isolate is obtained, and is widely used in the food industry.[9-11] Whole aqueous extractable soybean proteins can be separated into storage globulin and whey fractions by acidification.

The FDA defines the term “protein” to mean any α-amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.[12] The FDA considers a “peptide” to be any polymer composed of 40 or fewer amino acids; however, these definitions of protein and peptide are not necessarily adhered to in the naming of cosmetic ingredients.

The acid-precipitable fraction of whole aqueous extractable soybean proteins includes the major soybean storage proteins. The remaining part consists of the minor globulin, γ-conglycinin, and contaminating proteins, including whey proteins. Whey proteins are composed of lipoxygenase (102 kDa), bamylase (61.7 kDa), lectin (33 kDa), and Kunitz trypsin inhibitors (20 kDa). The proportion represented by these whey proteins in the acid-precipitated globulins is unknown. Soy protein isolate is a mixture of various proteins, and the main ingredients are classified into four protein categories according to their sedimentation coefficients 2S, 7S, 11S, and 15S which sediment at different gravitational forces when the solution is subjected to a centrifugal field. Among these proteins, 7S (β-conglycinin) and 11S (glycinin) represent 80%-90% of all soybean protein, and the ratio 7S/11S has been reported to be about 0.5-1.3 depending on varieties. The 7S globulin consists of three subunits α (ca 67 kDa), α' (ca 71 kDa) and β (ca 50 kDa). The 11S globulin is a hexamer, and is made up of five different subunits, each of which consists of an acidic subunit A (ca 35 kDa) and a basic subunit B (ca 20 kDa), linked by a disulfide bond. The 11S globulin was found to dissociate into 2S, 3S or 7S forms in solutions of various pH values and ionic strengths.

Amino acid compositions of β-conglycinin and glycinin have been analyzed, but the three dimensional structures are not well established in spite of many efforts.

Chemical and Physical Properties

Available information concerning chemical and physical properties, including molecular weights, for soy protein and soy peptide ingredients is presented in Table 2.

Soy Peptide

Dipeptide- or tripeptide-rich forms of soy peptide were described to have a mean molecular weight of around 500 Da.[13]

Hydrolyzed Soy Protein

A histogram showing the approximate distribution of molecular weights for a hydrolyzed soy protein product from one supplier is shown in Figure 1.[14] The figure shows that approximately 35% of the molecular weight distribution falls between 490 and 1030 Da. One source has indicated the average molecular weight is 300 Da[15]; however, other sources have reported the molecular weight of their hydrolyzed soy protein product to be approximately 1000-2000 Da.[16-18]

Hydrolyzed Soymilk Protein

A supplier has reported the molecular weight of their hydrolyzed soymilk protein product to be approximately 1000-2000 Da.[18]

Method of Manufacturing

Glycine Soja (Soybean) Protein

Glycine soja (soybean) protein can be prepared from defatted low-heat soybean meal.[10] A dispersion of soy flour is prepared by adding distilled water (1: l5, w/v) with final protein concentration of 3.1% (w/w). Then, 2 mol/L NaOH is used to adjust the dispersion to pH 8.5. The dispersion is stirred for 1 h at room temperature and then centrifuged (10000 × g, 20 min). The supernatant is adjusted to pH 4.5 with 2 mol/L HCl and centrifuged (10000 × g, 20 min). The obtained sediment is resuspended with distilled water (1: 5, v/v) and adjusted to pH 7.0 with 2 mol/L NaOH. Then it is dialyzed against deionized water and freeze-dried.

A supplier has indicated that a glycine soja (soybean) protein product is manufactured by adding water to the seed of *Glycine max* Merrill (Leguminosae), extracting, and then filtering.[19] The solvent 1,3-butylene glycol is then added to the filtrate. More than 80% of the resulting protein product has a molecular weight less than 5000 Da.

Hydrolyzed Soy Protein

A manufacturing flow chart from a hydrolyzed soy protein supplier is shown in Figure 2.

The preparation of hydrolysates can be afforded via acid and enzyme.[10] The above glycine soja (soybean) protein dispersion (4% w/v) is adjusted to pH 2.0 with 1 mol/L HCl, and incubated at 37 °C for 30 min. Then, an enzyme (such as pepsin) is added to each part at an enzyme to substrate ratio of 0.3% (w/w) to start the enzymatic hydrolysis reaction. Each fraction is incubated at 37 °C (10-900 min) and the enzyme is deactivated by adjusting the pH to 7.0 with 2 mol/L NaOH.

A supplier has reported that hydrolyzed soy protein is produced from isolated soy proteins that are hydrolyzed with a protease enzyme for 2 hours.[20] The enzyme is inactivated by heat once the target molecular weight is achieved. The resultant solution may then be concentrated.

Another supplier reported that hydrolyzed soy protein (MW = 300 Da) may be prepared by both alkaline and enzyme hydrolysis.[15] These processes occur for several hours until the desired molecular weight is reached. The final product is a 25% water solution of hydrolyzed soy protein.

In a hydrolyzed soy protein product of 8.5%, the supplier states that enzymatic hydrolysis yields a material with 87% of the proteins with a molecular weight less than 2000 Da, 11% of the proteins with a molecular weight between 2000 and 5000 Da, and 2% of the proteins with a molecular weight greater than 5000 Da.[21]

Hydrolyzed Soymilk Protein

While method of manufacturing for hydrolyzed soymilk protein was not discovered in the published literature nor was information provided by industry, soymilk is reported to be made through water extraction of whole soybeans.[22]

Composition and Impurities

A supplier has stated that hydrolyzed soy protein and hydrolyzed soymilk protein do not contain fragrance ingredients designated as sensitizing by the European Union's cosmetics regulations.[23-26]

Glycine Soja (Soybean) Protein

A supplier states that glycine soja (soybean) protein product (>80% has MW less than 5000 Da) is comprised of 0.4% protein, 30% butylene glycol, and 69.6% water.[19]

Soy Peptide

The amino acid composition of a soy peptide sample is presented in Table 3. The analysis found that soy peptide is rich in aspartic acid (12.6%) and glutamic acid (22.1%). [13]

Hydrolyzed Soy Protein

A supplier states that hydrolyzed soy protein (MW = 300 Da) has heavy metals, arsenic, and iron at levels $\leq$ 10 ppm, 1 ppm, and 10 ppm, respectively.[15] Another supplier states that hydrolyzed soy protein (87% has MW < 2000 Da) did not have detectable levels of alkaloids, pesticides, or aflatoxins.[21] No traces of arsenic or mercury were detected. Other metals were reported as cadmium (2 ppb), chromium (57 ppb), cobalt (15 ppb), nickel (0.7 ppm), lead (60 ppb), and iron (< 10 ppm).

The compositional breakdown of products containing 25% and 35% hydrolyzed soy protein included 74.6% or 64.6% water, respectively, and 0.2% methylparaben, and 0.2% quaternium-15, each.[23,24]

Hydrolyzed Soymilk Protein

The compositional breakdown of a product containing 21.5% hydrolyzed soymilk protein included 76.6% water, 1.2% phenoxyethanol, and 0.7% DMDM hydantoin.[25]

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the FDA and the cosmetics industry. The data received from the FDA are those it collects from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP), and those from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations by category conducted by the Council.

According to the 2015 VCRP data, hydrolyzed soy protein has the most reported uses in cosmetic products of the ingredients listed in this safety assessment, with a total of 862; about half of the uses are in non-coloring hair products (Table 4). Glycine soja (soybean) protein has the second greatest number of overall uses reported, with a total of 313; a third of those are used in leave-on skin care products and another third are used in hair dyes and colors. The results of the concentration of use survey conducted in 2014 by the Council indicate hydrolyzed soy protein has the highest reported maximum concentrations of use; the maximum concentration used is 3.5% in mascara. Glycine soja (soybean) protein is used at up to 0.9% in eye lotion. No use concentrations were reported for the remaining 4 ingredients.

Based on the VCRP data and the results of the Council's concentration of use survey, glycine soja (soybean) peptide and hydrolyzed soy protein extract are not in use.

As mentioned previously, some of these ingredients are used in products that are used near the eye. Additionally, some of these ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes. For example, hydrolyzed soy protein is used in bath soaps and detergents at up to 1.5%. Additionally, some of these ingredients were reported to be used in hair sprays and body and hand sprays and could possibly be inhaled. For example, glycine soja (soybean) protein was reported to be used in body and hand sprays at a maximum concentration of 0.07%. In practice, 95% to 99% of the droplets/particles released from

cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[27-30] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[28,29]

The soy peptide ingredients in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[26]

Non-Cosmetic

The FDA determined that the use of peptones as direct food substances is GRAS. These GRAS peptones are defined as "the variable mixture of polypeptides, oligopeptides, and amino acids that are produced by partial hydrolysis of …soy protein isolate…" (21 CFR §184.1553). Additionally, soybean protein (described as glycine soja (soybean) protein) is GRAS for substances migrating to food from paper and paperboard products (21CFR §182.90). The FDA requires allergen labeling when major allergens are included in food; these allergens include soybeans.[31]

The FDA has also reviewed soybean protein for use as an active ingredient in over-the-counter drugs. Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of this ingredient in weight control drug products (21CFR §310.545).

Soy proteins are used in adhesives and plastics industries.[32]

TOXICOKINETICS

Hydrolyzed Soy Protein

While no experimental data were available for the dermal absorption of hydrolyzed soy protein, gastrointestinal absorption would allow for significantly higher bioavailability than dermal absorption.[33] In worst-case scenarios, no signs of systemic toxicity were observed with oral exposures to greater than 2000 mg/kg hydrolyzed soy protein; therefore, it was concluded that systemic toxicity from cutaneous exposure would be negligible.

TOXICOLOGICAL STUDIES

The soy proteins that serve as the sources for the ingredients that are addressed in this safety assessment are found in the foods we consume daily. The potential for systemic effects, other than sensitization, from the possible absorption of soy ingredients through topical exposure is much less than the potential for systemic effects from absorption through oral exposures. This is because the rates of absorption and metabolism of these ingredients in the skin are expected to be negligible compared to the corresponding rates in the digestive tract. Thus, the potential for systemic effects, other than sensitization, are not discussed in detail in this report.

GENOTOXICITY

Glycine Soja (Soybean) Protein

A trade name mixture containing 0.4% glycine soja (soybean) protein (>80% with a MW < 5000 Da) produced no genotoxicity in a reverse mutation assay and in a chromosomal aberration study (with and without metabolic activation).[34] No further details were provided.

Hydrolyzed Soy Protein

Hydrolyzed soy protein product with 54% of the molecular weight distribution below 5000 Da was analyzed for mutagenic potential in an assay using *Salmonella typhimurium* TA 1535/pSK1002 with and without S9 metabolic activation.[33] Concentrations tested were 625, 1250, 2500, or 5000 μg/ml. No sign of mutagenicity was observed with or without S9. It was concluded that hydrolyzed soy protein was not mutagenic.

IRRITATION AND SENSITIZATION

Irritation

Dermal

In vitro, animal, and human dermal irritation studies are presented in Table 5.[14,17,33-40] Hydrolyzed soy protein (25% and 35%) and hydrolyzed soymilk protein (21.5%) were predicted to be non-irritating in in vitro studies. Glycine soja (soybean) protein (0.4%) was not irritating in rabbits and guinea pigs. Hydrolyzed soy protein was not a dermal irritant in rabbits when tested up to 25% and in human studies when tested up to 25%.

Ocular

Ocular irritation studies are presented in Table 6. [14,17,21,33,34,37-41] In in vitro assays, hydrolyzed soymilk protein (21.5%) was predicted to be not irritating while hydrolyzed soy protein (up to 35%) was predicted to be not irritating to slightly irritating. In rabbit studies, glycine soja (soybean) protein (0.4%) produced almost no irritation while hydrolyzed soy protein (tested neat and at concentrations ranging from 8.5% to 25%) was not irritating to slightly irritating.

Sensitization

Animal and human dermal sensitization studies are presented in Table 7.[21,33,34,37,42] Glycine soja (soybean) protein was not a dermal sensitizer when tested up to 0.4% in guinea pigs. Hydrolyzed soy protein was not a dermal sensitizer in non-human and human studies when tested up to 25%.

Type 1 Hypersensitivity

No occurrences of Type 1 (i.e., immediate) hypersensitivity reactions to personal care products that contain soy peptide ingredients were reported in the public literature. An allergen must have at least 2 IgE-binding epitopes, and each epitope must be at least 15 amino-acid residues long, to trigger a Type 1 hypersensitivity reaction.[43] Type 1 responses can be elicited in sensitized patients when pairs of IgE molecules against a specific allergen are bound to receptors on the surface of mast cells and other cells that mediate these types of immune reactions. The binding of an allergen molecule to two receptor-bound IgE molecules results in the crosslinking of the pair of IgE molecules. The cross-linking of sufficient numbers of IgE pairs bound to the receptors on the surface of a mast cell results in degranulation of the mast cell and the release of vasoactive amines, which are responsible for the Type 1 reaction.

Phototoxicity and Photosensitization

Glycine Soja (Soybean) Protein

An undiluted trade name mixture containing 0.4% glycine soja (soybean) protein (>80% with a MW < 5000 Da) produced no photo irritation in a phototoxicity study in 5 guinea pigs.[34] The test material was applied to 2 sites on clipped dorsal skin. One of the 2 sites was irradiated with ultraviolet (UV) light while the other site was covered and served as a control. Animals were examined for signs of erythema and edema on the first, second and third day after application. No further details were provided.

No photosensitization was observed in 20 guinea pigs exposed to an undiluted trade name mixture containing 0.4% glycine soja (soybean) protein (>80% with a MW < 5000 Da).[34] During the induction phase, the test sites were injected intradermally with Freund's complete adjuvant in water and then stripped with cellophane tape prior to topical application of the test material and UV irradiation. For the photochallenge, a group of 10 guinea pigs received the test material on clipped skin while a second group of 10 animals served as a negative control group. One side of all animals was irradiated and the other side was protected with a cover. The animals were observed for signs of erythema and edema 24 and 48 h post-challenge. No further details were provided.

CASE REPORTS

A 43-year-old female presented with a 4-year history of dramatic erythematous eruption of the cheeks and nasal tip.[44] The patient had rosacea but did not respond to topical and systemic treatments. On examination, erythema was observed on the nasal tip and erythematous plaques with fine scale and pustules were observed on the cheeks. Also noted was partially eczematized seborrheic dermatitis of the scalp. The patient's history included seborrheic dermatitis, lifelong atopic eczema and reactions to jewelry, perfumes, and certain cosmetics. The patient did not wear makeup but used topical products on her face, some of which contained soy ingredients. Previous patch testing yielded a +++ reaction to soy. The patient discontinued use of the facial products containing soy and was treated with hydrocortisone ointment, oral erythromycin, and clobetasol foam. At 48 h, the cheek erythema and edema had resolved, and by 96 h all pustules had cleared and the seborrheic dermatitis was nearly cleared.

SUMMARY

Soy protein and peptide ingredients function mainly as skin and hair conditioning agents in personal care products. Soy proteins are used as food, and daily exposure from food use would result in much larger systemic exposures than from use in cosmetic products. Additionally, the FDA determined that the use of peptones as direct food substances is GRAS and that soybean protein is GRAS for substances migrating to food from paper and paperboard products.

According to the 2015 VCRP data, hydrolyzed soybean protein has the most reported uses of the ingredients listed in this safety assessment in cosmetic products with a total of 862; about half of the uses are in non-coloring hair products. Glycine soja (soybean) protein has the second greatest number of overall uses reported, with a total of 313; a third of those are used in leave-on skin care products and another third are used in hair dyes and colors. The results of the concentration of use survey conducted in 2014 by the Council indicate hydrolyzed soy protein has the highest reported maximum concentration of use at up to 3.5% in mascara. Glycine soja (soybean) protein is used at up to 0.9% in eye lotion.

Soy proteins may also be used in adhesives and by the plastics industry.

While no experimental data were available for the dermal absorption of hydrolyzed soy protein, it was noted that gastrointestinal absorption allows for significantly higher bioavailability than from dermal exposures.

A trade name mixture containing 0.4% glycine soja (soybean) protein produced no genotoxicity in a reverse mutation assay and in a chromosomal aberration study (with and without metabolic activation). Hydrolyzed soy protein was not mutagenic in an assay using *S. typhimurium* TA 1535/pSK1002 with and without S9 metabolic activation at concentrations up to 5000 μg/ml.

Hydrolyzed soy protein (25% and 35%) and hydrolyzed soymilk protein (21.5%) were predicted to be non-irritating in in vitro dermal studies. Glycine soja (soybean) protein (0.4%) was not irritating in rabbits and guinea pigs. Hydrolyzed soy protein was not a dermal irritant in rabbits when tested up to 25% and in human studies when tested up to 25%.

In in vitro ocular assays, hydrolyzed soymilk protein (21.5%) was predicted to be not irritating while hydrolyzed soy protein (up to 35%) was predicted to be not irritating to slightly irritating. In rabbit ocular studies, glycine soja (soybean) protein (0.4%) produced almost no irritation while hydrolyzed soy protein (tested neat and at concentrations ranging from 8.5% to 25%) was not irritating to slightly irritating.

Glycine soja (soybean) protein was not a dermal sensitizer when tested at concentrations up to 0.4% in guinea pigs. Hydrolyzed soy protein was not a dermal sensitizer in non-human and human studies when tested at up to 25%. No occurrences of Type 1 (i.e., immediate) hypersensitivity reactions to personal care products that contain soy peptide ingredients were reported in the public literature.

No phototoxicity or photosensitization was observed in guinea pig studies with an undiluted trade name mixture containing 0.4% glycine soja (soybean) protein.

A case study described aggravation of rosacea in a patient following use of facial products containing soy.

DISCUSSION

The Panel noted that soy proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. However, the Panel was not concerned that such reactions would be induced by dermal exposure, because these ingredients are water soluble, would not penetrate the skin, and have molecular weights that are well below that which would cause IgE-cross-linking. The Panel reviewed studies showing no relevant ocular irritation in animals, no dermal irritation or sensitization in animals and human subjects, and no reported cases of Type I immediate hypersensitivity reactions from cosmetic use, which support their conclusion for these ingredients.

The Panel discussed the issue of incidental inhalation exposure from hair sprays and body and hand sprays. There were no inhalation toxicity data available. The Panel considered pertinent data indicating that incidental inhalation exposures to soy ingredients in such cosmetic products would not cause adverse health effects, including data characterizing the potential for soy ingredients to cause ocular or dermal irritation or sensitization. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

The Panel also addressed concerns about pesticide residues and heavy metals that may be present in plant-derived ingredients. They emphasized that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredients before blending into cosmetic formulations.

CONCLUSION

The CIR Expert Panel concluded that the following soy-based ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

glycine max (soybean) polypeptide
glycine soja (soybean) peptide*
glycine soja (soybean) protein
hydrolyzed soy protein
hydrolyzed soy protein extract*
hydrolyzed soymilk protein

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

FIGURES AND TABLES

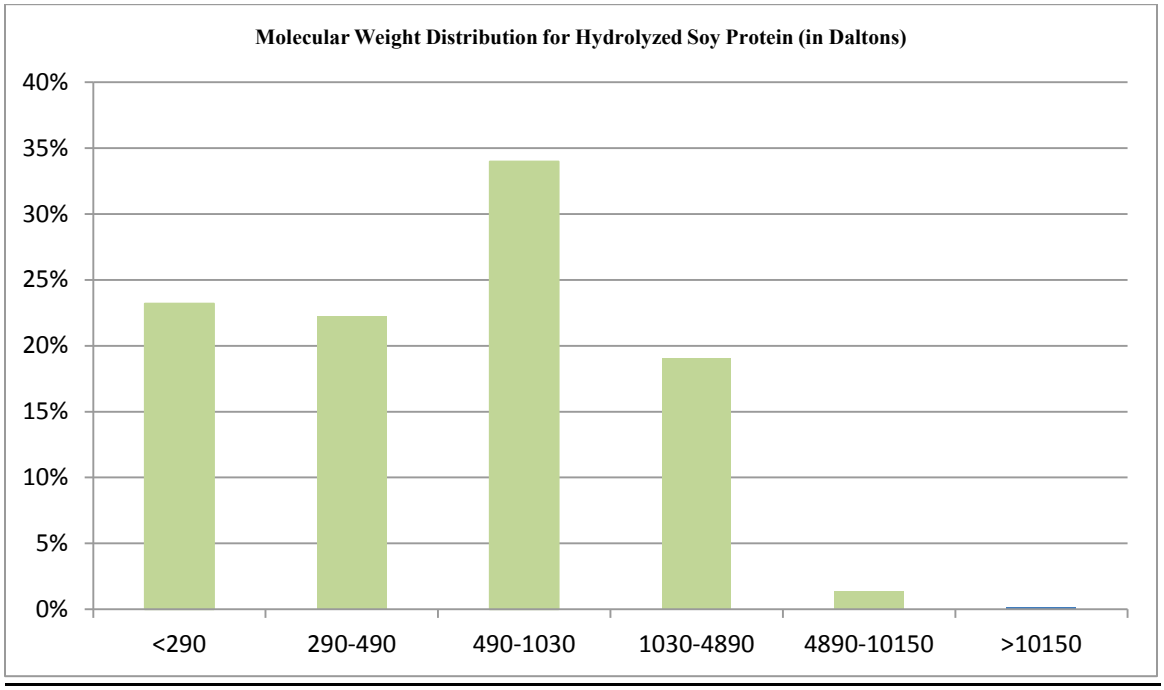

Figure 1. Molecular weight distribution of hydrolyzed soy protein from a supplier.[14]

Figure 2. **Manufacturing process of a hydrolyzed soy protein product from a supplier.**[45]

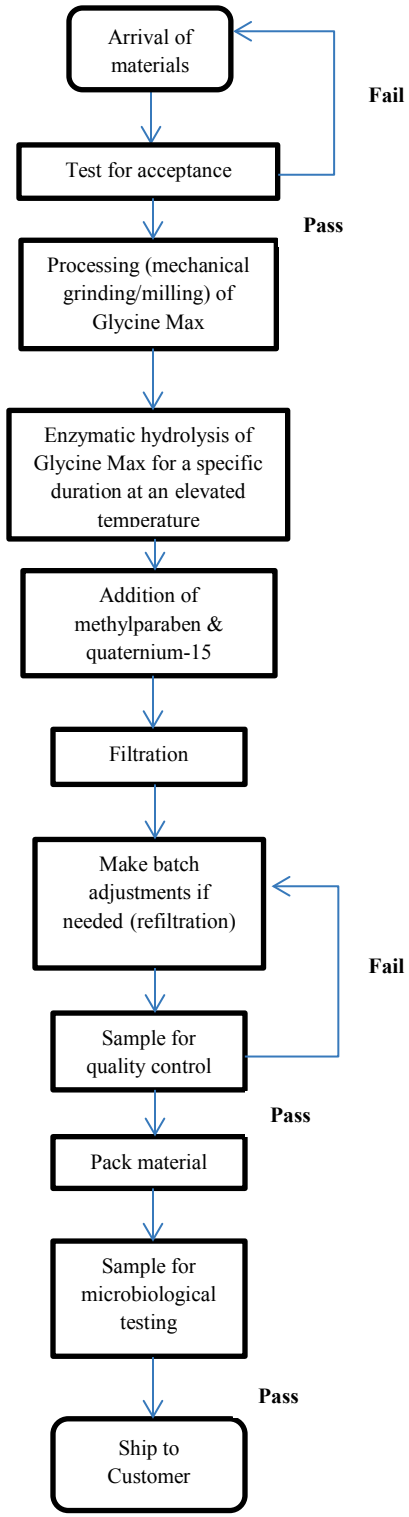

Table 1. Definitions and functions of the ingredients in this safety assessment.[1]

Ingredient and CAS No.	Definition	Function
Glycine Max (Soybean) Polypeptide	Glycine Max (Soybean) Polypeptide is a polypeptide fraction isolated from Glycine max soybean protein.	skin-conditioning agents - miscellaneous
Glycine Soja (Soybean) Peptide	Glycine Soja (Soybean) Peptide is the di-/tri- peptide fraction isolated from Glycine Soja (Soybean) Protein by ultra-membrane filtration.	film formers; hair conditioning agents; skin-conditioning agents - miscellaneous
Glycine Soja (Soybean) Protein 68153-28-6 9010-10-0	Glycine Soja (Soybean) Protein is a protein obtained from the soybean, *Glycine soja*.	hair conditioning agents; skin-conditioning agents – miscellaneous; surfactants – emulsifying agents
Hydrolyzed Soy Protein 68607-88-5 [generic to degree of hydrolyzation]	Hydrolyzed Soy Protein is the hydrolysate of soy protein derived by acid, enzyme or other method of hydrolysis.	hair conditioning agents; skin-conditioning agents – miscellaneous
Hydrolyzed Soy Protein Extract	Hydrolyzed Soy Protein Extract is the extract of the Hydrolyzed Soy Protein.	skin-conditioning agents – miscellaneous
Hydrolyzed Soymilk Protein	Hydrolyzed Soymilk Protein is the hydrolysate of the proteins obtained from Soymilk derived by acid, enzyme or other method of hydrolysis.	skin-conditioning agents – miscellaneous

Table 2. Chemical and physical properties

Property	Value	Reference
Glycine Soja (Soybean) Protein		
Molecular Weight (Da)	>80% less than 5000	[19,34]
Soy Peptide		
Molecular Weight (Da)	mean 500	[13]
Hydrolyzed Soy Protein		
Physical Form	Clear to slightly hazy, yellow or light tan to amber liquid	[46,47]
Odor	Characteristic	[46,47]
Molecular Weight (Da)	300 - <5000	[15,33,46,47]
Specific Gravity	1.05	[48,49]
Boiling Point (ºC)	100	[48]
Freezing Point (ºC)	0	[48]
Non-Volatile Matter (1g-2h-105ºC)	20.0-34.0%	[46,47]
pH	4.0-7.0	[46,47]
Ash (800ºC)	1.5% max	[46]
Solubility	Soluble in water	[48]
Hydrolyzed Soymilk Protein		
Physical Form	Slightly hazy colorless to amber liquid, may darken over time	[50]
Odor	Characteristic	[50]
Molecular Weight (Da)	1000-2000	[50]
Specific Gravity	1.20	[51]
Boiling Point (ºC)	100	[51]
Freezing Point (ºC)	0	[51]
Non-Volatile Matter (1g-2h-105ºC)	18.0-25.0%	[50]
pH (25ºC)	5.5-7.0	[50]
Solubility	Soluble in water	[51]

Table 3. Amino acid composition of a soy peptides sample.[13]

Amino Acid	% Composition
glutamic acid	22.1
aspartic acid	12.6
arginine	8.1
leucine	6.7
lysine	6.6
proline	5.6
serine	5.5
phenylalanine	4.6
glycine	4.2
valine	4.0
alanine	3.9
isoleucine	3.8
threonine	3.8
tyrosine	3.4
histidine	2.7
cysteine	1.3
methionine	1.1

Not detected: hydroxylysine and hydroxyproline

Table 4. Frequency (2015) and concentration of use (2014) according to duration and type of exposure for soy peptide ingredients.[52,53]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Glycine Max (Soybean) Polypeptide		**Glycine Soja (Soybean) Protein***		**Hydrolyzed Soy Protein**		**Hydrolyzed Soymilk Protein**	
Totals†	**2**	**NR**	**313**	**0.00004-0.9**	**862**	**0.00003-3.5**	**6**	**NR**
Duration of Use								
Leave-On	2	NR	166	0.00004-0.9	487	0.00003-3.5	3	NR
Rinse Off	NR	NR	147	0.0005-0.42	375	0.0001-0.63	3	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	0.0001-1.5	NR	NR
Exposure Type								
Eye Area	1	NR	36	0.00004-0.9	55	0.0038-3.5	NR	NR
Incidental Ingestion	NR	NR	5	0.25	1	0.0001-0.48	NR	NR
Incidental Inhalation-Spray	NR	NR	2; 56[a]; 51[b]	0.07; 0.00004[a]	12; 196[a]; 76[b]	0.00003-0.021; 0.0001-1.3[a]	1[a]	NR
Incidental Inhalation-Powder	NR	NR	51[b]	0.006-0.6[c]	3; 76[b]	0.01-0.23; 0.0018-2.9[c]	NR	NR
Dermal Contact	2	NR	175	0.00004-0.9	320	0.0001-2.9	1	NR
Deodorant (underarm)	NR	NR	NR	NR	1[a]	0.013[d]	NR	NR
Hair - Non-Coloring	NR	NR	36	0.0005-0.0055	405	0.00003-1.3	5	NR
Hair-Coloring	NR	NR	96	NR	78	0.0015-0.3	NR	NR
Nail	NR	NR	NR	0.23	37	0.0001-0.018	NR	NR
Mucous Membrane	NR	NR	8	0.0015-0.025	9	0.0001-1.5	NR	NR
Baby Products	NR	NR	3	NR	NR	0.003	NR	NR

NR = Not reported.

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

*The VCRP database lists entries for glycine max (soybean) protein, but not for glycine soja (soybean) protein. This ingredient is undergoing a name change and was surveyed by the Council as glycine soja (soybean) protein.

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

[d] Not a deodorant spray.

Table 5. Dermal irritation studies.

Ingredient	Concentration	Method	Results	Reference
In Vitro				
Hydrolyzed Soymilk Protein	21.5% (MW=1000-2000 Da)	EpiDerm dermal irritation test	Non-irritating	[40]
Hydrolyzed Soy Protein	25% (MW=1000-2000 Da)	EpiDerm dermal irritation test	Non-irritating	[38]
Hydrolyzed Soy Protein	35% (MW=1000-2000 Da)	EpiDerm dermal irritation test	Non-irritating	[39]
Animal				
Glycine Soja (Soybean) Protein	0.4% (>80% has MW < 5000 Da) in a tradename mixture; undiluted	Primary skin irritation study on clipped skin in 3 rabbits; animals observed for reactions at 24, 48, and 72 h after dosing (no further details)	No irritation	[34]
Glycine Soja (Soybean) Protein	0.4% (>80% has MW < 5000 Da) in a tradename mixture; undiluted	Cumulative skin irritation study on clipped skin in 5 guinea pigs; animals were dosed once a day for 2 weeks and were observed for reactions every day and 24 h after final dose (no further details)	No irritation	[34]
Hydrolyzed Soy Protein	Not reported	Dermal irritation study performed under OECD Guideline 404	Non-irritating	[14]
Hydrolyzed Soy Protein	20% in distilled water	Draize test in 6 male White New Zealand rabbits; occluded	Non-irritating	[33]
Hydrolyzed Soy Protein	20% (MW = 2000 Da)	Draize primary dermal irritation in 6 New Zealand white rabbits; occluded for 24 h	PII = 0.33. Not a primary irritant.	[17]
Hydrolyzed Soy Protein	25% in water (MW = 300 Da)	Primary dermal irritation in 6 New Zealand white rabbits; occluded for 24 h	PII = 0.46. Not a primary irritant	[35,37]
Human				
Hydrolyzed Soy Protein	20% in distilled water	50 subjects received 9 topical applications over 3 weeks; 24 h in duration; occluded	Non-irritating	[33]
Hydrolyzed Soy Protein	25% in water (MW = 300 Da)	20 female subjects received a single dermal dose under occlusive conditions for 24 h	Not a dermal irritant	[36,37]

Table 6. Ocular irritation studies.

Ingredient	Concentration	Method	Results	Reference
In Vitro				
Hydrolyzed Soymilk Protein	21.5% (MW=1000-2000 Da)	EpiOcular eye irritation test	Not irritating	[40]
Hydrolyzed Soy Protein	20% dilution, w/v	HET-CAM method	Slightly irritating	[33]
Hydrolyzed Soy Protein	25% (MW= 1000-2000 Da)	EpiOcular eye irritation test	Not irritating	[38]
Hydrolyzed Soy Protein	35% (MW=1000-2000 Da)	EpiOcular eye irritation test	Not irritating	[39]
Hydrolyzed Soy Protein	Up to 4.25% (87% has MW < 2000 Da)	Neutral red release method in rabbit cornea fibroblasts	Slightly irritating; cytotoxicity is negligible	[21]
Animal				
Glycine Soja (Soybean) Protein	0.4% (>80% has MW < 5000 Da) in a tradename mixture; undiluted	Ocular irritation study in 3 rabbits; test material applied to one eye while other eye served as control; animals examined at 0, 1, 24, 48, and 72 h after instillation (no further details)	Almost no irritation; the animals had congestion in conjunctiva immediately after instillation	[34]
Hydrolyzed Soy Protein	20% active matter in distilled water	Ocular irritation study performed under OECD guideline 405 in 3 albino White New Zealand rabbits	Very slight irritant reactions to the conjunctiva that appeared reversible in less than 72 h	[33]
Hydrolyzed Soy Protein	Neat	Ocular irritation study performed under OECD guideline 405	Very slight irritant	[14]
Hydrolyzed Soy Protein	20% (MW = 2000 Da)	Ocular irritation study in 6 New Zealand white rabbits; unrinsed eyes	Not irritating	[17]
Hydrolyzed Soy Protein	25% in water (MW = 300 Da)	Ocular irritation study in 6 albino rabbits; unrinsed	Not a primary eye irritant	[37,41]
Hydrolyzed Soy Protein	8.5% (87% has MW < 2000 Da)	Ocular irritation study performed under OECD guideline 405 in 3 rabbits	Slightly irritating	[21]

Table 7. Dermal sensitization studies.

Ingredient	Concentration	Method	Results	Reference
Animal				
Glycine Soja (Soybean) Protein	0.4% (>80% has MW < 5000 Da) in a tradename mixture; undiluted	Skin sensitization study with Freund's complete adjuvant in 20 guinea pigs; test sites were clipped and occluded; animals examined at 24 and 48 h after the removal of the challenge patch (no further details)	No sensitization	[34]
Hydrolyzed Soy Protein	20% for the intracutaneous and epicuaneous induction, 10% and 20% solutions for challenge	Maximization test in male and female albino Dunkin Hartley guinea pigs	No skin reactions	[33]
Hydrolyzed Soy Protein	8.5% (87% has MW < 2000 Da)	Magnusson and Kligman maximization test in albino guinea pigs, OECD 406	No skin reactions	[21]
Human				
Hydrolyzed Soy Protein	25% in water (MW = 300 Da)	HRIPT in 50 subjects; occlusive	No dermal irritation or sensitization	[37,42]
Hydrolyzed Soy Protein	20% dilution	HRIPT in 41subjects; occlusive	No dermal irritation or sensitization	[33]

REFERENCES

1. Nikitakis J and Breslawec H. International Cosmetic Ingredient Dictionary and Handbook. 15th *ed*. Washington, DC: Personal Care Products Council, 2014.

2. Elder RL (ed.). Final Report on the Safety Assessment of Hydrolyzed Collagen. *JACT*. 1985;4(5):199-221.

3. Andersen FA, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG, Shank RC, Slaga TJ, and Snyder PW. Final Report of the Safety Assessment of Cosmetic Ingredients Derived from Zea Mays (Corn). *Int J Toxicol*. 2011;30(Suppl. 1):17S-39S.

4. Andersen FA (ed.). Annual Review of Cosmetic Ingredient Safety Assessments - 2004/2005. *Int J Toxicol*. 2006;25(Suppl. 2):1-89.

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

6. Johnson WJ, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG, Shank RC, Slaga TJ, Snyder PW, and Gill LJ. Safety Assessment of Silk Protein Ingredients as Used in Cosmetics. 1620 L St NW, Suite 1200, Washington, DC 20036, Cosmetic Ingredient Review. 2015.

7. Burnett CL, Heldreth B, Boyer I, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG, Shank RC, Slaga TJ, Snyder PW, and Gill LJ. Safety Assessment of Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten as Used in Cosmetics. 1620 L St, NW, Suite 1200, Washington, DC 20036, Cosmetic Ingredient Review. 2014.

8. The Plant List (Version 1.1). Glycine max (L.) Merr. http://www.theplantlist.org/tpl1.1/record/ild-2760. Last Updated 2013. Date Accessed 6-19-2015.

9. Nishinari K, Fang Y, Guo S, and Phillips GO. Soy proteins: A review on composition, aggregation and emulsification. *Food Hydrocolloids*. 2014;39:301-318.

10. Cui C, Zhao M, Yuan B, Zhang Y, and Ren J. Effect of pH and pepsin limited hydrolysis on the structure and functional properties of soybean protein hydrolysates. *J Food Sci*. 2013;78(12):C1871-C1877.

11. Shutov AD, Kakhovskaya IA, Bastrygina AS, Bulmaga VP, Horstmann C, and Müntz K. Limited proteolysis of β-conglycinin and glycinin, the 7S and 11S storage globulins from soybean [*Glycine max* (L.) Merr.]: Structural and evolutionary implications. *Eur J Biochem*. 1996;241:221-228.

12. Food and Drug Administration (FDA). Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009: Questions and Answers Part II. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm271790.htm#QIII.2. Last Updated 2-9-2012. Date Accessed 2-24-2015.

13. Tokudome Y, Nakamura K, Kage M, Todo H, Sugibayashi K, and Hashimoto F. Effects of soybean peptide and collagen peptide on collagen synthesis in normal human dermal fibroblasts. *Int J Food Sci Nutr*. 2012;63(6):689-695.

14. Personal Care Products Council. 5-14-2012. Information concerning Hydrolyzed Proteins. 2 pages.

15. Anonymous. 2012. Information on Hydrolyzed Soy Protein-1 (method of manufacture; molecular weight, impurities, summary of safety data).

16. Personal Care Products Council. 5-14-2012. Method of manufacture and Molecular Weights: Hydrolyzed Protein Ingredients. 8 pages.

17. Consumer Product Testing Co. 1984. Primary dermal irritation in rabbits; primary ocular irritation in rabbits; acute oral toxicity in rats: Hydrolyzed Soy Protein (MW ~ 2,000 Da) Experiment Reference No. 84287-1.

18. Personal Care Products Council. 4-2-2015. Information on Hydrolyzed Soy Protein and Hydrolyzed Soymilk Protein.

19. Personal Care Products Council. 5-22-2015. Information on Glycine Soja (Soybean) Protein.

20. Arch Personal Care Products LP. 2012. Solu-Soy EN-25 PF (Hydrolyzed Soy Protein) Manufacturing Method. 8 pages.

21. Anonymous. 5-7-2015. Safety assessment for human health Hydrolyzed Soy Protein.

22. Berk Z. Soymilk and Related Products. Chapter: 8. In: *Technology of Production of Edible Flours and Protein Products from Soybeans*. Rome: Food and Agriculture Organization of the United Nations; 1992:

23. Active Concepts. 2011. Compositional breakdown: AC Soy Hydrolysate - 20603.

24. Active Concepts. 2011. Compositional breakdown: AC Soy Hydrolysate 30-20627.

25. Active Concepts. 2014. Compositional breakdown: AC Soy Milk Hydrolysate- 20574.

26. European Union. Regulation (EC) No. 1223/2009 of the European Parliament and of the Council of 30 November 2009 on Cosmetic Products. 2009. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:en:PDF

27. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.

28. Rothe H. Special Aspects of Cosmetic Spray Evalulation. 9-26-2011.

29. Bremmer HJ, Prud'homme de Lodder LCH, and Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. Report No. RIVM 320104001/2006. pp. 1-77.

30. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27.

31. Food and Drug Administration (FDA). Guidance for Industry: Questions and Answers Regarding Food Allergens, including the Food Allergen Labeling and Consumer Protection Act of 2004 (Edition 4); Final Guidance. http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm059116.htm. Last Updated 4-23-2012. Date Accessed 2-24-2015.

32. O'Neil MJ (ed). The Merck Index. 15th *ed*. The Royal Society of Chemistry, 2013.

33. Anonymous. 2000. Safety assessment for human health Hydrolyzed Soy Protein. 7 pages.

34. Anonymous. 2013. Toxicity and safety of a trade name mixture containing 0.4% Glycine Soja (Soybean) Protein.

35. Leberco Testing Inc. 1994. Primary dermal irritation in rabbits Hydrolyzed Soy Protein. Assay Number 947860.

36. Dermis Research Center Co Ltd. 2006. Human patch test under occlusive patch for 48 hours Hydrolyzed Soy Protein.

37. Personal Care Products Council. 4-2-2015. Information on Hydrolyzed Soy Protein.

38. Active Concepts. 2012. Dermal and ocular irritation tests: AC Soy Hydrolysate- 20603.

39. Active Concepts. 2012. Dermal and ocular irritation tests: AC Soy Hydrolysate 30-20627.

40. Active Concepts. 2012. Dermal and ocular irritation tests: AC Soy Milk Hydrolysate- 20574.

41. Leberco Testing Inc. 1994. Eye irritation assay Hydrolyzed Soy Protein. Assay Number 947859.

42. AMA Laboratories Inc. 2006. 50 Human subject repeat insult patch test skin irritation/sensitization evaluation (occlusive patch) Hydrolyzed Soy Protein. AMA Ref No: MS06.K9019O.50.

43. Huby RD, Dearman RJ, and Kimber I. Why are some proteins allergens? *Toxicol Sci*. 2000;55:235-246.

44. Guin JD and Hoskyn J. Aggravation of rosacea by protein contact dermatitis to soy. *Contact Dermatitis*. 2005;53:235-236.

45. Active Concepts. 2010. Manufacturing flow chart: AC Soy Hydrolysate- 20603.

46. Active Concepts. 2012. Product specification: AC Soy Hydrolysate- 20603.

47. Active Concepts. 2011. Product specification: AC Soy Hydrolysate 30-20627.

48. Active Concepts. 2014. Safety data sheet: AC Soy Hydrolysate 20603.

49. Active Concepts. 2013. Material safety data sheet: AC Soy Hydrolysate 30.

50. Active Concepts. 2014. Product specification: AC Soy Milk Hydrolysate- 20574.

51. Active Concepts. 2014. Safety data sheet: AC Soy Milk Hydrolysate 20574.

52. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2015. Washington, DC: FDA.

53. Personal Care Products Council. 1-6-2015. Concentration of Use by FDA Product Category: Soy Protein Ingredients. 1 pages.