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

Status:	Draft Final Report for Panel Review
Release Date:	August 18, 2017
Panel Meeting Date:	September 11-12, 2017

 This safety assessment was prepared by Christina L. Burnett, Scientific Analyst/Writer and Ivan Boyer, Ph.D., Toxicologist CIR.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: August 18, 2017
Subject: Draft Final Safety Assessment on Plant-Derived Proteins and Protein Derivatives

Enclosed is the Draft Final Report of the Safety Assessment of Plant-Derived Proteins and Protein Derivatives as Used in Cosmetics. (It is identified as *pltpep092017rep* in the pdf document).

In June 2017, the CIR Expert Panel (Panel) issued a Tentative Report with the conclusion that 18 of the 19 plant-derived proteins and peptides are safe in cosmetics in the present practices of use and concentration. The Panel also concluded that the data on Hydrolyzed Maple Sycamore are insufficient to determine safety.

No new unpublished data were received since the June meeting. Comments received from the Council prior to the April meeting and on the Tentative Report have been considered. The comments are identified as *pltpep092017pcpc1-pcpc2*, respectively. The Council suggested expanding information regarding tree nut allergies with information from a review article. This new information in the Type 1 Hypersensitivity section has been highlighted in |brackets|.

The Panel should carefully review the Abstract, Discussion, and Conclusion of this report. If these are satisfactory, the Panel should issue a Final Report.

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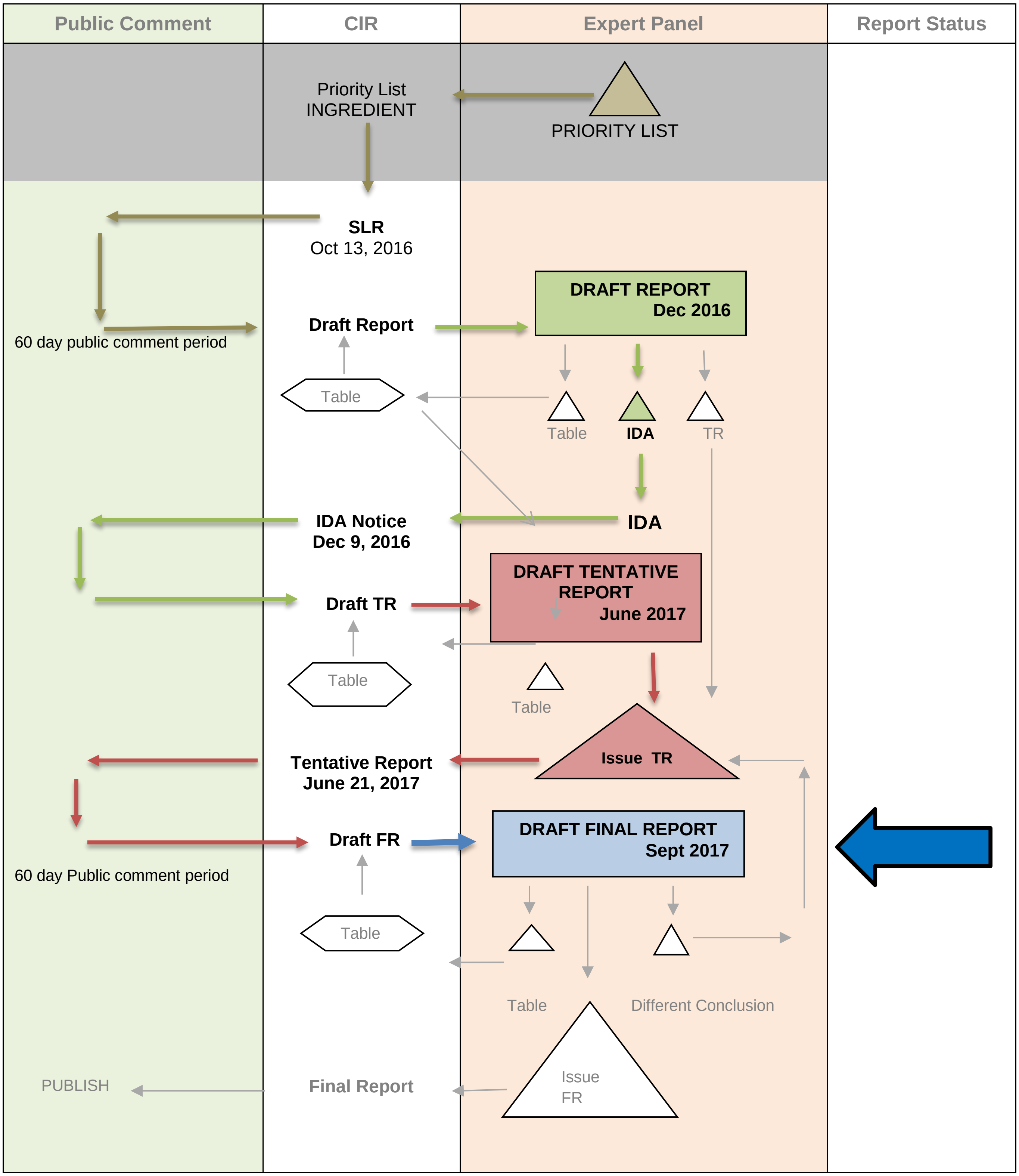
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Plant-Derived Proteins and Peptides

MEETING Sept 2017



Plant-Derived Proteins and Peptides History

October 2016 – Scientific Literature Review announced.

December 2016 - The Panel issued an insufficient data announcement on this ingredient group. The additional data needed to evaluate the safety of Hydrolyzed Maple Sycamore Protein were:

- 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

The Panel determined that the data were sufficient to support safety of the remaining 18 plant-derived protein and peptide ingredients in the present practices of use and concentration. The Panel acknowledged that Type I immediate hypersensitivity reactions could possibly occur following exposure to a protein-derived ingredient. Traditional 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.

June 2017 - The Panel issued a tentative report for the 19 plant-derived proteins and peptides with the conclusion that 18 ingredients are safe in cosmetics in the present practices of use and concentration. The Panel concluded that the data on Hydrolyzed Maple Sycamore Protein are insufficient to determine safety. The 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 if 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.

Plant-Derived Protein and Peptide Ingredients Data Profile –September 2017 – Writer, Christina Burnett

	In-Use	Physical/Chemical Properties	Molecular Weight Range	Method of Manufacturing	Composition/Impurities	Acute Toxicity	Repeated Dose Toxicity	Genotoxicity	Reproductive and Developmental Toxicity	Carcinogenicity	Other Relevant Toxicity Studies	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Human	Ocular/Mucosal	Phototoxicity	Case Studies
Hydrolyzed Amaranth Protein	X		X	X	X							X	X	X		
Hydrolyzed Avocado Protein			X	X	X							X	X	X	X	
Hydrolyzed Barley Protein	X															
Hydrolyzed Brazil Nut Protein	X		X	X	X						X					
Hydrolyzed Cottonseed Protein	X		X	X	X											
Hydrolyzed Extensin	X															
Hydrolyzed Hazelnut Protein	X		X	X	X						X	X		X	X	
Hydrolyzed Hemp Seed Protein	X										X					
Hydrolyzed Jojoba Protein	X															
Hydrolyzed Lupine Protein	X		X	X	X			X				X	X	X	X	
Hydrolyzed Maple Sycamore Protein																
Hydrolyzed Pea Protein	X		X	X	X			X				X	X	X		
Hydrolyzed Potato Protein	X												X			
Hydrolyzed Sesame Protein	X															
Hydrolyzed Sweet Almond Protein	X		X	X	X			X			X	X	X	X		
Hydrolyzed Vegetable Protein	X		X	X	X			X				X		X		X
Hydrolyzed Zein																
Lupinus Albus Protein	X						X				X					
Pisum Sativum (Pea) Protein	X										X					

"X" indicates that data were available in the category for that ingredient.

Search Strategy for Plant-Derived Protein and Peptide Ingredients
(Performed by Christina Burnett)

- SciFinder
  - Search for ingredients by INCI names and available CAS#, only Pea, Hydrolyzed; Protein Hydrolyzates, Pea; Protein Hydrolyzates, Potato; Protein Hydrolyzates, Jojoba; Protein Hydrolyzates, Vegetable; and Almond, Ext., Hydrolyzed had entries –0 reference hits

Search Terms	TOXLINE Hits (excluding PUBMED)	PUBMED Hits	SCCS/SCCP Opinion	ECHA Hits	NICNAS
Hydrolyzed Amaranth Protein	0	6, 4 retrieved	No	0	No
Hydrolyzed Avocado Protein	0	3, 1 retrieved	No	0	No
Hydrolyzed Barley Protein	0	82, 1 retrieved	No	0	No
Hydrolyzed Brazil Nut Protein	0	2, 0 retrieved	No	0	No
Hydrolyzed Cottonseed Protein	0	9, 0 retrieved	No	0	No
Hydrolyzed Extensin	0	0	No	0	No
Hydrolyzed Hazelnut Protein	0	2, 2 retrieved	No	0	No
Hydrolyzed Hemp Seed Protein	0	2, 1 retrieved	No	0	No
Hydrolyzed Jojoba Protein and/or CAS #100684-35-3	0	1, 0 retrieved	No	0	No
Hydrolyzed Lupine Protein and/or CAS#73049-73-7	0	7, 0 retrieved	No	0	No
Hydrolyzed Maple Sycamore Protein and/or CAS#73049-73-7	0	0	No	0	No
Hydrolyzed Pea Protein and/or CAS#222400-29-5 or 227024-36-4	0	45, 1 retrieved	No	0	No
Hydrolyzed Potato Protein and/or CAS#169590-59-4	0	40, 0 retrieved	No	0	No
Hydrolyzed Sesame Protein	0	4, 0 retrieved	No	0	No
Hydrolyzed Sweet Almond Protein and/or CAS#100209-19-6	0	0	No	0	No
Hydrolyzed Vegetable Protein and/or CAS#73049-73-7 or 100209-45-8	0	76, 5 retrieved	No	0	No
Hydrolyzed Zein	0	11, 0 retrieved	No	0	No

Search Terms	TOXLINE Hits (excluding PUBMED)	PUBMED Hits	SCCS/SCCP Opinion	ECHA Hits	NICNAS
Lupinus Albus Protein	0	222, refined to Lupinus Albus Protein Toxicity = 2 hits, 1 retrieved	No	0	No
Lupinus Albus Protein Dermal OR Lupinus Albus Protein Sensitization	N/A	1, 0 retrieved	N/A	N/A	N/A
Lupinus Albus Protein Irritation	N/A	0	N/A	N/A	N/A
Pisum Sativum (Pea) Protein	0	3498, refined to Pisum Sativum (Pea) Protein Toxicity = 75 hits, 0 retrieved	No	0	No
Pisum Sativum (Pea) Protein Skin	N/A	17, 4 retrieved	N/A	N/A	N/A
Pisum Sativum (Pea) Protein Sensitization	N/A	5, 2 retrieved	N/A	N/A	N/A

Total references ordered or downloaded: 24

Search updated end of October, 2016 = 0 relevant references found.

Search updated April 27, 2017 = 0 relevant references found.

Search updated July 2017 = 0 relevant references found.

Plant-Derived Proteins and Peptides
June 12-13, 2017

Dr. Belsito's Team
DR. BELSITO: Okay. Let me get rid of this and then we are moving over to plant derived proteins. Okay. So at the December meeting we issued a report with data were sufficient with 18 of the 19 materials reviewed. And safe in the present practice and use concentration. However we went insufficient for hydrolyzed maple sycamore protein. The data needed was method of manufacturing, chemical composition, clarification of food safety status. We have not got any of that so I presume we are going forward with safe as used except for the maple sycamore which still needs all those data needs. Is that a fair assessment?

DR. LIEBLER: Agree.

DR. KLAASSEN: Yes.

DR. BELSITO: Yes, so very interestingly just for the heck of it I did a data surge on maple sycamore and there isn't even a manufacturer for that cosmetic ingredient review. It's not considered a flavoring material so I don't, you know, its jackfruit is not in there category so I doubt that it is GRAS. So I don't think we are going to get anywhere with it so.

DR. HELDRETH: If it were to go insufficient it will likely to go into the zero use bucket at some point.

DR. BELSITO: Yes, I think it already has zero uses and if you search there is no manufacturer for it.

DR. ANSELL: Yes, we were unable to identify a supplier.

DR. BELSITO: Right.

DR. SNYDER: I have a question about the title. Plant derived proteins and peptides. There are really no peptides unless it's the, is the hydrolyzed form considered a peptide of the protein?

DR. HELDRETH: Yes.

DR. BELSITO: Yes.

DR. SNYDER: Because then it's all peptides because they are all hydrolyzed, right?

DR. HELDRETH: It depends on your degree of hydroxylation. If you hydrolyze it for just a few seconds in acid at a room temperature you probably still have essentially a protein with a few little pieces chopped off but if you crank up the heat and run it all night long you might just have amino acids. So you can vary how much, how much hydrolization occurs here and we are somewhere on a spectrum between protein and amino acids or dimers or trimers or.

DR. KLAASSEN: And what's the definition these days for peptides?

DR. ANSELL: Less than 50 amino acids. I looked it up.

DR. LIEBLER: I thought it was 40 for FDA. I thought they used that but that's an FDA thing and, you know, as far as I can tell in the field of protein and peptide chemistry, there is no magic number so, you know it depends on what -- certainly we would tend to call smaller sequences peptides and larger sequences proteins. And something, you know, 40 and less most people would call a peptide so in that responded the FDA it's not, I'm looking, I don't see it in this document but I have seen it in one of our documents at some point the FDA is reasonable on that. So but in any case I think the title is fine because these are peptides. If they are hydrolyzed depending on the conditions and reagents they can be very thoroughly hydrolyzed to much smaller sequences or they might not be. Most of the time if they bother to try and hydrolyze they end up with mostly very small sequences.

DR. BELSITO: So are we happy with the title?

CHORUS: Um-hum.

DR. BELSITO: Okay. The only issue that I had was in the discussion, Christina, where we brought in the botanical boiler plate about mixtures. There was really nothing that I was concerned about in these and didn't really feel that we needed the mixture at least from a sensitization or an irritation standpoint and so I just throw it out to my colleagues if there are no materials that they are concerned about from their tox end points then, you know, I think that we need to throw that boiler plate in. It's not like they have sesquiterpene lactones or other sensitizers. There's nothing in them. They are peptides and proteins.

DR. BERGFELD: I thought it should stay on because of the wheat protein that is sensitizing and this just declares that we have looked at it. Even though it's not in that ballpark.

DR. BELSITO: But it wouldn't be an additive effect. It's not like adding oat to wheat increases your risk of wheat.

DR. BERGFELD: I am not saying that, I'm just saying it's a protein, it is not, not considering as an (inaudible).

DR. BELSITO: But that sentence refers to the fact that we have said that this is okay, you know, when used but hey guys if you're going to be adding, you know, chamomile, German chamomile or Roman chamomile with, you know, lavender you need to start to be concerned about concentrations of linalool or blah, blah, blah that could be sensitizing. Here it doesn't really matter if you combine wheat with oat with whatever, you know, what I mean, there is nothing that's, you know, with the wheat issue it has to do with the size of the peptides linking NIG crosslinking. I just thought that it was to begin using boiler plates across the board when there is no reason of concern I think dilutes their efficacy.

DR. LIEBLER: So I had similar reaction to that. I hadn't thought about the wheat, I was thinking more about whether any of the small molecule constituents of concern that we usually use this language for would be present in these ingredients and it seems to me based on the way that they are produced they would likely not be captured. So, you know, the protein extraction conditions are different than the sort of the organic extraction conditions that pull out the small organic flavonoids and other, you know, typical sensitizing materials so I wasn't really worried about it and that's why I, you know, kind of what are the constituents of concern in this case. If you layered this in with the wheat it would just be the effect of the wheat and not anything from any of the other ingredients that we have identify in this report so.

DR. BELSITO: So you would strike it too?

DR. LIEBLER: I would strike it, yes, I don't think it is necessary.

MS. BURNETT: Would you strike the paragraph below too with the pesticide residues and --

DR. BELSITO: No.

MS. BURNETT: No leave that but the constituents of concern.

DR. BELSITO: Yes. That was it otherwise. I thought it was fine.

DR. LIEBLER: Yes, I did too, I thought it looks really good.

DR. BELSITO: Okay. Moving -- any other comments on the plant derived? Okay.

Dr. Marks' Team

DR. MARKS: So at the December 2016 meeting, the Panel issued an insufficient data announcement for hydrolyzed maple sycamore protein. And Christina's memo, it documents the needs, method, manufacturer can make a composition in impurities clarification of food safety status and if not, grass, then systemic endpoints. And we still have not received any more data, is that correct?

MS. FIUME: Yes.

DR. MARKS: So there wasn't any in wave two nor this morning's -- and the Panel thought the other 18 plant derived proteins and peptides were safe at that time, so I assume we can move forward with a tentative report with a conclusion that the 18 plant derived proteins in peptides are safe and the one hydrolyzed maple sycamore protein was insufficient because of those reasons. Rons and Tom, comments? Do you like that conclusion?

DR. SHANK: it's fine with me.

DR. SLAGA: Fine with me. It's surprising we didn't get any data on (inaudible) --

MS. BURNETT: It's not used?

DR. HILL: It's not used. Oh, okay. I just wondered if anybody else noticed that hydrolyzed cottonseed protein, as -- in terms of the ingredient has 20 or 30 percent carbohydrate in -- my -- we need to have some information about that fraction of it as produced. It's 20 or 30 percent carbohydrate -- I don't know if that's cellulose or simple sugars or exactly what. We have a carbohydrates report, so if we have some information about what was in there, probably could know exactly how to deal.

DR. MARKS: So does that change the conclusion?

DR. HILL: I don't believe so. I mean, we don't have any direct -- what we have in terms of direct data on this. Yeah, actually quite a bit. I think we should be fine.

MS. BURNETT: And so now, I'll note that it's not used.

DR. HILL: It's not.

MS. BURNETT: You have data on it, but it's not used.

DR. HILL: Okay. Or at least not reported to be used.

MS. BURNETT: Correct.

DR. MARKS: Okay, any other comments? If not, then presumably, I'll be seconding a tentative report with a conclusion 18 are safe. The one is still insufficient.

DR. HILL: Could, in the discussion, we make note of that? Because when you say it's not in use, it suggests nothing came back on the survey, so try to get information about that, should be no pun intended, fruitless. But although I guess I have a (inaudible), right, but anyhow, could we at least make note somewhere ideally, the discussion that we note that that's there and we have no information about it as part of the ingredient as reported to be produced. I mean, we have a method manufacturer, how did we get that for composition and impurities rather?

DR. MARKS: Okay, any other comments?

MS. BURNETT: Where -- was the rest of the discussion as worded okay?

DR. MARKS: Yes.

DR. HILL: I believe it was.

DR. MARKS: Any other comments? If not, we'll move on to the next ingredient which is tissue derived proteins.

DR. HILL: So going back to that one more time, it explicitly says in the hydrolyzed avocado that it had data supplied by the Personal Care Products Council and they reported a bunch of impurities and so forth on that, but then you're still saying it's not in use.

MS. BURNETT: The supplier -- they did not report a concentration of use during survey and it's not in the VCRP. Yes, it is -- it's possible that it's being used, but --

DR. HILL: Okay.

MS. BURNETT: -- no one has reported (inaudible) that they are (inaudible).

DR. HILL: So when you say in current practices of use and it's not reported to be used, then you're down to the were it to be used, it would be similar to others in that category, et cetera, et cetera, et cetera, so again, at least making sure it's noted in the discussion about that unknown.

DR. MARKS: Yeah, that's -- well, that's actually in the conclusion always as an asterisk at the bottom.

DR. HILL: I do have one other question about that, that I forgot and it's actually important more generally. Is it reasonable -- do we think it's reasonable to be referring to these protein hydrolyzed - as botanicals because I guess -- I realize they come from plants, but I don't think about them in the same way we talk about some of these other botanical ingredients and I think the question was, do we even need this boilerplate in the discussion? Sorry I didn't bring this up. I was trying to go back and find out why I had so much information about a (inaudible) if it's not in use, but I really wonder if we need that boilerplate at all and I think maybe Dr. Belsito will have --

DR. MARKS: Well, Ron and Tom, what do you feel?

DR. SLAGA: I think we should leave it in because it is derived from --

DR. MARKS: And it's a mixture.

DR. SLAGA: Yeah.

DR. MARKS: Yeah. Yeah, it's a natural mixture. Yeah, I agree with you, Tom. Ron Shank?

DR. SHANK: The reason I ask about it is the way the wording is, is that, yeah, I agree. There are complex mixtures, but it says there's concerned (inaudible) multiple botanical ingredients in one formulation may each contribute the final concentration of the single constituent and while, I guess there are proteins that are the same in avocado versus others and the hydrolyzed protein, it would be almost coincidence if that's, in fact, the case. So I just wonder if we need to revisit the use of that boilerplate in that way on these ones that are hydrolyzed proteins or protein products. That's -- we can just leave that hanging for today, I think.

DR. MARKS: Yeah, Ron, you can bring that up in discussion (crosstalk) --

DR. SHANK: Okay, great.

DR. HILL: And see what, again, as you mentioned, Ron and what the end feel. Okay, because we're going to another protein one now, so --

Full Panel Meeting

DR. BELSITO: Okay. So plant-derived proteins. We're there?

DR. BERGFELD: Yes.

DR. BELSITO: Okay.

DR. BERGFELD: Please, proceed.

DR. BELSITO: At the December meeting, we determined that the data were sufficient for 18 of the 19 plant-derived proteins and peptides and concluding that these ingredients were safe as used in the present practice of use and concentration. We thought that the data for hydrolyzed maple sycamore protein were insufficient and we wanted method of manufacture and chemical composition, clarification on food safety status. It turns out there's not even a supplier for this ingredient, so we're not going to get any of that data. And we're just going to move ahead with our conclusion as final.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Second?

DR. MARKS: So this is a tentative report, the conclusion 18 are safe and one is insufficient?

DR. BELSITO: Right.

DR. MARKS: Second.

DR. BERGFELD: Any further discussion? Seeing none, call the question. All those in favor of this conclusion? Unanimous.

(The motion passed unanimously.)

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

Status: Draft Final Report for Panel Review
Release Date: August 18, 2017
Panel Meeting Date: September 11-12, 2017

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 (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.[1] 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 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.[2-8] 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.[9]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

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.[1] The FDA has defined the term "protein" to mean any α-amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.[10] 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.[1]

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.[11,12] 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.[13] 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.[14]

Hydrolyzed Cottonseed Protein

A supplier reported that a formulation containing 10% to 25% Hydrolyzed Cottonseed Protein (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.[14]

Hydrolyzed Lupine Protein

A supplier reported that Hydrolyzed Lupine Protein is comprised of >90% peptides (w/w) and <4% carbohydrates (w/w). [15]

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.[16] 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.[14]

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.[16]

Hydrolyzed Vegetable Protein

Monosodium glutamate (MSG) occurs naturally in ingredients such as hydrolyzed vegetable protein (generic) and some protein isolates.[17] Hydrolyzed vegetable protein may contain 10%-30% MSG.[18]

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.[14] 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.[19] 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.[20]

Hydrolyzed Hazelnut Protein

A supplier reported that Hydrolyzed Hazelnut Protein has less than 20 ppm heavy metals and less than 2 ppm arsenic.[21]

Hydrolyzed Lupine Protein

A supplier reported that Hydrolyzed Lupine Protein has <0.042 µg/kg benzo[a]pyrene.[15] 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.[20] 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.[16] 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, chlorpyriphos 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.[22]

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%).[16]

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).[23,24] 3-MCPD is formed from the reaction of triglycerides in the vegetable protein and hydrochloric acid.[25] These are Group 2B compounds (possibly carcinogenic to humans) according to the International Agency for Research on Cancer (IARC).[26] 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.[27]

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).[28] 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 Council survey indicate Hydrolyzed Potato Protein has a maximum concentration of use of 2.4% in nighttime skin care products.[29] Hydrolyzed Hazelnut Protein and Hydrolyzed Lupine Protein have maximum use concentrations of 0.99% in body and hand skin care preparations.[29,30] 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%[30] and Hydrolyzed Vegetable Protein is used in eye lotions at up to 0.3%.[29] 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% and Hydrolyzed Vegetable Protein was reported to be used in a face powder (concentration of use not reported). 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.[31-34] 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.[31,33] 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.[35-37]

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.[38]

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%.[18,25] 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.[39] 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.[40] 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.[41] 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.[16,22,42,43] 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.[44] 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 is 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. A review article reports that the prevalence of “probable” tree nut allergy in the population ranges from 0.05% to 4.9%, with the prevalence of allergies to specific tree nuts varying among the main regions where cases were reported (i.e., Europe, the United States, and the United Kingdom).[45] Walnut and cashew allergies are the most common tree nut allergies in the United Sates, while hazelnut and almond and walnut are the most common tree nut allergies in Europe and the United Kingdom, respectively.

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.[46] 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.[47] 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.[48] 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.[15,16,19-22,49-52] 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**.[15,16,19-22,53-55] 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 inTable 8.[15,19-21] 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.[15,16,19-22,56-59] 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).[18] 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.

Relevant to the ingredient, Lupinus Albus Protein, 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.

Relevant to the ingredient, Hydrolyzed Hemp Seed Protein, 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.

Relevant to the ingredients, Hydrolyzed Brazil Nut Protein, Hydrolyzed Hazelnut Protein, and Hydrolyzed Sweet Almond Protein, 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, which is relevant to the ingredients Hydrolyzed Lupine Protein, Hydrolyzed Pea Protein, Lupinus Albus Protein, and Pisum Sativum (Pea) Protein.

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.[1] (Italicized text below represents additions made by CIR).

Ingredient CAS No.	Definition	Function
Hydrolyzed Amaranth Protein	Hydrolyzed Amaranth Protein is the *partial* 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 *partial* 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 *partial* 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 *partial* 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 *partial* 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 *partial* hydrolysate of extensin protein derived by acid, enzyme or other method of hydrolysis. *Wherein, extensins are defined as wall-located, basic, hydroxyproline rich structural glycoproteins with alternating hydrophilic and hydrophobic motifs.*[60]	Hair conditioning Agent; Skin-Conditioning Agent - Misc.
Hydrolyzed Hazelnut Protein	Hydrolyzed Hazelnut Protein is the *partial* 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 *partial* 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 *partial* 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 *partial* 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 *partial* hydrolysate of the protein derived from the maple sycamore tree, *Acer pseudoplatanus*, 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 *partial* 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 *partial* 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 *partial* 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 *partial* 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 *partial* 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 *partial* hydrolysate of Zein derived by acid, enzyme or other method of hydrolysis. *Wherein, Zein is an alcohol-soluble protein obtained from corn, Zea mays.*	Hair Conditioning Agent; Skin-Conditioning Agent-Misc.
Lupinus Albus Protein	Lupinus Albus Protein is the protein derived from the seeds of *Lupinus albus.*	Skin-Conditioning Agents – Emollient; Skin-Conditioning Agents – Misc.
Pisum Sativum (Pea) Protein	Pisum Sativum (Pea) Protein is the protein isolated from *Pisum sativum.*	Skin-Conditioning Agents – Misc.

Table 2. Reported molecular weights of some plant-derived hydrolyzed proteins

Ingredients	Value (Da)	Reference
Hydrolyzed Amaranth Protein	~1500	61
Hydrolyzed Avocado Protein	<500 (20%-50%); 500-1000 (50%-75%); 1000-3500 (20%); >3500 (5%)	19,20
Hydrolyzed Brazil Nut Protein	~150; 1000	14,62
Hydrolyzed Cottonseed Protein	1700	14
Hydrolyzed Hazelnut Protein	<300 (~23%); 300-510 (~22%); 510-1000 (~34%); 1000-2990 (~19%); 2990-5020 (~1.4%); >5020 (0.16%)	21
Hydrolyzed Lupine Protein	<500 (<25%); 500-1000 (50%-75%); 1000-3500 (<25%); >3500 (<10%)	15,20
Hydrolyzed Pea Protein	500 (acid, alkaline, and/or enzyme hydrolysis); 1500 (enzyme hydrolysis)	14,22
Hydrolyzed Sweet Almond Protein	~3000	62
Hydrolyzed Vegetable Protein	~1000	63
Hydrolyzed Vegetable Protein (potato source)	750 (enzyme hydrolysis); 100,000 (alkaline hydrolysis)	14

Table 3. Method of manufacturing

Ingredient	Procedure	Reference
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	61
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).	19
Hydrolyzed Brazil Nut Protein	Prepared by acid hydrolysis	62
Hydrolyzed Brazil Nut Protein (concentration 10% -25%; MW=1000 Da)	Prepared by enzyme hydrolysis	14
Hydrolyzed Cottonseed Protein (concentration 10%-25%; MW=1700 Da)	Prepared by enzyme hydrolysis	14
Hydrolyzed Hazelnut Protein	Prepared by enzyme hydrolysis	21
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.	15
Hydrolyzed Pea Protein (concentration 10%-25%; MW=1500 Da)	Prepared by enzyme hydrolysis	14
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.	22
Hydrolyzed Sweet Almond Protein	Prepared by enzyme hydrolysis	62
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 *Dictionary* name Hydrolyzed Vegetable Protein.	64
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.	25
Hydrolyzed Vegetable Protein (source: potato; concentration 10%-25%; MW=750 Da)	Prepared by enzyme hydrolysis	14
Hydrolyzed Vegetable Protein (source: potato; concentration 7.5%-15%; MW=100,000 Da)	Prepared by alkaline hydrolysis	14

Table 4. Frequency and concentration of use according to duration and type of exposure for plant-derived hydrolyzed proteins.[28-30]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Hydrolyzed Amaranth Protein		**Hydrolyzed Barley Protein**		**Hydrolyzed Brazil Nut Protein**		**Hydrolyzed Cottonseed Protein**	
Totals[†]	**6**	**0.011**	**14**	**0.002**	**16**	**0.000026-0.023**	**37**	**NR**
Duration of Use								
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
Exposure Type								
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[a]	0.011	8[a]	NR	5[a]	0.000026; 0.016[a]	7; 21[a]; 4[b]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	4[b]	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

	Hydrolyzed Extensin		**Hydrolyzed Hazelnut Protein**		**Hydrolyzed Hemp Seed Protein**		**Hydrolyzed Jojoba Protein**	
Totals[†]	**33**	**0.01-0.13**	**24**	**0.25-0.99**	**NR**	**0.0002**	**18**	**0.001-0.025**
Duration of Use								
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
Exposure Type								
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[a]; 10[b]	NR	2[a]; 18[b]	0.25	NR	NR	3[a]; 1[b]	NR
Incidental Inhalation-Powder	10[b]	0.13[c]	18[b]	0.99[c]	NR	NR	1[b]	0.001-0.025[c]
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.[28-30]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Hydrolyzed Lupine Protein		**Hydrolyzed Pea Protein**		**Hydrolyzed Potato Protein**		**Hydrolyzed Sesame Protein**	
Totals[†]	**96**	**0.0001-0.99**	**18**	**0.001**	**12**	**0.75-2.4**	**NR**	**0.001**
Duration of Use								
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
Exposure Type								
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[a]; 19[b]	0.6[a]	8[s]; 9[b]	NR	9[a]; 2[b]	NR	NR	NR
Incidental Inhalation-Powder	19[b]	0.0001-0.99[c]	9[b]	0.001[c]	2[b]	0.75[c]	NR	0.001[c]
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

	Hydrolyzed Sweet Almond Protein[d]		**Hydrolyzed Vegetable Protein**		**Lupinus Albus Protein**		**Pisum Sativum (Pea) Protein**	
Totals[†]	**68**	**0.001-0.063**	**142**	**0.0004-0.3**	**NR**	**0.0025**	**NR**	**0.001-0.0025**
Duration of Use								
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
Exposure Type								
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[a]; 19[b]	NR	2; 41[a]; 8[b]	0.3[a]	NR	NR	NR	NR
Incidental Inhalation-Powder	19[b]	0.001-0.05[c]	1; 8[b]; 1[c]	0.0011[c]	NR	NR	NR	0.001[c]
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.

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

[a.] It is possible 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.] Two uses for other skin care preparations were categorized under Hydrolyzed Almond Protein in the VCRP.

Table 5. In vitro genotoxicity studies

Ingredient	Concentration/Dose	Study Protocol	Results	Reference
Hydrolyzed Lupine Protein	up to 26.7%	Ames test; no further details provided	Not mutagenic or pro-mutagenic	16
Hydrolyzed Pea Protein	19% in a solution of 75% water and 4.5% sodium chloride; 50-5000 µg/plate	Ames test in *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and *Escherichia coli* WP2uvrA; with and without S9 metabolic activation	Not mutagenic	42
Hydrolyzed Pea Protein	25% solution in water; MW = 500 Da; 50-5000 µg/plate	Ames test in *S. typhimurium* TA1535, TA1537, TA98, TA100 and *E. coli* WP2uvrA; with and without S9 metabolic activation	Not mutagenic	22
Hydrolyzed Sweet Almond Protein	2.3% to 3.3%	Ames test; no further details provided	Not mutagenic or pro-mutagenic	16
Hydrolyzed Vegetable Protein (source: potato)	10.9% in a solution of 87% water	Ames test in *S. typhimurium* TA1535, TA1537, TA98, TA100 and *E. coli* WP2uvrA; with and without S9 metabolic activation	Not mutagenic	43

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

Ingredient	Concentration	Method	Results	Reference
		In Vitro		
Hydrolyzed Amaranth Protein	20% in water	EpiDerm MTT Viability assay	Non-irritating	49
Hydrolyzed Avocado Protein	20%	3D human skin model (MTT + IL1α) performed under OECD draft guidelines and ECVAM protocol	Non-irritating	19,20
Hydrolyzed Lupine Protein	100%	3D human skin model (MTT + IL1α) performed under OECD draft guidelines and ECVAM protocol	Non-irritating	15,20
Hydrolyzed Pea Protein	10% to 25% in a solution of > 50% water	Episkin reconstructed human epidermis model	Predicted to be non-irritating	51
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	52
Hydrolyzed Vegetable Protein (source not reported)	100% (MW = 750 Da)	EpiDerm skin model	Non-irritating	50
		Animal		
Hydrolyzed Hazelnut Protein	100%	Dermal irritation study performed under OECD Guideline 404; no further details provided	Non-irritating	21
Hydrolyzed Lupine Protein	4.5% to 5.5%	Cutaneous tolerance test in rabbits; no further details provided	Non-irritating	16
Hydrolyzed Sweet Almond Protein	2.3% to 3.3%	Cutaneous tolerance test in rabbits; no further details provided	Non-irritating	16
		Human		
Hydrolyzed Avocado Protein	20%	Human patch test with 10 volunteers; no further details provided	Very well tolerated	19,20
Hydrolyzed Lupine Protein	0.005%	Human patch test with 20 volunteers; no further details provided	Well tolerated	15,20
Hydrolyzed Lupine Protein	1.92% to 2.67%	Acute skin tolerance patch test; no further details provided	Not irritating	16
Hydrolyzed Lupine Protein	4.5% to 6%	Acute skin tolerance patch test; no further details provided	Not irritating	16
Hydrolyzed Pea Protein	25% solution in water (MW = 500 Da)	24 hour human patch test with 20 volunteers; Finn chambers (occlusive)	Not irritating	22

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

Ingredient	Concentration	Method	Results	Reference
		Animal		
Hydrolyzed Avocado Protein	12.5%	LLNA	Non-sensitizing	19,20
Hydrolyzed Hazelnut Protein	100%	Guinea pig dermal sensitization study performed according to OECD guideline 406	Non-sensitizing	21
Hydrolyzed Hazelnut Protein	5%	Sensitization study using the Marzulli-Maibach method	Non-irritating and non-sensitizing	21
Hydrolyzed Lupine Protein	25%	LLNA	Non-sensitizing	15,20
Hydrolyzed Lupine Protein	4.5% to 5.5%	Sensitization study in albino guinea pigs; no further details provided	Non-sensitizing	16
Hydrolyzed Sweet Almond Protein	2.3% to 3.3%	Sensitization study in albino guinea pigs; no further details provided	Very slight sensitizing agent	16
		Human		
Hydrolyzed Amaranth Protein	Tested as received	HRIPT with 108 subjects; semi-occlusive	No dermal irritation or sensitization	54
Hydrolyzed Avocado Protein	Not reported	HRIPT (Marzulli-Maibach method) in 50 subjects	Non-sensitizing	19
Hydrolyzed Lupine Protein	0.005%	HRIPT (Marzulli-Maibach method) in 100 subjects	Non-sensitizing	15,20
Hydrolyzed Lupine Protein	0.192% to 0.267%	HRIPT (Marzulli-Maibach method); no further details provided	No dermal irritation or sensitization	16
Hydrolyzed Lupine Protein	4.5% to 6%	HRIPT (Marzulli-Maibach method); no further details provided	No dermal irritation or sensitization	16
Hydrolyzed Pea Protein	25% solution in water; MW = 500 Da	HRIPT with 50 subjects; 0.2 ml test material on occlusive patch	Non-sensitizing	22
Hydrolyzed Potato Protein	1.5% in a face cream	HRIPT with 100 subjects; occlusive	No dermal irritation or sensitization	53
Hydrolyzed Potato Protein	2.4% in a night cream	HRIPT with 100 subjects; occlusive	No dermal irritation or sensitization	53
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.	55

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

Ingredient	Concentration	Method	Results	Reference
Hydrolyzed Avocado Protein	50%	3T3 Neural Red Uptake (NRU) method	Not phototoxic	19,20
Hydrolyzed Hazelnut Protein	Not reported	3T3 NRU method	Not phototoxic	21
Hydrolyzed Lupine Protein	100%	3T3 NRU method	Not phototoxic	15,20

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

Ingredient	Concentration	Method	Results	Reference
		In Vitro		
Hydrolyzed Amaranth Protein	20% dilutions	EpiOcular MTT viability irritation study	Non-irritating	56
Hydrolyzed Avocado Protein	20%	HET-CAM method	Moderately irritating	19,20
Hydrolyzed Avocado Protein	10%	BCOP ocular irritation study	Not severely irritating	19,20
Hydrolyzed Avocado Protein	20%	Neutral red release assay	Negligible cytotoxicity	19,20
Hydrolyzed Lupine Protein	0.005%	HET-CAM method	Weakly irritating	15,20
Hydrolyzed Lupine Protein	100%	BCOP ocular irritation study	Weakly irritating	15,20
Hydrolyzed Lupine Protein	0.005%	Neutral red release assay	Negligible cytotoxicity	15,20
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	59
Hydrolyzed Pea Protein	1.25%	HET-CAM method	Predicted to be non-irritating	22
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	58
Hydrolyzed Vegetable Protein (source not reported)	25%, 50%, and 100% (MW = 750 Da)	HET-CAM method	Practically no irritation potential	57
		Animal		
Hydrolyzed Hazelnut Protein	Neat	Ocular irritation study performed under OECD guideline 405; no further details provided	Non-irritating	21
Hydrolyzed Lupine Protein	4.5% to 5.5%	Ocular tolerance test in rabbits; no further details provided	Very slight irritant	16
Hydrolyzed Sweet Almond Protein	2.3% to 3.3%	Ocular tolerance test in rabbits; no further details provided	Very slight irritant	16

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2017 FDA VCRP RAW DATA

05B - Hair Spray (aerosol fixatives)	HYDROLYZED AMARANTH PROTEIN	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROLYZED AMARANTH PROTEIN	1
12F - Moisturizing	HYDROLYZED AMARANTH PROTEIN	1
12H - Paste Masks (mud packs)	HYDROLYZED AMARANTH PROTEIN	2
01C - Other Baby Products	HYDROLYZED BARLEY PROTEIN	1
05A - Hair Conditioner	HYDROLYZED BARLEY PROTEIN	1
05F - Shampoos (non-coloring)	HYDROLYZED BARLEY PROTEIN	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROLYZED BARLEY PROTEIN	8
05I - Other Hair Preparations	HYDROLYZED BARLEY PROTEIN	2
05A - Hair Conditioner	HYDROLYZED BRAZIL NUT PROTEIN	6
05F - Shampoos (non-coloring)	HYDROLYZED BRAZIL NUT PROTEIN	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROLYZED BRAZIL NUT PROTEIN	5
05I - Other Hair Preparations	HYDROLYZED BRAZIL NUT PROTEIN	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	HYDROLYZED BRAZIL NUT PROTEIN	3
04E - Other Fragrance Preparation	HYDROLYZED COTTONSEED PROTEIN	7
10A - Bath Soaps and Detergents	HYDROLYZED COTTONSEED PROTEIN	1
10E - Other Personal Cleanliness Products	HYDROLYZED COTTONSEED PROTEIN	2
12A - Cleansing	HYDROLYZED COTTONSEED PROTEIN	2
12D - Body and Hand (exc shave)	HYDROLYZED COTTONSEED PROTEIN	4
12F - Moisturizing	HYDROLYZED COTTONSEED PROTEIN	21
03D - Eye Lotion	HYDROLYZED EXTENSIN	2
05A - Hair Conditioner	HYDROLYZED EXTENSIN	1
05C - Hair Straighteners	HYDROLYZED EXTENSIN	2
07C - Foundations	HYDROLYZED EXTENSIN	1
07I - Other Makeup Preparations	HYDROLYZED EXTENSIN	1
11G - Other Shaving Preparation Products	HYDROLYZED EXTENSIN	1
12C - Face and Neck (exc shave)	HYDROLYZED EXTENSIN	7
12D - Body and Hand (exc shave)	HYDROLYZED EXTENSIN	3
12F - Moisturizing	HYDROLYZED EXTENSIN	9
12G - Night	HYDROLYZED EXTENSIN	3
12H - Paste Masks (mud packs)	HYDROLYZED EXTENSIN	1
12I - Skin Fresheners	HYDROLYZED EXTENSIN	1
12J - Other Skin Care Preps	HYDROLYZED EXTENSIN	1
03D - Eye Lotion	HYDROLYZED HAZELNUT PROTEIN	2
03G - Other Eye Makeup Preparations	HYDROLYZED HAZELNUT PROTEIN	1
12C - Face and Neck (exc shave)	HYDROLYZED HAZELNUT PROTEIN	13

12D - Body and Hand (exc shave)	HYDROLYZED HAZELNUT PROTEIN	5
12F - Moisturizing	HYDROLYZED HAZELNUT PROTEIN	2
12H - Paste Masks (mud packs)	HYDROLYZED HAZELNUT PROTEIN	1
03F - Mascara	HYDROLYZED JOJOBA PROTEIN	1
05A - Hair Conditioner	HYDROLYZED JOJOBA PROTEIN	6
05F - Shampoos (non-coloring)	HYDROLYZED JOJOBA PROTEIN	3
10A - Bath Soaps and Detergents	HYDROLYZED JOJOBA PROTEIN	1
10E - Other Personal Cleanliness Products	HYDROLYZED JOJOBA PROTEIN	1
11G - Other Shaving Preparation Products	HYDROLYZED JOJOBA PROTEIN	1
12C - Face and Neck (exc shave)	HYDROLYZED JOJOBA PROTEIN	1
12F - Moisturizing	HYDROLYZED JOJOBA PROTEIN	3
12H - Paste Masks (mud packs)	HYDROLYZED JOJOBA PROTEIN	1
03D - Eye Lotion	HYDROLYZED LUPINE PROTEIN	13
03F - Mascara	HYDROLYZED LUPINE PROTEIN	6
05A - Hair Conditioner	HYDROLYZED LUPINE PROTEIN	1
05F - Shampoos (non-coloring)	HYDROLYZED LUPINE PROTEIN	2
05I - Other Hair Preparations	HYDROLYZED LUPINE PROTEIN	1
06D - Hair Shampoos (coloring)	HYDROLYZED LUPINE PROTEIN	7
07C - Foundations	HYDROLYZED LUPINE PROTEIN	1
08C - Nail Creams and Lotions	HYDROLYZED LUPINE PROTEIN	1
12C - Face and Neck (exc shave)	HYDROLYZED LUPINE PROTEIN	14
12D - Body and Hand (exc shave)	HYDROLYZED LUPINE PROTEIN	5
12F - Moisturizing	HYDROLYZED LUPINE PROTEIN	23
12G - Night	HYDROLYZED LUPINE PROTEIN	10
12H - Paste Masks (mud packs)	HYDROLYZED LUPINE PROTEIN	2
12I - Skin Fresheners	HYDROLYZED LUPINE PROTEIN	1
12J - Other Skin Care Preps	HYDROLYZED LUPINE PROTEIN	9
03D - Eye Lotion	HYDROLYZED PEA PROTEIN	1
12C - Face and Neck (exc shave)	HYDROLYZED PEA PROTEIN	9
12F - Moisturizing	HYDROLYZED PEA PROTEIN	7
12G - Night	HYDROLYZED PEA PROTEIN	1
12C - Face and Neck (exc shave)	HYDROLYZED POTATO PROTEIN	2
12F - Moisturizing	HYDROLYZED POTATO PROTEIN	6
12G - Night	HYDROLYZED POTATO PROTEIN	3
12J - Other Skin Care Preps	HYDROLYZED POTATO PROTEIN	1
03E - Eye Makeup Remover	HYDROLYZED SWEET ALMOND PROTEIN	1
03F - Mascara	HYDROLYZED SWEET ALMOND PROTEIN	7
03G - Other Eye Makeup Preparations	HYDROLYZED SWEET ALMOND PROTEIN	2
05A - Hair Conditioner	HYDROLYZED SWEET ALMOND PROTEIN	12
05E - Rinses (non-coloring)	HYDROLYZED SWEET ALMOND PROTEIN	1
05F - Shampoos (non-coloring)	HYDROLYZED SWEET ALMOND PROTEIN	1
05G - Tonics, Dressings, and Other	HYDROLYZED SWEET ALMOND PROTEIN	2

Hair Grooming Aids		
05I - Other Hair Preparations	HYDROLYZED SWEET ALMOND PROTEIN	5
06H - Other Hair Coloring Preparation	HYDROLYZED SWEET ALMOND PROTEIN	1
10A - Bath Soaps and Detergents	HYDROLYZED SWEET ALMOND PROTEIN	2
10E - Other Personal Cleanliness Products	HYDROLYZED SWEET ALMOND PROTEIN	1
12A - Cleansing	HYDROLYZED SWEET ALMOND PROTEIN	2
12C - Face and Neck (exc shave)	HYDROLYZED SWEET ALMOND PROTEIN	17
12D - Body and Hand (exc shave)	HYDROLYZED SWEET ALMOND PROTEIN	2
12F - Moisturizing	HYDROLYZED SWEET ALMOND PROTEIN	4
12G - Night	HYDROLYZED SWEET ALMOND PROTEIN	1
12H - Paste Masks (mud packs)	HYDROLYZED SWEET ALMOND PROTEIN	1
12J - Other Skin Care Preps	HYDROLYZED SWEET ALMOND PROTEIN	3
13C - Other Suntan Preparations	HYDROLYZED SWEET ALMOND PROTEIN	1
01B - Baby Lotions, Oils, Powders, and Creams	HYDROLYZED VEGETABLE PROTEIN	1
01C - Other Baby Products	HYDROLYZED VEGETABLE PROTEIN	1
03D - Eye Lotion	HYDROLYZED VEGETABLE PROTEIN	2
03G - Other Eye Makeup Preparations	HYDROLYZED VEGETABLE PROTEIN	3
05A - Hair Conditioner	HYDROLYZED VEGETABLE PROTEIN	17
05B - Hair Spray (aerosol fixatives)	HYDROLYZED VEGETABLE PROTEIN	2
05F - Shampoos (non-coloring)	HYDROLYZED VEGETABLE PROTEIN	14
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROLYZED VEGETABLE PROTEIN	17
05I - Other Hair Preparations	HYDROLYZED VEGETABLE PROTEIN	10
06C - Hair Rinses (coloring)	HYDROLYZED VEGETABLE PROTEIN	22
06D - Hair Shampoos (coloring)	HYDROLYZED VEGETABLE PROTEIN	1
07B - Face Powders	HYDROLYZED VEGETABLE PROTEIN	1
07C - Foundations	HYDROLYZED VEGETABLE PROTEIN	3
12A - Cleansing	HYDROLYZED VEGETABLE PROTEIN	9
12C - Face and Neck (exc shave)	HYDROLYZED VEGETABLE PROTEIN	5
12D - Body and Hand (exc shave)	HYDROLYZED VEGETABLE PROTEIN	3
12F - Moisturizing	HYDROLYZED VEGETABLE PROTEIN	15
12G - Night	HYDROLYZED VEGETABLE PROTEIN	6
12H - Paste Masks (mud packs)	HYDROLYZED VEGETABLE PROTEIN	7
12I - Skin Fresheners	HYDROLYZED VEGETABLE PROTEIN	1
13B - Indoor Tanning Preparations	HYDROLYZED VEGETABLE PROTEIN	1
13C - Other Suntan Preparations	HYDROLYZED VEGETABLE PROTEIN	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: June 6, 2017

SUBJECT: Draft Tentative Report: Safety Assessment of Plant-Derived Proteins and Peptides as Used in Cosmetics (draft prepared for the June 12-13, 2017 CIR Expert Panel Meeting)

Definition - The VCRP (reference 10 which is the 2016 data [reference 31 is the 2017 data]) does not seem to be an appropriate reference for the statement that protein hydrolysates are used as conditioning agents.

Impurities, Hydrolyzed Avocado Protein, Hydrolyzed Lupine Protein - Rather than stating that "Data supplied by the Personal Care Products Council...", it would be more consistent to state that this information came from a supplier. The references indicate that the information came through the Personal Care Products Council.

Cosmetic Use - The Council survey had only one use concentration reported for Hydrolyzed Hemp Seed Protein, 0.0002% in hair conditioners. When discussing this concentration, it would be helpful to be specific and state the product category.

Ocular Irritation, Summary - Please state the concentration of Hydrolyzed Avocado Protein used in the BCOP assay (10%). It is not appropriate to say that the results for Hydrolyzed Avocado Protein were "mixed" with a result of moderate irritation in the HET-CAM and "no severe irritation" in a BCOP. Based on these results, it would be appropriate to state that the *in vitro* studies predicted Hydrolyzed Avocado Protein at the concentrations tested (20% HET-CAM; 10% BCOP) may be an eye irritant.

Summary - Concentrations for the *in vitro* phototoxicity studies were stated for Hydrolyzed Avocado Protein (50%) and Hydrolyzed Lupine Protein (100%). Therefore, in the summary it is not correct to state: "The concentrations of these test materials were not reported."

Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D., Interim Director
COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: June 21, 2017

SUBJECT: Tentative Report: Safety Assessment of Plant-Derived Proteins and Peptides as Used in Cosmetics

Composition, Hydrolyzed Cottonseed Protein - The word "Protein" needs to be added after "Hydrolyzed Cottonseed"

Type 1 Hypersensitivity - It is not clear why there are details concerning Type 1 hypersensitivity to lupine proteins but no details concerning tree nut allergy. The addition of some general information about the prevalence of tree nut allergy, such as information from the following review paper (abstract attached) would be helpful. The abstract of this paper indicates that tree nut allergy prevalence ranged from 0.05 to 4.9%, with hazelnut the most common tree nut allergy in Europe, walnut and cashew in the United States and Brazil nut, almond and walnut the most common allergies in the UK.

McWilliam V, Kopin J, Lodge C, et al. 2015. The prevalence of tree nut allergy: A systematic review. *Curr Allergy Asthma Rep* 15(9): 54.

Conclusion - Since no uses of Hydrolyzed Maple Sycamore Protein were reported, it should also be marked with as asterisk in the Conclusion.

PubMed ▾

Format: Abstract

Full text links

SpringerLink FULL-TEXT ARTICLE

Curr Allergy Asthma Rep. 2015 Sep;15(9):54. doi: 10.1007/s11882-015-0555-8.

The Prevalence of Tree Nut Allergy: A Systematic Review.

McWilliam V[1], Koplin J, Lodge C, Tang M, Dharmage S, Allen K.

Author information

Abstract

Tree nuts are one of the most common foods causing acute allergic reactions and nearly all **tree** nuts have been associated with fatal allergic reactions. Despite their clinical importance, **tree nut allergy** epidemiology remains understudied and the prevalence of **tree nut allergy** in different regions of the world has not yet been well characterised. We aimed to systematically **review** the population prevalence of **tree nut allergy** in children and adults. We searched three electronic databases (OVID MEDLINE, EMBASE and PubMed) from January 1996 to December 2014. Eligible studies were categorised by age, region and method of assessment of **tree nut allergy**. Of the 36 studies identified most were in children (n = 24) and from Europe (n = 18), UK (n = 8) or USA (n = 5). Challenge-confirmed IgE-mediated **tree nut allergy** prevalence was less than 2 % (although only seven studies used this gold standard) while probable **tree nut allergy** prevalence ranged from 0.05 to 4.9 %. Prevalence estimates that included oral **allergy** syndrome (OAS) reactions to **tree nut** were significantly higher (8-11.4 %) and were predominantly from Europe. Prevalence of individual **tree nut** allergies varied significantly by region with hazelnut the most common **tree nut allergy** in Europe, walnut and cashew in the USA and Brazil **nut**, almond and walnut most commonly reported in the UK. Monitoring time trends of **tree nut allergy** prevalence (both overall and by individual nuts) as well as the prevalence of OAS should be considered given the context of the overall recent rise in IgE-mediated food **allergy** prevalence in the developed world.

PMID: 26233427 DOI: 10.1007/s11882-015-0555-8

[Indexed for MEDLINE]

Publication types, MeSH terms

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