Safety Assessment of Soy Peptides as Used in Cosmetics

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

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.

INTRODUCTION

Soy 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 peptides:

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

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) previously has reviewed the safety of α-amino acids, plant and animal derived amino acids, hydrolyzed collagen, and hydrolyzed corn protein, and concluded that these ingredients are safe for use in cosmetic ingredients.[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 peptides 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 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 for substances migrating to food from paper and paperboard products. Thus, 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 of these soy peptides ingredients as used in cosmetics is on the potential for irritation and sensitization from dermal exposure.

Note: Ingredients with the name glycine soja (soybean) are undergoing a name change to glycine max (soybean). This change represents more commonly accepted nomenclature.

CHEMISTRY

Definition and Manufacture

The definitions and functions of the soy peptide ingredients included in this report are provided in Table 1. The soy peptides, or soy protein derivatives, form a broad category of materials which are prepared by extraction from soy and partial hydrolysis to yield cosmetic ingredients. Protein hydrolysates, including those of soy, are used as conditioning agents in hair and skin products. Soy 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.[8-10] Whole aqueous extractable soybean proteins can be separated into storage globulin and whey fractions by acidification.

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. 11S was found to dissociate into 2S, 3S or 7S forms in various pH and ionic strengths. Amino acid compositions of β-conglycinin and glycinin have been analyzed, but the three dimensional structure is not well established in spite of many efforts.

Glycine soja (soybean) protein can be prepared from defatted low-heat soybean meal. 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.

The preparation of hydrolysates can be afforded via acid and enzyme. The above 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.

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.[22] 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.

Chemical and Physical Properties

Soy Peptide

Dipeptide- or tripeptide-rich forms of soy peptide were described to have a molecular weight of around 500 Da.[14]

Hydrolyzed Soy Protein

A histogram showing the approximate distribution of molecular weights for hydrolyzed soy protein from one supplier is shown in Figure 1. 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[13]; however, other sources have reported the molecular weight of their hydrolyzed soy protein product to be approximately 1000-2000 Da.[15,16]

Method of Manufacturing

Hydrolyzed Soy Protein

Soy hydrolysate may be dephosphorylated, deglycosylated and digested by a variety of endoproteases to generate oligopeptides.[11] A supplier has reported that hydrolyzed soy protein is produced from isolated soy proteins that are hydrolyzed with a protease enzyme for 2 hours.[12] 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) may be prepared by both alkaline and enzyme hydrolysis.[13] 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.

Composition and Impurities

Soy Peptide

The amino acid composition of a soy peptide sample is presented in Table 2. The analysis found that soy peptide is rich in aspartic acid (12.6%) and glutamic acid (22.1%). [14]

Hydrolyzed Soy Protein

A supplier states that hydrolyzed soy protein (MW = 300) has heavy metals, arsenic, and iron at levels $\leq$ 10 ppm, 1 ppm, and 10 ppm, respectively.[13]

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 in determining the expected cosmetic use. 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 Personal Care Products Council (Council).

According to the 2015 VCRP survey data, hydrolyzed soybean protein has the most reported uses in cosmetic products, with a total of 862; about half of the uses are in non-coloring hair products (Table 3). 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; it is used at up to 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.

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.[17-20] 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.[18,19]

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.[21]

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 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).

The FDA requires allergen labeling when major allergens are included in food.[23] The major allergens include wheat, milk, egg, fish, Crustacean shellfish, tree nuts, peanuts, and soybeans.

Soy proteins are used in adhesives and plastics industries.[24]

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.[25] In worst-case scenarios of oral exposures greater than 2000 mg/kg, no signs of systemic toxicity were observed and therefore it was concluded that no systemic toxicity would occur for cutaneous exposure. It was also noted that hydrolyzed soy protein has a high molecular weight and polarity, which would allow for limited skin penetration and consequent systemic availability.

TOXICOLOGICAL STUDIES

The soy peptides 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 peptide ingredients through the skin 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. This assessment focuses on evaluating the potential for these ingredients to cause sensitization reactions and irritation.

GENOTOXICITY

Hydrolyzed Soy Protein

Hydrolyzed soy protein was analyzed for mutagenic potential in an assay using *Salmonella typhimurium* TA 1535/pSK1002 with and without S9 metabolic activation.[25] 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

Non-human and human dermal irritation studies are presented in Table 4. Hydrolyzed soy protein was not a dermal irritant in non-human and human studies when tested neat and at 20%.[16,25-28]

Ocular

Ocular irritation studies are presented in Table 5. Hydrolyzed soy protein was not irritating to slightly irritating in non-human studies when tested neat and at 20%.[16,25,26,29]

Sensitization

Non-human and human dermal sensitization studies are presented in Table 6. Hydrolyzed soy protein was not a dermal sensitizer in non-human and human studies when tested up to 20%.[25,30]

CASE STUDIES

A 43-year-old female presented with a 4-year history of dramatic erythematous eruption of the cheeks and nasal tip.[31] 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 peptide ingredients function mainly as skin and hair conditioning agents in personal care products. Soy peptides 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 survey data, hydrolyzed soybean protein has the most reported uses 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; it is used 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 plastics industries.

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 dermal absorption. It was also noted that hydrolyzed soy protein has a high molecular weight and polarity, which would allow for limited skin penetration and consequent systemic availability.

Biologically active peptides may be derived from hydrolysis of soy protein.

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 was not a dermal irritant in non-human and human studies when tested neat and at 20%. This ingredient was also not an ocular irritant in non-human studies when tested at these same concentrations. Hydrolyzed soy protein was not a dermal sensitizer in non-human and human studies when tested up to 20%.

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

DATA NEEDS

CIR is seeking clarification on the method of manufacture and types and concentrations of impurities and/or general composition of cosmetic-grade soy peptide ingredients. Additional toxicological data, especially from dermal or ocular exposure, that would help the CIR Expert Panel assess the safety of the use of these ingredients in cosmetics is always welcomed as they would improve the resulting safety assessment.

FIGURES AND TABLES

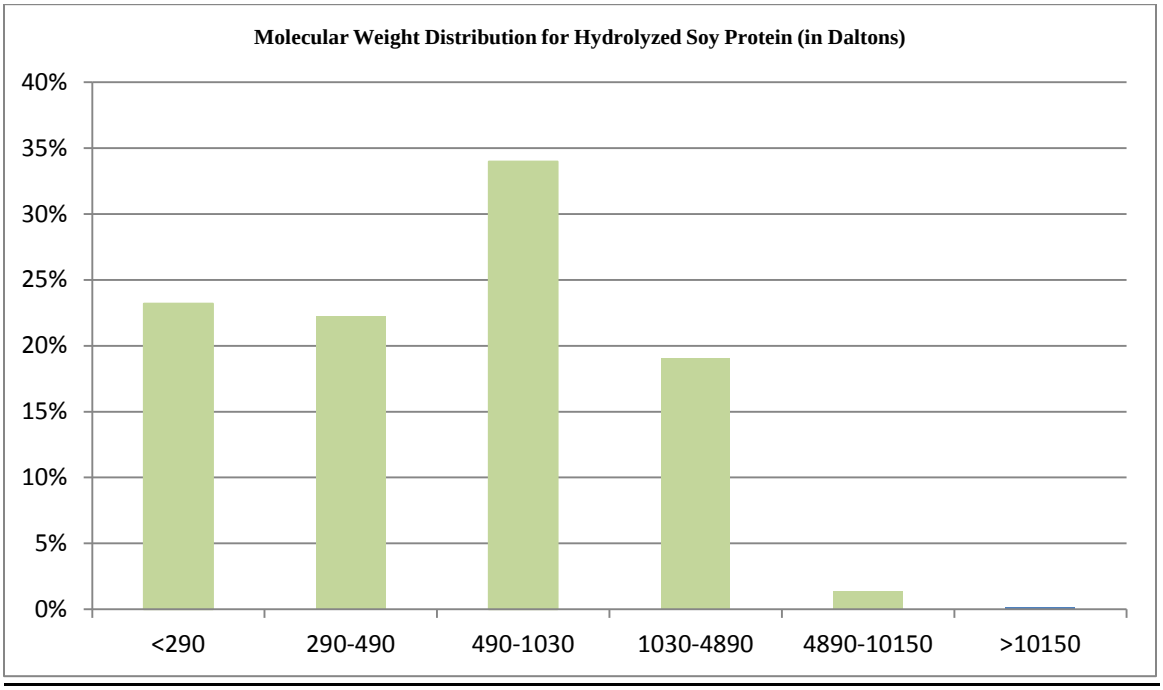

Figure 1. Molecular weight distribution of hydrolyzed soy protein.[26]

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. Amino acid composition for soy peptides.[14]

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 3. Frequency (2015) and concentration of use (2014) according to duration and type of exposure for soy peptide ingredients.[32,33]

	# 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 4. Dermal irritation studies.

Ingredient	Concentration	Method	Results	Reference
Non-Human				
Hydrolyzed Soy Protein	Not reported	Dermal irritation study performed under OECD Guideline 404	Non-irritating	[26]
Hydrolyzed Soy Protein	20% in distilled water	Draize test in 6 male White New Zealand rabbits; occluded	Non-irritating	[25]
Hydrolyzed Soy Protein	Neat (MW = 2000)	Draize primary dermal irritation in 6 New Zealand white rabbits; occluded for 24 h	PII = 0.33. Not a primary irritant.	[16]
Hydrolyzed Soy Protein	Neat (MW = 300)	Primary dermal irritation in 6 New Zealand white rabbits; occluded for 24 h	PII = 0.46. Not a primary irritant	[27]
Human				
Hydrolyzed Soy Protein	20% in distilled water	50 subjects received 9 topical applications over 3 weeks; 24 h in duration; occluded	Non-irritating	[25]
Hydrolyzed Soy Protein	Neat (MW = 300)	20 female subjects received a single dermal dose under occlusive conditions for 24 h	Not a dermal irritant	[28]

Table 5. Ocular irritation studies.

Ingredient	Concentration	Method	Results	Reference
Non-Human				
Hydrolyzed Soy Protein	20% dilution, w/v	HET-CAM method	Slightly irritating	[25]
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	[25]
Hydrolyzed Soy Protein	Neat	Ocular irritation study performed under OECD guideline 405	Very slight irritant	[26]
Hydrolyzed Soy Protein	Neat (MW = 2000)	Ocular irritation study in 6 New Zealand white rabbits; unrinsed eyes	Not irritating	[16]
Hydrolyzed Soy Protein	Not reported (MW = 300)	Ocular irritation study in 6 albino rabbits; unrinsed	Not a primary eye irritant	[29]

Table 6. Dermal sensitization studies.

Ingredient	Concentration	Method	Results	Reference
Non-Human				
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	[25]
Human				
Hydrolyzed Soy Protein	Not reported (MW = 300)	HRIPT in 50 subjects; occlusive	No dermal irritation or sensitization	[30]
Hydrolyzed Soy Protein	20% dilution	HRIPT in 41subjects; occlusive	No dermal irritation or sensitization	[25]

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