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# Safety Assessment of Plant-Derived Proteins and Peptides as Used in Cosmetics

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*All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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 Interim Director, Dr. Bart Heldreth.*

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 Interim Director is Dr. Bart Heldreth. This safety assessment was prepared by Christina L. Burnett, Scientific Analyst/Writer and Ivan Boyer, Ph.D., Toxicologist CIR.

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## **ABSTRACT**

The Cosmetic Ingredient Review (CIR) Expert Panel (the Panel) reviewed the safety of 19 plant-derived proteins and peptides, which function mainly as skin and/or hair conditioning agents in personal care products. The Panel concluded that 18 plant-derived proteins and peptides are safe as used in the present practices of use and concentration as described in this safety assessment, while the data on Hydrolyzed Maple Sycamore Protein are insufficient to determine safety.

## **INTRODUCTION**

The plant-derived proteins and peptides detailed in this report are described by the *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)* to function mainly as skin and/or hair conditioning agents in personal care products.<sup>1</sup> This report assesses the safety of the following 19 plant-derived ingredients:

Hydrolyzed Amaranth Protein  
Hydrolyzed Avocado Protein  
Hydrolyzed Barley Protein  
Hydrolyzed Brazil Nut Protein  
Hydrolyzed Cottonseed Protein  
Hydrolyzed Extensin  
Hydrolyzed Hazelnut Protein  
Hydrolyzed Hemp Seed Protein  
Hydrolyzed Jojoba Protein  
Hydrolyzed Lupine Protein

Hydrolyzed Maple Sycamore Protein  
Hydrolyzed Pea Protein  
Hydrolyzed Potato Protein  
Hydrolyzed Sesame Protein  
Hydrolyzed Sweet Almond Protein  
Hydrolyzed Vegetable Protein  
Hydrolyzed Zein  
Lupinus Albus Protein  
Pisum Sativum (Pea) Protein

The safety of several hydrolyzed proteins as used in cosmetics has been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) in several previously published assessments. The Panel concluded that Hydrolyzed Keratin (finalized in 2016), Hydrolyzed Collagen (published in 1985, re-review published in 2006) Hydrolyzed Soy Protein (finalized in 2015), Hydrolyzed Silk (finalized in 2015), Hydrolyzed Rice Protein (published in 2006), and Hydrolyzed Corn Protein (published in 2011) are safe for use in cosmetics.<sup>2-8</sup> 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.<sup>9</sup>

## **CHEMISTRY**

### **Definition**

The definitions and functions of the plant-derived protein and peptide ingredients in this report are provided in Table 1. The plant peptides, or plant protein derivatives, form a broad category of materials that are prepared by extraction of proteins from plants and partial hydrolysis to yield cosmetic ingredients.<sup>1</sup> The FDA has defined the term “protein” to mean any  $\alpha$ -amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.<sup>38</sup> The FDA considers a “peptide” to be any polymer composed of 40 or fewer amino acids. The proteins and protein hydrolysates described in this safety assessment are used as conditioning agents in hair and skin products.<sup>1</sup>

The preparation of protein hydrolysates can be accomplished via acid (e.g., hydrochloric acid), enzyme (e.g., papain hydrolysis) or other methodologies (e.g., steam). The degree of hydrolysis (i.e., how much the proteins are broken down into smaller polypeptides) may profoundly affect the size and reactivity of such hydrolysates. The degree of hydrolysis can be attenuated by altering the reaction conditions (e.g., changing the temperature or concentration of the hydrolyzing agents). The ingredients in this report, even those ingredients without “hydrolyzed” in the name, may be hydrolyzed to at least some degree in the processes of extraction or solubilization.

### **Physical and Chemical Properties**

Molecular weights have been provided (by individual suppliers) for several of the plant-derived hydrolyzed proteins; this information is presented in Table 2.

### **Method of Manufacturing**

Methods used to manufacture protein hydrolysates typically yield broad molecular weight distributions of peptides, ranging from 500 to 30,000 daltons (Da) and equating to 4 to 220 amino acids in length.<sup>10,11</sup> Treatment with certain enzymes, such as papain, can routinely yield narrower distributions of 500 to 10,000 Da, equating to 4

to 74 amino acids in length. The available methods of manufacturing for the plant-derived proteins and peptides are summarized in Table 3.

## **Composition**

### ***Hydrolyzed Amaranth Protein***

Unprocessed and extruded amaranth flour were hydrolyzed sequentially, first with pepsin (for 180 min) and then with pancreatin (for 180 min), and aliquots were collected for analysis at 10, 25, 60, 90, 120 and 180 min after initiating hydrolysis with each of these enzymes.<sup>12</sup> The greater the duration of the hydrolysis the greater the amount of polypeptides with lower molecular masses (e.g., hydrolysis of unprocessed amaranth yielded molecular masses around 2064 Da at 10 min, 802 Da after 120 min, and 567 Da after 180 min). Extrusion of the amaranth flour yielded more peptides with a lower molecular mass (< 1000 Da) immediately after 10 min of hydrolysis. The enzymatic hydrolysis of amaranth flour in this study produced peptides with biological activity, including an angiotensin converting enzyme inhibitor (ACE-inhibitor) and a dipeptidyl peptidase 4 inhibitor (DPP-IV inhibitor).

### ***Hydrolyzed Brazil Nut Protein***

A supplier reported that a formulation containing 10% to 25% Hydrolyzed Brazil Nut Protein (MW = 1000 Da) is also composed of greater than 50% water, 0 to 7% ash (post pyrolysis; mostly sodium chloride), 0.5% sodium benzoate, and 0.3% potassium sorbate.<sup>13</sup>

### ***Hydrolyzed Cottonseed Protein***

A supplier reported that a formulation containing 10% to 25% Hydrolyzed Cottonseed (MW = 1700 Da) is also composed of greater than 50% water, 0 to 6% ash (post pyrolysis; mostly sodium chloride), 0.2% disodium EDTA, 1% phenoxyethanol, and 0.3% potassium sorbate.<sup>13</sup>

### ***Hydrolyzed Lupine Protein***

A supplier reported that Hydrolyzed Lupine Protein is comprised of >90% peptides (w/w) and <4% carbohydrates (w/w).<sup>14</sup>

Another supplier of three formulations containing Hydrolyzed Lupine Protein reported that two of its formulations (one contained the hydrolyzed protein at up to 26.7% and the other at up to 5.5%) also contained nearly 73% to nearly 81% water, approximately 0.3% to 0.4% phenoxyethanol, and 0.1% parabens.<sup>15</sup> A third formulation (containing up to 24% of the hydrolyzed protein) did not contain parabens and instead had approximately 1.4% to 1.7% phenoxyethanol. The formulation that contained up to 26.7% of the hydrolyzed protein was reported to have phenolic compounds consisting of flavones (~100%) that represented less than 0.5% of the formulation.

### ***Hydrolyzed Pea Protein***

A supplier reported that a product containing 10% to 25% Hydrolyzed Pea Protein product (MW = 1500 Da) is also composed of greater than 50% water, 0 to 6% ash (post pyrolysis; mostly sodium chloride), 1% phenoxyethanol, and 0.3% potassium sorbate.<sup>13</sup>

### ***Hydrolyzed Sweet Almond Protein***

A supplier reported that a formulation containing 2.3% to 3.3% Hydrolyzed Sweet Almond Protein also contains 96.15% to 97.25% water, 0.324% to 0.396% phenoxyethanol, and 0.126% to 0.154% parabens.<sup>15</sup>

### ***Hydrolyzed Vegetable Protein***

Monosodium glutamate (MSG) occurs naturally in ingredients such as hydrolyzed vegetable protein (generic) and some protein isolates.<sup>16</sup> Hydrolyzed vegetable protein may contain 10%-30% MSG.<sup>17</sup>

A supplier reported that a formulation containing 10% to 25% Hydrolyzed Vegetable Protein (potato source; MW = 750 Da) is also composed of greater than 50% water, 0 to 6.5% ash (post pyrolysis; mostly sodium chloride), 0.2% disodium EDTA, 1% phenoxyethanol, and 0.3% potassium sorbate.<sup>13</sup> The same supplier reported that another formulation containing 7.5% to 15% Hydrolyzed Vegetable Protein (potato source; MW = 100,000) was also composed of greater than 50% water, 0 to 2.5% ash (post pyrolysis; mostly sodium chloride), 0.1% ethylhexylglycerin, 0.9% phenoxyethanol, 0.5% sodium benzoate, and 0.3% potassium sorbate.

## **Impurities**

### ***Hydrolyzed Avocado Protein***

A supplier reported that Hydrolyzed Avocado Protein contains < 0.042 µg/kg benzo[a]pyrene; < 0.10 ppm arsenic; 0.70 ppm barium; < 0.10 ppm cadmium; < 0.75 ppm chromium; 0.40 ppm cobalt; < 0.05 ppm lead; and < 0.10 ppm mercury.<sup>18</sup> Aflatoxins B&G combined were < 1.86 µg/kg. Organochlorinated, organophosphorylated, and organosulfur compounds from pesticides were not detected. The 26 allergenic compounds regulated by the European Union were not detected.<sup>19</sup>

### ***Hydrolyzed Hazelnut Protein***

A supplier reported that Hydrolyzed Hazelnut Protein has less than 20 ppm heavy metals and less than 2 ppm arsenic.<sup>20</sup>

### ***Hydrolyzed Lupine Protein***

A supplier reported that Hydrolyzed Lupine Protein has < 0.042 µg/kg benzo[a]pyrene.<sup>14</sup> Aflatoxins B&G combined were < 1.86 µg/kg. Organo-pesticide residues were not detected. When tested on a product with an active concentration of 10%, heavy metals (arsenic, cadmium, mercury, lead, cobalt, nickel, barium, and chromium) were below the quantification limit of 1 ppm.<sup>19</sup> The 26 allergenic compounds regulated by the European Union were not detected.

A supplier of three Hydrolyzed Lupine Protein products reported that one product composed of 4.5% to 5.5% Hydrolyzed Lupine Protein had 25 ppm *p*-anisyl alcohol and less than 0.5 ppm heavy metals.<sup>15</sup> Pesticides were not detected. Another product composed of 18% to 24% Hydrolyzed Lupine Protein did not contain the 26 allergenic compounds regulated by the European Union, but trace amounts of pesticides (lindane, chlorpyrifos ethyl, malathion) were detected. Heavy metals were less than 0.5 ppm. The third product composed of 19.2% to 26.7% Hydrolyzed Lupine Protein had less than 0.6 ppm heavy metals. Alkaloids and pesticides were not detected in this third product.

### ***Hydrolyzed Pea Protein***

A supplier reported that a Hydrolyzed Pea Protein product (25% solution in water; MW = 500 Da) contains no more than 10 ppm heavy metals and no more than 1 ppm arsenic.<sup>21</sup>

### ***Hydrolyzed Sweet Almond Protein***

A supplier reported that the 26 allergenic compounds regulated by the European Union were not detected in a Hydrolyzed Sweet Almond Protein product (2.3% to 3.3%).<sup>15</sup>

### ***Hydrolyzed Vegetable Protein***

Free and esterified forms of 3-monochloro-1,2-propanediol (3-MCPD) and 1,3-dichloro-2-propanol (1,3-DCP) are reported to be found in acid-hydrolyzed vegetable proteins (generic).<sup>22,23</sup> 3-MCPD is formed from the reaction of triglycerides in the vegetable protein and hydrochloric acid.<sup>24</sup> These are Group 2B compounds (possibly carcinogenic to humans) according to the International Agency for Research on Cancer (IARC).<sup>25</sup> The European Food Safety Authority (EFSA) established a tolerable daily intake (TDI) for 3-MCPD and its fatty acid esters to be 0.8 µg/kg/day with wide margins of exposure for food intake.<sup>26</sup>

## **USE Cosmetic**

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. 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 Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2017 VCRP data, Hydrolyzed Vegetable Protein is used in 142 formulations; approximately half the uses are in leave-on products (Table 4).<sup>27</sup> Hydrolyzed Lupine Protein has the second greatest number of overall uses reported, with a total of 96; the majority of the uses are in leave-on formulations. The results of a 2016 survey indicate Hydrolyzed Potato Protein has a maximum concentration of use of 2.4% in nighttime skin care

products.<sup>28</sup> Hydrolyzed Hazelnut Protein and Hydrolyzed Lupine Protein have maximum use concentrations of 0.99% in body and hand skin care preparations.<sup>28,29</sup> No uses were reported for Hydrolyzed Avocado Protein, Hydrolyzed Maple Sycamore Protein, or Hydrolyzed Zein in the VCRP or by Council.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, Hydrolyzed Cottonseed Protein is reported to be used in 37 formulations, but no use concentration data were provided. In other cases, no uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example, Hydrolyzed Hemp Seed Protein was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 0.0002% in hair conditioners. It should be presumed that Hydrolyzed Hemp Seed Protein is used in at least one cosmetic formulation.

Some of these ingredients may be used in products that can come into contact with mucous membranes and the eyes. For example, Hydrolyzed Lupine Protein is used in bath soaps and detergents at up to 0.6%<sup>29</sup> and Hydrolyzed Vegetable Protein is used in eye lotions at up to 0.3%.<sup>28</sup> Additionally, some of these ingredients were reported to be used in hair sprays, face powders, and fragrances and could possibly be inhaled. For example, Hydrolyzed Hazelnut Protein was reported to be used in perfume at a maximum concentration of 0.25%. 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.<sup>30-33</sup> 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.<sup>30,32</sup> 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.<sup>34-36</sup>

The plant-derived protein and peptide ingredients described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.<sup>37</sup>

### **Non-Cosmetic**

Hydrolyzed vegetable proteins (generic) are widely used as seasonings and as ingredients in processed savory food products and range in concentration of use in foods from 0.1% to 40%.<sup>17,24</sup> Generally, hydrolyzed proteins (acid hydrolyzed or enzymatically hydrolyzed) do not pose a hazard to humans at levels at which they are used as flavoring agents in foods.<sup>39</sup> Plant protein products are approved food additives according to the FDA (21CFR§170.3).

The FDA requires allergen labeling when major allergens, such as tree nuts, are included in food.<sup>40</sup> A major food allergen is an ingredient from a food or food group, such as tree nuts, that contains protein derived from the food.

## **TOXICOKINETICS**

No published toxicokinetics studies on plant-derived hydrolyzed proteins and peptides were discovered and no unpublished data were submitted.

## **TOXICOLOGICAL STUDIES**

### **Subchronic Toxicity Studies**

#### ***Lupinus Albus Protein***

The toxicity of *Lupinus albus* was studied in a 112-day dietary protein study in Charles River rats.<sup>41</sup> Diet consisting of 20% dietary protein from *Lupinus albus*, *L. luteus*, or casein (the control) was fed to groups of 12 animals (sex not reported) ad libitum. The lupine diets were supplemented with DL-methionine. At the end of the experimental period, the animals were killed and the weights of the liver, kidneys, spleen, heart, and adrenals were recorded. Tissue samples of the liver, kidneys, and lungs were examined microscopically. The rats fed the *L. albus* diets gained weight at a slightly lower rate than those fed *L. luteus* and casein. There were no differences in the feed intakes and feed efficiencies of both lupine groups during weeks 1-6. There were no differences observed in organ-to-body weight ratios of liver, spleen, heart, and adrenals of rats fed either lupines or casein. No adverse effects were reported. No significant differences were observed in the gross necropsy findings or the microscopic examinations.

## **GENOTOXICITY**

### **In Vitro**

In vitro genotoxicity studies are presented in Table 5.<sup>15,21,42,43</sup> Hydrolyzed Lupine Protein (up to 26.7%), Hydrolyzed Pea Protein (up to 25%), Hydrolyzed Sweet Almond Protein (up to 3.3%) and Hydrolyzed Vegetable Protein (10.9%) were not mutagenic in Ames tests.

## **CARCINOGENICITY**

No published carcinogenicity studies on plant-derived hydrolyzed proteins and peptides were discovered and no unpublished data were submitted.

## **OTHER RELEVANT STUDIES**

### **Antioxidant Effects**

#### ***Hydrolyzed Hemp Seed Protein***

No adverse effects were mentioned in a study of rats fed hydrolyzed hemp seed meal protein.<sup>44</sup> This study investigated the antioxidant effects of hydrolyzed hemp seed meal protein in spontaneously hypertensive rats. Groups of 8 male rats were fed diets containing 0%, 0.5%, or 1.0% (w/w) hydrolyzed hemp seed meal protein for 8 weeks. Half of the rats were killed for blood collection while the remaining half underwent a 4-week washout, during which they were all fed the diet without hydrolyzed hemp seed meal protein added, and then fed the experimental diets an additional 4 weeks before terminal blood collection. Plasma total antioxidant capacity (TAC), superoxide dismutase (SOD), and catalase (CAT) levels were decreased in the rats that were allowed to live through the wash-out phase, when compared to those killed prior. Significant ( $p < 0.05$ ) increases in plasma SOD and CAT levels accompanied by decreases in total peroxide levels were observed in both the pre- and post-wash-out rats. The hemp seed meal protein in this study was hydrolyzed by pepsin and pancreatin, consecutively.

### **Type 1 Hypersensitivity**

#### ***Hydrolyzed Brazil Nut Protein, Hydrolyzed Hazelnut Protein, Hydrolyzed Sweet Almond Protein***

As commonly known, tree nuts, including *Bertholletia excelsa* (Brazil nut), *Corylus* spp. (hazelnut), and *Prunus dulcis* (sweet almond) are major food allergens that produce Type 1 (immediate) reactions in sensitized individuals.

#### ***Lupinus Albus Protein and Pisum Sativum (Pea) Protein***

A clinical study examined 3 patients with a history of anaphylactic reactions to peas who subsequently developed signs of sensitization after ingesting peanuts.<sup>45</sup> All 3 patients had positive skin prick tests, as well as elevated serum levels of IgE antibodies against protein extracts of both peas and peanuts. IgE-binding experiments revealed strong binding mainly to vicilin in pea extracts and exclusively to Ara h 1 in a crude peanut extract. IgE binding to the purified Ara h 1 of peanuts was definitively inhibited by purified pea vicilin, but the IgE binding to the pea vicilin was not inhibited to any significant extent by peanut Ara h 1. The authors concluded that clinically-relevant cross-reactivity can occur between vicilin homologs in peanuts (i.e., Ara h1) and in peas. They noted that the allergic reactions to peanuts was attributable to cross-reactive IgE antibodies raised previously against pea allergens in these patients, based on the course of the development of allergic reactions, skin prick test results, specific IgE levels, and the potent inhibition by pea vicilin of IgE binding to Ara h1, compared with the lack of inhibition by Ara h 1 of IgE binding to pea vicilin.

Immunological cross-reactivity was studied among the seeds of widely different species (lupine and pea, as well as peanut, lentil kidney bean and soybean) using the sera of 12 peanut-sensitive children.<sup>46</sup> IgE binding to the seed proteins of these plant species varied widely among the subjects. IgE binding to peanut polypeptides was prevalent among the subjects, as expected, but binding to the polypeptides of other legumes was also observed. Often the binding was to the basic subunits of 11S globulins. In this study, the subjects exhibited skin prick test results that generally paralleled the results of the IgE binding studies. The most sensitive subjects had strong reactions to peanut, pea and lentil protein extracts.

Skin prick tests were performed using a panel of protein extracts from the seeds of several legume species on patients (n=36) with allergies to peanuts and/or other legumes.<sup>47</sup> The plant species tested included lupine and green pea, as well as the dun pea, chick pea, lentil, soybean, white bean and broad bean. The patients were divided into 2 groups. Group 1 included 6 subjects who were not allergic to peanuts but were allergic to lentils (4), dun pea (3), green pea (3), soybean (2), broad bean (2), lupine (1), and/or chickpeas (1). Each of these patients had positive skin prick tests to at least 4 of the legume extracts tested. Group 2 included 30 patients with peanut allergy, and was

subdivided into 3 subgroups. Group 2a included 13 patients who were not allergic to other legumes, all of whom exhibited negative skin prick tests to the protein extracts of legumes other than peanuts or ate all legumes other than peanuts without reactions. Group 2b included 8 patients who were sensitized to legumes, in addition to peanuts, without having previously experienced clinical reactions to legumes other than peanuts. These patients exhibited positive skin prick tests to the proteins of at least 1 and up to 5 legumes, in addition to peanut proteins. Group 2c included 9 patients with allergies to peanuts and to other legumes, including green peas (4), dun peas (3), lentils (3), soybeans (2), and lupine (1), and positive skin prick tests to the proteins of at least 1 and up to 5 legumes. In this study, 96% (22/23) of the patients who were sensitized or allergic to legumes other than peanuts (whether or not they were also allergic to peanuts) and 100% (17/17) of the patients allergic to peanuts and other legumes had specific IgE against Ara h 1. Only 54% (7/13) of the patients with peanut allergy who were not also sensitized to other legumes had specific IgE against Ara h 1. Further, peanut protein extracts inhibited the binding of dun pea specific IgE to dun pea proteins. The authors concluded, based on the overall results of their study that peanut-allergic patients sensitized to Ara h 1 are at greater risk of becoming sensitized or developing allergies to other legumes, compared with those not sensitized to Ara h 1.

## **DERMAL IRRITATION AND SENSITIZATION STUDIES**

### **Irritation**

Dermal irritation studies are presented in Table 6.<sup>14,15,18-21,48-51</sup> Irritation was not predicted in in vitro studies or observed in animal studies with the following hydrolyzed protein ingredients: amaranth (20% in water), avocado (20%), hazelnut (100%), lupine (up to 100%), pea (up to 25% in water), and vegetable (up to 100%). No irritation was observed in human dermal studies for Hydrolyzed Avocado Protein (20%), Hydrolyzed Lupine Protein (up to 6%), and Hydrolyzed Pea Protein (25% solution in water).

### **Sensitization**

Animal and human dermal sensitization studies are presented in Table 7.<sup>14,15,18-21,52-54</sup> No sensitization was observed in animal studies of Hydrolyzed Avocado Protein (12.5%), Hydrolyzed Hazelnut Protein (up to 100%), and Hydrolyzed Lupine Protein (25%). No sensitization was observed in human studies of the following hydrolyzed protein test materials: amaranth (tested as received), avocado (concentration not reported), lupine (0.005%), potato (up to 2.4% in formulation), and sweet almond (concentration not reported).

### **Phototoxicity**

In vitro phototoxicity studies are presented in Table 8.<sup>14,18-20</sup> Hydrolyzed Avocado Protein (50%), Hydrolyzed Hazelnut Protein (concentration not reported), and Hydrolyzed Lupine Protein (100%) were not phototoxic in studies using the 3T3 Neural Red Uptake (NRU) method.

## **OCULAR IRRITATION STUDIES**

In vitro and animal ocular irritation studies are presented in Table 9.<sup>14,15,18-21,55-58</sup> In in vitro studies, Hydrolyzed Amaranth Protein (20%), Hydrolyzed Pea Protein (19%), and Hydrolyzed Vegetable Protein (up to 100%) were not irritating. In vitro studies predicted Hydrolyzed Avocado Protein (tested at 20% in a hen's egg test-chorioallantoic membrane (HET-CAM) assay, 10% in a bovine cornea opacity permeability (BCOP) test) may be an eye irritant. Hydrolyzed Lupine Protein (up to 100%) was weakly irritating in both the HET-CAM and BCOP tests. In animal studies, Hydrolyzed Hazelnut Protein was not irritating when tested neat, while Hydrolyzed Lupine Protein (up to 5.5%) and Hydrolyzed Sweet Almond Protein (up to 3.3%) were very slight irritants in rabbit eyes.

## **CLINICAL STUDIES**

### **Case Studies**

#### ***Hydrolyzed Vegetable Protein***

MSG symptom complex has been reported in sensitive people that have consumed foods containing hydrolyzed vegetable protein (generic).<sup>17</sup> No adverse effects from cosmetic use were discovered in the published literature.

## SUMMARY

Plant-derived proteins and peptides function primarily as skin and/or hair conditioning agents in personal care products. These protein derivatives are prepared by subjecting vegetable proteins to hydrolysis via enzymes, acid, or other methodologies such as steam.

Hydrolyzed Vegetable Protein has the most reported uses in personal care products, with a total of 142 formulations; approximately half of the uses are in leave-on products. Hydrolyzed Lupine Protein has the second greatest number of overall uses reported, with a total of 96; the majority of the uses are in leave-on formulations.

Hydrolyzed Potato Protein is used at up to 2.4% in nighttime skin care products. Hydrolyzed Hazelnut Protein and Hydrolyzed Lupine Protein have maximum use concentrations of 0.99% in body and hand skin care preparations.

No uses were reported for Hydrolyzed Avocado Protein, Hydrolyzed Maple Sycamore Protein, or Hydrolyzed Zein in the VCRP or by Council.

Hydrolyzed vegetable proteins (generic) are widely used as seasonings and as ingredients in processed savory food products and range in concentration of use in foods from 0.1% to 40%. Generally, hydrolyzed proteins (acid hydrolyzed or enzymatically hydrolyzed) at levels used as flavoring agents in foods do not pose a hazard to humans. Plant protein products are approved food additives according to the FDA. The FDA requires allergen labeling when major allergens, such as tree nuts, are included in food.

The toxicity of *Lupinus albus* was studied in a 112-day study in rats where diets comprised 20% dietary protein from *L. albus*, *L. luteus*, or casein (the control). The rats fed the *L. albus* diets gained weight at a slightly lower rate than those fed *L. luteus* and casein. There were no differences in the feed intakes and feed efficiencies of both lupine groups during weeks 1-6. There were no differences observed in organ-to-body weight ratios of liver, spleen, heart, and adrenals of rats fed either lupines or casein. No adverse effects were reported. No significant differences were observed in the gross necropsy findings or the microscopic examinations.

No adverse effects were reported in rats fed hydrolyzed hemp seed meal protein. The rats were fed diets containing 0%, 0.5%, or 1.0% (w/w) hydrolyzed hemp seed meal protein for 8 weeks.

Hydrolyzed Lupine Protein (up to 26.7%), Hydrolyzed Pea Protein (up to 25%), Hydrolyzed Sweet Almond Protein (up to 3.3%) and Hydrolyzed Vegetable Protein (10.9%) were not mutagenic in Ames tests.

Tree nuts, including *Bertholletia excelsa* (Brazil nut), *Corylus* spp. (hazelnut), and *Prunus dulcis* (sweet almond) are well known major food allergens that produce Type 1 (immediate) reactions in sensitive individuals. Type 1 allergic responses also have been reported following the consumption of legumes such as peanut, lupine, and pea.

In in vitro and animal dermal irritation studies, Hydrolyzed Amaranth Protein (20% in water), Hydrolyzed Avocado Protein (concentration not reported), Hydrolyzed Hazelnut Protein (100%), Hydrolyzed Lupine Protein (concentration not reported), and Hydrolyzed Vegetable Protein (100%) were not irritants. No irritation was observed in human dermal studies for Hydrolyzed Avocado Protein (20%), Hydrolyzed Lupine Protein (up to 6%), and Hydrolyzed Pea Protein (25% solution in water).

No sensitization was observed in animal studies of Hydrolyzed Avocado Protein (concentration not reported), Hydrolyzed Hazelnut Protein (up to 100%), and Hydrolyzed Lupine Protein (concentration not reported). No sensitization was observed in human studies of the following hydrolyzed protein ingredients: amaranth (concentration not reported), avocado (concentration not reported), lupine (concentration not reported), potato (up to 2.4% in formulation), and sweet almond (concentration not reported).

Hydrolyzed Avocado Protein (50%), Hydrolyzed Hazelnut Protein (concentration not reported), and Hydrolyzed Lupine Protein (100%) were not phototoxic in in vitro studies.

In in vitro ocular studies, Hydrolyzed Amaranth Protein (20%) and Hydrolyzed Vegetable Protein (up to 100%) were not irritating. In vitro studies predicted Hydrolyzed Avocado Protein (tested at 20% in a HET-CAM assay; 10% in a BCOP test) may be an eye irritant. Hydrolyzed Lupine Protein (concentration not reported) was weakly irritating in both the HET-CAM and BCOP tests. In animal studies, Hydrolyzed Hazelnut Protein was not irritating when tested neat, while Hydrolyzed Lupine Protein (up to 5.5%) and Hydrolyzed Sweet Almond Protein (up to 3.3%) were very slight irritants in rabbit eyes.

## DISCUSSION

The Panel noted that these plant-derived protein and peptide ingredients are processed extensively during production, which substantially reduces or eliminates any constituents of concern that may be present in the plant material from which they are derived. The Panel expressed concern about aflatoxins, pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.



Most of the protein-derived ingredients in this assessment are found in foods, and daily exposures from the consumption of foods can be expected to yield much larger systemic exposures to these ingredients than those from use in cosmetic products. Plant proteins are approved food additives. The Panel did acknowledge that Type I immediate hypersensitivity reactions could possibly occur following exposure to a protein-derived ingredient by sensitized individuals, especially via incidental inhalation. HRIPTs and related test data do not detect Type I reactions. Thus, the Panel recommends that people with known allergies to tree nut, seed, and avocado proteins avoid using personal care products that contain these ingredients.

The Panel discussed the issue of incidental inhalation exposure from hair sprays, fragrance preparations, and face powders. There were no inhalation toxicity data available. The Panel noted that droplets/particles from spray and loose-powder cosmetic products would not be respirable to any appreciable amount; however, 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 in users without known allergies to tree nut, seed, and avocado proteins. 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 determined that the data were sufficient to support safety of 18 plant-derived protein and peptide ingredients in the present practices of use and concentration. The Panel found the data were insufficient to determine safety of Hydrolyzed Maple Sycamore Protein and issued an insufficient data announcement in December 2016. The data needs were not met. The additional data needed to evaluate the safety of Hydrolyzed Maple Sycamore Protein are:

- Method of manufacturing
- Chemical composition and impurities
- Clarification on food safety status, specifically whether this ingredient is generally recognized as safe (GRAS)
- If this ingredient is not GRAS, then studies of systemic endpoints such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity are needed, as well as UV absorption spectra

### **CONCLUSION**

The Panel concluded that the 18 plant-derived proteins and peptides listed below are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Hydrolyzed Amaranth Protein  
Hydrolyzed Avocado Protein\*  
Hydrolyzed Barley Protein  
Hydrolyzed Brazil Nut Protein  
Hydrolyzed Cottonseed Protein  
Hydrolyzed Extensin  
Hydrolyzed Hazelnut Protein  
Hydrolyzed Hemp Seed Protein  
Hydrolyzed Jojoba Protein

Hydrolyzed Lupine Protein  
Hydrolyzed Pea Protein  
Hydrolyzed Potato Protein  
Hydrolyzed Sesame Protein  
Hydrolyzed Sweet Almond Protein  
Hydrolyzed Vegetable Protein  
Hydrolyzed Zein\*  
Lupinus Albus Protein  
Pisum Sativum (Pea) Protein

The Panel concluded that the data on Hydrolyzed Maple Sycamore Protein are insufficient to determine safety.

\*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.

## **TABLES**

**Table 1.** Definitions and functions of the ingredients in this safety assessment.<sup>1</sup> (Italicized text below represents additions made by CIR).

<b>Ingredient CAS No.</b>	<b>Definition</b>	<b>Function</b>
Hydrolyzed Amaranth Protein	Hydrolyzed Amaranth Protein is the <i>partial</i> hydrolysate of amaranth protein derived by acid, enzyme or other method of hydrolysis.	Skin-Conditioning Agent - Misc.
Hydrolyzed Avocado Protein	Hydrolyzed Avocado Protein is the <i>partial</i> hydrolysate of avocado protein derived by acid, enzyme or other method of hydrolysis.	Skin-Conditioning Agent - Misc.
Hydrolyzed Barley Protein	Hydrolyzed Barley Protein is the <i>partial</i> hydrolysate of barley protein derived by acid, enzyme or other method of hydrolysis.	Hair conditioning Agent; Skin-Conditioning Agent - Misc.
Hydrolyzed Brazil Nut Protein	Hydrolyzed Brazil Nut Protein is the <i>partial</i> hydrolysate of brazil nut protein derived by acid, enzyme or other method of hydrolysis.	Hair conditioning Agent; Skin-Conditioning Agent - Misc.
Hydrolyzed Cottonseed Protein	Hydrolyzed Cottonseed Protein is the <i>partial</i> hydrolysate of cottonseed protein derived by acid, enzyme or other method of hydrolysis.	Hair conditioning Agent; Skin-Conditioning Agent - Misc.
Hydrolyzed Extensin 73049-73-7	Hydrolyzed Extensin is the <i>partial</i> hydrolysate of extensin protein derived by acid, enzyme or other method of hydrolysis. <i>Wherein, extensins are defined as wall-located, basic, hydroxyproline rich structural glycoproteins with alternating hydrophilic and hydrophobic motifs.</i> <sup>59</sup>	Hair conditioning Agent; Skin-Conditioning Agent - Misc.
Hydrolyzed Hazelnut Protein	Hydrolyzed Hazelnut Protein is the <i>partial</i> hydrolysate of hazelnut protein derived by acid, enzyme, or other method of hydrolysis.	Skin-Conditioning Agent - Misc.
Hydrolyzed Hemp Seed Protein	Hydrolyzed Hemp Seed Protein is the <i>partial</i> hydrolysate of hemp seed protein derived by acid, enzyme or other method of hydrolysis.	Hair conditioning Agent; Skin-Conditioning Agent - Misc.
Hydrolyzed Jojoba Protein 100684-35-3	Hydrolyzed Jojoba Protein is the <i>partial</i> hydrolysate of jojoba seed protein derived by acid, enzyme or other method of hydrolysis.	Hair conditioning Agent; Skin-Conditioning Agent – Emollient
Hydrolyzed Lupine Protein 73049-73-7	Hydrolyzed Lupine Protein is the <i>partial</i> hydrolysate of lupine protein derived by acid, enzyme or other method of hydrolysis.	Hair Conditioning Agent; Light Stabilizer; Skin-Conditioning Agent - Misc.
Hydrolyzed Maple Sycamore Protein 73049-73-7	Hydrolyzed Maple Sycamore Protein is the <i>partial</i> hydrolysate of the protein derived from the maple sycamore tree, <i>Acer pseudoplatanus</i> , obtained by acid, enzyme, or other method of hydrolysis.	Hair Conditioning Agent; Skin-Conditioning Agent-Humectant; Skin-Conditioning Agent-Misc.
Hydrolyzed Pea Protein 222400-29-5 227024-36-4	Hydrolyzed Pea Protein is the <i>partial</i> hydrolysate of pea protein derived by acid, enzyme or other method of hydrolysis.	Hair Conditioning Agent; Skin-Conditioning Agent-Emollient; Skin-Conditioning Agent-Misc.
Hydrolyzed Potato Protein 169590-59-4	Hydrolyzed Potato Protein is the <i>partial</i> hydrolysate of potato protein derived by acid, enzyme or other method of hydrolysis.	Hair Conditioning Agent; Skin-Conditioning Agent-Misc.
Hydrolyzed Sesame Protein	Hydrolyzed Sesame Protein is the <i>partial</i> hydrolysate of sesame protein derived by acid, enzyme or other method of hydrolysis.	Hair Conditioning Agent; Skin-Conditioning Agent-Misc.
Hydrolyzed Sweet Almond Protein 100209-19-6	Hydrolyzed Sweet Almond Protein is the <i>partial</i> hydrolysate of sweet almond protein derived by acid, enzyme or other method of hydrolysis.	Hair Conditioning Agent; Skin-Conditioning Agent-Misc.
Hydrolyzed Vegetable Protein 73049-73-7 100209-45-8	Hydrolyzed Vegetable Protein is the <i>partial</i> hydrolysate of vegetable protein derived by acid, enzyme or other method of hydrolysis.	Hair Conditioning Agent; Skin-Conditioning Agent-Misc.
Hydrolyzed Zein	Hydrolyzed Zein is the <i>partial</i> hydrolysate of Zein derived by acid, enzyme or other method of hydrolysis. <i>Wherein, Zein is an alcohol-soluble protein obtained from corn, Zea mays.</i>	Hair Conditioning Agent; Skin-Conditioning Agent-Misc.
Lupinus Albus Protein	Lupinus Albus Protein is the protein derived from the seeds of <i>Lupinus albus</i> .	Skin-Conditioning Agents – Emollient; Skin-Conditioning Agents – Misc.
Pisum Sativum (Pea) Protein	Pisum Sativum (Pea) Protein is the protein isolated from <i>Pisum sativum</i> .	Skin-Conditioning Agents – Misc.

**Table 2.** Reported molecular weights (Da) of some plant-derived hydrolyzed proteins

Ingredients	Value	Reference
Hydrolyzed Amaranth Protein	~1500	60
Hydrolyzed Avocado Protein	<500 (20%-50%); 500-1000 (50%-75%); 1000-3500 (20%); >3500 (5%)	18,19
Hydrolyzed Brazil Nut Protein	~150; 1000	13,61
Hydrolyzed Cottonseed Protein	1700	13
Hydrolyzed Hazelnut Protein	<300 (~23%); 300-510 (~22%); 510-1000 (~34%); 1000-2990 (~19%); 2990-5020 (~1.4%); >5020 (0.16%)	20
Hydrolyzed Lupine Protein	<500 (<25%); 500-1000 (50%-75%); 1000-3500 (<25%); >3500 (<10%)	14,19
Hydrolyzed Pea Protein	500 (acid, alkaline, and/or enzyme hydrolysis); 1500 (enzyme hydrolysis)	13,21
Hydrolyzed Sweet Almond Protein	~3000	61
Hydrolyzed Vegetable Protein	~1000	62
Hydrolyzed Vegetable Protein (potato source)	750 (enzyme hydrolysis); 100,000 (alkaline hydrolysis)	13

**Table 3.** Method of manufacturing

<b>Ingredient</b>	<b>Procedure</b>	<b>Reference</b>
Hydrolyzed Amaranth Protein (MW=1500 Da)	Produced by filtering a solution of finely ground amaranth powder in water and then reacting the resultant colloidal protein solution with acid for a prescribed period of time and temperature until the hydrolyzed protein solution is obtained	60
Hydrolyzed Avocado Protein	Prepared from sliced and dried avocado fruits. Cold pressure is used to extract lipids from the fruits, and then the proteins are hydrolyzed by enzymatic reactions with a cellulase and a protease. Following centrifugation, the solution is purified by ultrafiltration to remove residual proteins and enzymes. The solution is further purified by nanofiltration to remove salts. The resulting solution consists of 20%-50% peptides (w/w) and 20%-30% carbohydrates (w/w).	18
Hydrolyzed Brazil Nut Protein	Prepared by acid hydrolysis	61
Hydrolyzed Brazil Nut Protein (concentration 10% -25%; MW=1000 Da)	Prepared by enzyme hydrolysis	13
Hydrolyzed Cottonseed Protein (concentration 10%-25%; MW=1700 Da)	Prepared by enzyme hydrolysis	13
Hydrolyzed Hazelnut Protein	Prepared by enzyme hydrolysis	20
Hydrolyzed Lupine Protein	Prepared by hydrolyzing lupine proteins in water through an enzymatic reaction with a protease. The solution is then centrifuged and purified by ultrafiltration to remove residual proteins and protease. The solution is further purified by nanofiltration to remove salts.	14
Hydrolyzed Pea Protein (concentration 10%-25%; MW=1500 Da)	Prepared by enzyme hydrolysis	13
Hydrolyzed Pea Protein (concentration 25% in water; MW=500Da)	Prepared by acidic, alkaline, and/or enzymatic hydrolysis of the pea until the desired molecular weight is reached.	21
Hydrolyzed Sweet Almond Protein	Prepared by enzyme hydrolysis	61
Hydrolyzed Vegetable Protein (source: corn and soy combined)	Prepared by enzyme hydrolysis under mild conditions for several hours until the target molecular weight is achieved. The resultant hydrolyzed proteins may then be concentrated. This mixture of hydrolyzed corn and hydrolyzed soy protein is sold under the <i>Dictionary</i> name Hydrolyzed Vegetable Protein.	63
Hydrolyzed Vegetable Protein (generic)	Prepared by hydrochloric acid hydrolysis of the proteinaceous by-products of the edible oils or starches of soybean, rapeseed meals, and maize gluten.	24
Hydrolyzed Vegetable Protein (source: potato; concentration 10%-25%; MW=750 Da)	Prepared by enzyme hydrolysis	13
Hydrolyzed Vegetable Protein (source: potato; concentration 7.5%-15%; MW=100,000 Da)	Prepared by alkaline hydrolysis	13

**Table 4.** Frequency and concentration of use according to duration and type of exposure for plant-derived hydrolyzed proteins.<sup>27-29</sup>

	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>
	<b>Hydrolyzed Amaranth Protein</b>		<b>Hydrolyzed Barley Protein</b>		<b>Hydrolyzed Brazil Nut Protein</b>		<b>Hydrolyzed Cottonseed Protein</b>	
<b>Totals<sup>†</sup></b>	<b>6</b>	<b>0.011</b>	<b>14</b>	<b>0.002</b>	<b>16</b>	<b>0.000026-0.023</b>	<b>37</b>	<b>NR</b>
<b><i>Duration of Use</i></b>								
Leave-On	4	0.011	11	NR	6	0.000026-0.016	32	NR
Rinse Off	2	NR	3	0.002	10	0.000026-0.023	5	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
<b><i>Exposure Type</i></b>								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2; 2 <sup>a</sup>	0.011	8 <sup>a</sup>	NR	5 <sup>a</sup>	0.000026; 0.016 <sup>a</sup>	7; 21 <sup>a</sup> ; 4 <sup>b</sup>	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	4 <sup>b</sup>	NR
Dermal Contact	3	NR	1	NR	NR	NR	37	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	0.011	13	0.002	13	0.000026-0.023	NR	NR
Hair-Coloring	NR	NR	NR	NR	3	0.00013	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	3	NR
Baby Products	NR	NR	1	NR	NR	NR	NR	NR
	<b>Hydrolyzed Extensin</b>		<b>Hydrolyzed Hazelnut Protein</b>		<b>Hydrolyzed Hemp Seed Protein</b>		<b>Hydrolyzed Jojoba Protein</b>	
<b>Totals<sup>†</sup></b>	<b>33</b>	<b>0.01-0.13</b>	<b>24</b>	<b>0.25-0.99</b>	<b>NR</b>	<b>0.0002</b>	<b>18</b>	<b>0.001-0.025</b>
<b><i>Duration of Use</i></b>								
Leave-On	28	0.13	23	0.25-0.99	NR	NR	5	0.001-0.025
Rinse Off	5	0.01	1	NR	NR	0.0002	13	0.001-0.0026
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
<b><i>Exposure Type</i></b>								
Eye Area	2	NR	3	NR	NR	NR	1	0.0027
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	13 <sup>a</sup> ; 10 <sup>b</sup>	NR	2 <sup>a</sup> ; 18 <sup>b</sup>	0.25	NR	NR	3 <sup>a</sup> ; 1 <sup>b</sup>	NR
Incidental Inhalation-Powder	10 <sup>b</sup>	0.13 <sup>c</sup>	18 <sup>b</sup>	0.99 <sup>c</sup>	NR	NR	1 <sup>b</sup>	0.001-0.025 <sup>c</sup>
Dermal Contact	30	0.13	24	0.25-0.99	NR	NR	8	0.001-0.025
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	0.01	NR	NR	NR	0.0002	9	0.001-0.0026
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	2	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

**Table 4.** Frequency and concentration of use according to duration and type of exposure for plant-derived hydrolyzed proteins.<sup>27-29</sup>

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	<b>Hydrolyzed Lupine Protein</b>		<b>Hydrolyzed Pea Protein</b>		<b>Hydrolyzed Potato Protein</b>		<b>Hydrolyzed Sesame Protein</b>	
<b>Totals<sup>†</sup></b>	<b>96</b>	<b>0.0001-0.99</b>	<b>18</b>	<b>0.001</b>	<b>12</b>	<b>0.75-2.4</b>	<b>NR</b>	<b>0.001</b>
<b><i>Duration of Use</i></b>								
Leave-On	84	0.0001-0.99	18	0.001	12	0.75-2.4	NR	0.001
Rinse Off	12	0.0001-0.6	NR	0.001	NR	NR	NR	0.001
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
<b><i>Exposure Type</i></b>								
Eye Area	19	0.005-0.18	1	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	34 <sup>a</sup> ; 19 <sup>b</sup>	0.6 <sup>a</sup>	8 <sup>a</sup> ; 9 <sup>b</sup>	NR	9 <sup>a</sup> ; 2 <sup>b</sup>	NR	NR	NR
Incidental Inhalation-Powder	19 <sup>b</sup>	0.0001-0.99 <sup>c</sup>	9 <sup>b</sup>	0.001 <sup>c</sup>	2 <sup>b</sup>	0.75 <sup>c</sup>	NR	0.001 <sup>c</sup>
Dermal Contact	78	0.0001-0.99	18	0.001	12	0.75-2.4	NR	0.001
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	4	0.001-0.6	NR	0.001	NR	NR	NR	0.001
Hair-Coloring	7	NR	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.6	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	<b>Hydrolyzed Sweet Almond Protein<sup>d</sup></b>		<b>Hydrolyzed Vegetable Protein</b>		<b>Lupinus Albus Protein</b>		<b>Pisum Sativum (Pea) Protein</b>	
<b>Totals<sup>†</sup></b>	<b>68</b>	<b>0.001-0.063</b>	<b>142</b>	<b>0.0004-0.3</b>	<b>NR</b>	<b>0.0025</b>	<b>NR</b>	<b>0.001-0.0025</b>
<b><i>Duration of Use</i></b>								
Leave-On	46	0.001-0.05	72	0.0011-0.3	NR	0.0025	NR	0.001-0.0025
Rinse Off	22	0.001-0.063	70	0.0004-0.3	NR	NR	NR	0.001-0.0025
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
<b><i>Exposure Type</i></b>								
Eye Area	10	NR	5	0.0012-0.3	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	8 <sup>a</sup> ; 19 <sup>b</sup>	NR	2; 41 <sup>a</sup> ; 8 <sup>b</sup>	0.3 <sup>a</sup>	NR	NR	NR	NR
Incidental Inhalation-Powder	19 <sup>b</sup>	0.001-0.05 <sup>c</sup>	1; 8 <sup>b</sup> ; 1 <sup>c</sup>	0.0011 <sup>c</sup>	NR	NR	NR	0.001 <sup>c</sup>
Dermal Contact	39	0.001-0.05	59	0.0004-0.3	NR	0.0025	NR	0.001
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	21	0.001-0.063	60	0.0004-0.17	NR	NR	NR	0.001-0.0025
Hair-Coloring	1	NR	23	0.0019	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	3	NR	NR	0.0004-0.25	NR	NR	NR	NR
Baby Products	NR	NR	2	NR	NR	NR	NR	NR

NR = Not reported.

<sup>†</sup> 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.<sup>a</sup>. It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.<sup>b</sup>. Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.<sup>c</sup>. It is possible these products may be powders, but it is not specified whether the reported uses are powders.<sup>d</sup>. Two uses for other skin care preparations were categorized under Hydrolyzed Almond Protein in the VCRP.

**Table 5.** In vitro genotoxicity studies

<b>Ingredient</b>	<b>Concentration/Dose</b>	<b>Study Protocol</b>	<b>Results</b>	<b>Reference</b>
Hydrolyzed Lupine Protein	up to 26.7%	Ames test; no further details provided	Not mutagenic or pro-mutagenic	<sup>15</sup>
Hydrolyzed Pea Protein	19% in a solution of 75% water and 4.5% sodium chloride; 50-5000 µg/plate	Ames test in <i>Salmonella typhimurium</i> TA1535, TA1537, TA98, TA100 and <i>Escherichia coli</i> WP2uvrA; with and without S9 metabolic activation	Not mutagenic	<sup>42</sup>
Hydrolyzed Pea Protein	25% solution in water; MW = 500 Da; 50-5000 µg/plate	Ames test in <i>S. typhimurium</i> TA1535, TA1537, TA98, TA100 and <i>E. coli</i> WP2uvrA; with and without S9 metabolic activation	Not mutagenic	<sup>21</sup>
Hydrolyzed Sweet Almond Protein	2.3% to 3.3%	Ames test; no further details provided	Not mutagenic or pro-mutagenic	<sup>15</sup>
Hydrolyzed Vegetable Protein (source: potato)	10.9% in a solution of 87% water	Ames test in <i>S. typhimurium</i> TA1535, TA1537, TA98, TA100 and <i>E. coli</i> WP2uvrA; with and without S9 metabolic activation	Not mutagenic	<sup>43</sup>

**Table 6.** Dermal irritation studies for plant-derived hydrolyzed proteins and peptides.

<b>Ingredient</b>	<b>Concentration</b>	<b>Method</b>	<b>Results</b>	<b>Reference</b>
<b><i>In Vitro</i></b>				
Hydrolyzed Amaranth Protein	20% in water	EpiDerm MTT Viability assay	Non-irritating	48
Hydrolyzed Avocado Protein	20%	3D human skin model (MTT + IL1 $\alpha$ ) performed under OECD draft guidelines and ECVAM protocol	Non-irritating	18,19
Hydrolyzed Lupine Protein	100%	3D human skin model (MTT + IL1 $\alpha$ ) performed under OECD draft guidelines and ECVAM protocol	Non-irritating	14,19
Hydrolyzed Pea Protein	10% to 25% in a solution of > 50% water	Episkin reconstructed human epidermis model	Predicted to be non-irritating	50
Hydrolyzed Vegetable Protein (source: potato)	10% in a solution of 87% water and 1% sodium chloride (MW ~ 100,000 Da)	Episkin reconstructed human epidermis model	Predicted to be non-irritating	51
Hydrolyzed Vegetable Protein (source not reported)	100% (MW = 750 Da)	EpiDerm skin model	Non-irritating	49
<b><i>Animal</i></b>				
Hydrolyzed Hazelnut Protein	100%	Dermal irritation study performed under OECD Guideline 404; no further details provided	Non-irritating	20
Hydrolyzed Lupine Protein	4.5% to 5.5%	Cutaneous tolerance test in rabbits; no further details provided	Non-irritating	15
Hydrolyzed Sweet Almond Protein	2.3% to 3.3%	Cutaneous tolerance test in rabbits; no further details provided	Non-irritating	15
<b><i>Human</i></b>				
Hydrolyzed Avocado Protein	20%	Human patch test with 10 volunteers; no further details provided	Very well tolerated	18,19
Hydrolyzed Lupine Protein	0.005%	Human patch test with 20 volunteers; no further details provided	Well tolerated	14,19
Hydrolyzed Lupine Protein	1.92% to 2.67%	Acute skin tolerance patch test; no further details provided	Not irritating	15
Hydrolyzed Lupine Protein	4.5% to 6%	Acute skin tolerance patch test; no further details provided	Not irritating	15
Hydrolyzed Pea Protein	25% solution in water (MW = 500 Da)	24 hour human patch test with 20 volunteers; Finn chambers (occlusive)	Not irritating	21



**Table 7.** Dermal sensitization studies for plant- derived hydrolyzed proteins and peptides.

<b>Ingredient</b>	<b>Concentration</b>	<b>Method</b>	<b>Results</b>	<b>Reference</b>
<i>Animal</i>				
Hydrolyzed Avocado Protein	12.5%	LLNA	Non-sensitizing	18,19
Hydrolyzed Hazelnut Protein	100%	Guinea pig dermal sensitization study performed according to OECD guideline 406	Non-sensitizing	20
Hydrolyzed Hazelnut Protein	5%	Sensitization study using the Marzulli-Maibach method	Non-irritating and non-sensitizing	20
Hydrolyzed Lupine Protein	25%	LLNA	Non-sensitizing	14,19
Hydrolyzed Lupine Protein	4.5% to 5.5%	Sensitization study in albino guinea pigs; no further details provided	Non-sensitizing	15
Hydrolyzed Sweet Almond Protein	2.3% to 3.3%	Sensitization study in albino guinea pigs; no further details provided	Very slight sensitizing agent	15
<i>Human</i>				
Hydrolyzed Amaranth Protein	Tested as received	HRIPT with 108 subjects; semi-occlusive	No dermal irritation or sensitization	53
Hydrolyzed Avocado Protein	Not reported	HRIPT (Marzulli-Maibach method) in 50 subjects	Non-sensitizing	18
Hydrolyzed Lupine Protein	0.005%	HRIPT (Marzulli-Maibach method) in 100 subjects	Non-sensitizing	14,19
Hydrolyzed Lupine Protein	0.192% to 0.267%	HRIPT (Marzulli-Maibach method); no further details provided	No dermal irritation or sensitization	15
Hydrolyzed Lupine Protein	4.5% to 6%	HRIPT (Marzulli-Maibach method); no further details provided	No dermal irritation or sensitization	15
Hydrolyzed Pea Protein	25% solution in water; MW = 500 Da	HRIPT with 50 subjects; 0.2 ml test material on occlusive patch	Non-sensitizing	21
Hydrolyzed Potato Protein	1.5% in a face cream	HRIPT with 100 subjects; occlusive	No dermal irritation or sensitization	52
Hydrolyzed Potato Protein	2.4% in a night cream	HRIPT with 100 subjects; occlusive	No dermal irritation or sensitization	52
Multiple Hydrolyzed Proteins including Hydrolyzed Sweet Almond Protein	Not reported	Sensitization study of protein hydrolysates in hair care products in 3 groups of patients. Group 1 was comprised of 11 hairdressers with hand dermatitis, group2 was comprised of 2160 consecutive adults with suspected allergic respiratory disease, and group 3 was comprised of 28 adults with atopic dermatitis. Subjects submitted to scratch and/or prick tests.	No adverse reactions to Hydrolyzed Sweet Almond Protein were observed.	54

**Table 8.** In vitro phototoxicity studies for plant-derived hydrolyzed proteins and peptides.

<b>Ingredient</b>	<b>Concentration</b>	<b>Method</b>	<b>Results</b>	<b>Reference</b>
Hydrolyzed Avocado Protein	50%	3T3 Neural Red Uptake (NRU) method	Not phototoxic	18,19
Hydrolyzed Hazelnut Protein	Not reported	3T3 NRU method	Not phototoxic	20
Hydrolyzed Lupine Protein	100%	3T3 NRU method	Not phototoxic	14,19

**Table 9.** Ocular irritation studies for plant-derived hydrolyzed proteins and peptides.

<b>Ingredient</b>	<b>Concentration</b>	<b>Method</b>	<b>Results</b>	<b>Reference</b>
<i>In Vitro</i>				
Hydrolyzed Amaranth Protein	20% dilutions	EpiOcular MTT viability irritation study	Non-irritating	55
Hydrolyzed Avocado Protein	20%	HET-CAM method	Moderately irritating	18,19
Hydrolyzed Avocado Protein	10%	BCOP ocular irritation study	Not severely irritating	18,19
Hydrolyzed Avocado Protein	20%	Neutral red release assay	Negligible cytotoxicity	18,19
Hydrolyzed Lupine Protein	0.005%	HET-CAM method	Weakly irritating	14,19
Hydrolyzed Lupine Protein	100%	BCOP ocular irritation study	Weakly irritating	14,19
Hydrolyzed Lupine Protein	0.005%	Neutral red release assay	Negligible cytotoxicity	14,19
Hydrolyzed Pea Protein	19% in a solution of 75% water and 4.5% sodium chloride	SkinEthic reconstructed human corneal epithelial model (10 min exposure)	Predicted to be non-irritating	58
Hydrolyzed Pea Protein	1.25%	HET-CAM method	Predicted to be non-irritating	21
Hydrolyzed Vegetable Protein (source: potato)	7.5% to 15% in a solution of > 50% water (MW ~ 100,000 Da)	SkinEthic reconstructed human corneal epithelial model (10 min exposure)	Predicted to be non-irritating	57
Hydrolyzed Vegetable Protein (source not reported)	25%, 50%, and 100% (MW = 750 Da)	HET-CAM method	Practically no irritation potential	56
<i>Animal</i>				
Hydrolyzed Hazelnut Protein	Neat	Ocular irritation study performed under OECD guideline 405; no further details provided	Non-irritating	20
Hydrolyzed Lupine Protein	4.5% to 5.5%	Ocular tolerance test in rabbits; no further details provided	Very slight irritant	15
Hydrolyzed Sweet Almond Protein	2.3% to 3.3%	Ocular tolerance test in rabbits; no further details provided	Very slight irritant	15

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