Safety Assessment of Ectodermal-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 Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Scientific Analyst/Writer.

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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 Ectodermal-Derived Proteins and Peptides

Enclosed is the Draft Final Report of the Safety Assessment of Ectodermal-Derived Proteins and Peptides as Used in Cosmetics. (It is identified as *tsupep092017rep* in the pdf document). This report was previously named the Safety Assessment of Tissue-Derived Proteins and Peptides.

At the June 2017 meeting, the Panel issued a tentative report with the conclusion that these 19 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Since the June meeting, CIR staff have received updated concentration of use data on Soluble Collagen and the results of the concentration of use survey on Atelocollagen (identified as *tsupep092017data1* through *tsupep092017data4* in this package). The maximum leave-on concentration for Atelocollagen is 0.005% in skin care products. The use table (Table 5) has been updated accordingly and notable changes are highlighted.

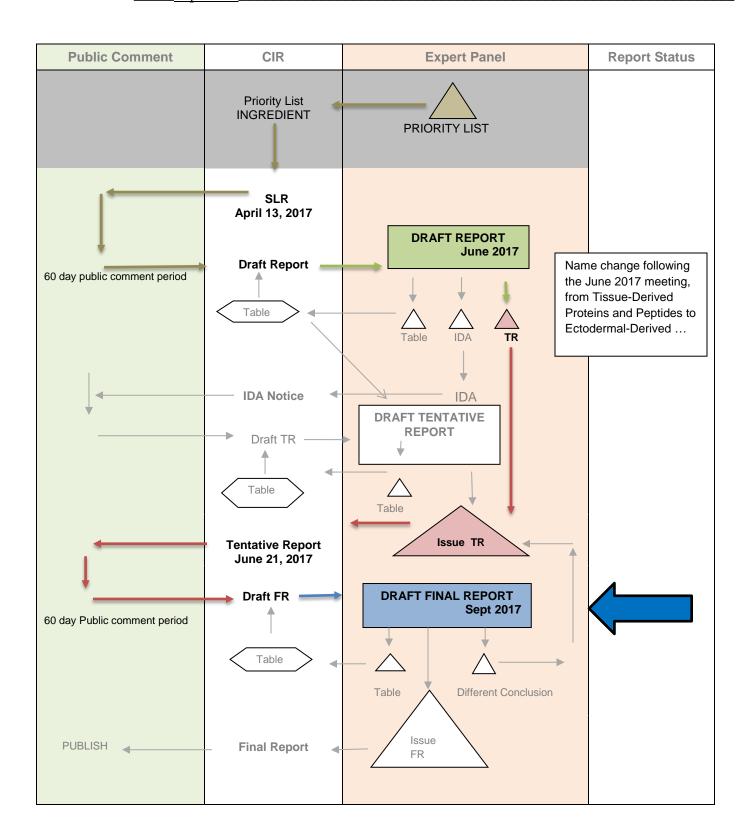
The Council provided comments on the tentative report. Included in those comments was a recommendation to change the name of the report to the "Safety Assessment of Skin and Connective Tissue-Derived Proteins and Peptides." Also, inclusion of information from the Hydrolyzed Wheat Protein report regarding molecular weight size and Type 1 sensitivity reactions was suggested. The CIR Science and Support committee have also suggested incorporating information this information to the discussion of the report. CIR staff have included limited relevant information and supporting discussion language from the Hydrolyzed Wheat Protein report for the Panel's review (highlighted in the text with |brackets|), but have refrained from making significant changes to the discussion until the Panel has the opportunity to confer at the meeting. The Panel will need to determine if these additions are appropriate for this report and if further language is needed. Council comments that were received on the draft report prior to the June meeting and the Council and CIR Science and Support committee comments on the tentative report are identified as *tsupep092017pcpc1* through *tsupep092017pcpc3*, respectively.

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

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY ____Ectodermal-Derived Proteins and Peptides _____

MEETING _____Sept 2017_____



Tissue-Derived Proteins and Peptides History

April 2017 – Scientific Literature Review announced.

June 2017 - The Panel issued a tentative report with the conclusion that the 19 ectodermal-derived proteins and peptides are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

These proteins and peptides, which are similar to the other proteins and peptides reviewed by the Panel, 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. The Panel also found that the earlier assessments of Hydrolyzed Collagen supported the safety of these ingredients in cosmetic products. The Panel noted a lack of systemic toxicity data (i.e. reproductive and developmental toxicity, genotoxicity, and carcinogenicity data). However, they did not believe that these proteins and peptides would cause adverse systemic effects in the general population.

The Panel noted that fish proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. Case reports suggest that individuals with fish allergies may react to topical exposures of fish-derived cosmetic ingredients. The Panel expressed concern that sensitized individuals would not easily recognize cosmetic products containing fish-derived collagen based on the current naming conventions used in the ingredient lists on product labels (e.g. Collagen and Hydrolyzed Collagen may be sourced from fish, though "fish" is not in the ingredient name). The Panel strongly urged manufacturers to place a warning on the label of products that may contain fish-derived ingredients so that sensitive individuals may avoid exposure.

Tissue-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	Toxicokinetics
Ammonium Hydrolyzed Collagen	X																
Atelocollagen	X															X	
Calcium Hydrolyzed Collagen																	
Collagen	X	X	X	X	X	X	X										
Elastin	X	X		X	X											X	
Fibronectin	X	X	X														
Gelatin	X	X		X	X		X				X						X
Hydrolyzed Actin	X		X														
Hydrolyzed Collagen	X	X	X	X	X	X	X	X				X	X	X	X	X	
Hydrolyzed Collagen Extract																	
Hydrolyzed Elastin	X		X	X	X							X	X	X			
Hydrolyzed Fibronectin	X																
Hydrolyzed Gelatin											X						
Hydrolyzed Reticulin	X																
Hydrolyzed Spongin																	
MEA-Hydrolyzed Collagen	X																
Soluble Collagen	X		X	X	X							X		X			
Soluble Elastin		X		X													
Zinc Hydrolyzed Collagen																	

[&]quot;X" indicates that data were available in the category for that ingredient.

<u>Tissue-Derived Proteins and Peptides</u> (prepared by Christina Burnett)

Ingredient	CAS#	InfoB	SciFin	PubMed	ToxNet	FDA	EU	ЕСНА	SIDS	ECETOC	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Ammonium Hydrolyzed Collagen		√ √	√ √	13	0	No	No	No	512.5		No	1,125	1,122	,,,,,,,	No	1,10,511	No	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
Atelocollagen	55963-88-7	1		492	8274	No									No		No	
Calcium Hydrolyzed Collagen	No	1	√	29	0	No	No	No			No				No		No	
Collagen	9007-34-5	$\sqrt{}$	√	192,707	8274	No	No	No			No				No		No	
Elastin	9007-58-3	$\sqrt{}$	V	12,315	792	No	No	No			No				No		No	
Fibronectin	98725-78-1	$\sqrt{}$	√	38,849	2180	No	No	No			No				No		No	
Gelatin	9000-70-8	1	√	25,412	1730	21CFR182.70; 21CFR349-12; 21CFR522.1020	No	No			Tier 1				Yes		Yes	
Hydrolyzed Actin	73049-73-7 (generic to animal peptones)	V	$\sqrt{}$	156	8	No	No	No			No				No		No	
Hydrolyzed Collagen (limited from 2003- 2017)	73049-73-7 (generic to animal peptones); 92113-31-0	1	V	190	0	No	No	No			No				No		No	
Hydrolyzed Collagen Extract	No	V	V	27	0	No	No	No			No				No		No	
Hydrolyzed Elastin	73049-73-7 (generic to animal peptones); 100085-10-7; 91080- 18-1	V	V	86	0	No	No	No			No				No		No	
Hydrolyzed Fibronectin	73049-73-7 (generic to animal peptones); 100085-35-6	V	V	69	0	No	No	No			No				No		No	
Hydrolyzed Gelatin	68410-45-7 (specific to enzymatic digest product)	1	V	249	9	21CFR184.1553	No	No			No				No		No	
Hydrolyzed Reticulin	73049-73-7 (generic to animal peptones); 99924-37-5	V	V	0	0	No	No	No			No				No		No	
Hydrolyzed Spongin	No	V	V	0	0	No	No	No			No				No		No	
MEA-Hydrolyzed Collagen	No	V	V	0	0	No	Annex III/61	No			No				No		No	
Soluble Collagen	No	V	V	5003	218	No	No	No			No				No		No	
Soluble Elastin	No	V	V	617	28	No	No	No			No				No		No	
Zinc Hydrolyzed Collagen	No	V	1	17	0	No	Annex III/24	No			No				No		No	

Search Strategy

3/8/17 – all ingredients searched by INCI name and CAS-No, when available. Refinements and those results are listed below. Search updated July 2017.

ToxLine (excluding PubMed) – hits with details

Atelocollagen = 8274 hits; refined to "cosmetic atelocollagen" = 63 hits/2 useful (same as Collagen below)

Collagen = 8274 hits; refined to "cosmetic collagen" = 63 hits/2 useful (same as Atelocollagen above)

Elastin = 792 hits: refined to "cosmetic elastin" = 10 hits/3 useful

Fibronectin = 2180 hits; refined to "cosmetic fibronectin" = 3 hits/1 useful

Gelatin = 1730 hits; refined to "cosmetic gelatin" = 10 hits/0 useful

Hydrolyzed Actin = 8 hits/0 useful

Hydrolyzed Gelatin = 9 hits/1 useful

Soluble collagen = 218; revised to "cosmetic soluble collagen" = 4 hits/1 useful

Soluble elastin = 28 hits/1 useful

PubMed – hits with details

Ammonium hydrolyzed collagen = 13 hits/0 useful

Atelocollagen = 492 hits; revised to "cosmetic atelocollagen = 4 hits/0 useful

Calcium hydrolyzed collagen = 29 hits/1 useful

Collagen = 192,707 hits; revised to "cosmetic collagen" = 1386 hits; revised to "cosmetic collagen toxicity" = 32 hits OR "cosmetic collagen irritation" = 19 hits/7 useful

Elastin = 12,315 hits; revised to "cosmetic elastin" = 146 hits/1 useful

Fibronectin = 38,849 hits; revised to "cosmetic fibronectin" = 75 hits/0 useful

Gelatin = 25,412 hits; revised to "cosmetic gelatin" = 132 hits/4 useful

Hydrolyzed actin = 156 hits/0 useful

Hydrolyzed collagen (limited to 2003-2017) = 190 hits/5 useful

Hydrolyzed collagen extract = 27 hits/2 useful

Hydrolyzed elastin = 86 hits/1 useful

Hydrolyzed fibronectin = 69 hits/0 useful

Hydrolyzed gelatin = 249 hits/2 useful

Soluble collagen = 5003 hits; revised to "cosmetic soluble collagen" = 29 hits/4 useful

Soluble elastin = 617 hits; revised to "cosmetic soluble elastin" = 2 hits/0 useful

Zinc hydrolyzed collagein = 17 hits/0 useful

LINKS

online database (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase wINCI (to cite publicly) - http://webdictionary.personalcarecouncil.org

ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder

PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed;

Also search: PubMed Dietary Supplement Subset https://ods.od.nih.gov/Research/PubMed Dietary Supplement Subset.aspx and https://ods.od.nih.gov/Health Information/IBIDS.aspx

Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse (CFR); then,

list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,

http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);

http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);

http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);

http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);

http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);

http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);

http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions http://ec.europa.eu/growth/tools-databases/cosing/

and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm

 $ECHA \ (European \ Chemicals \ Agency-REACH \ dossiers) - \underline{http://echa.europa.eu/information-on-chemicals; jsessionid} = \underline{A978100B4E4CC39C78C93A851EB3E3C7.live1}$

IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search

OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org

 $HPVIS \ (EPA\ High-Production\ Volume\ Info\ Systems) - \underline{https://ofmext.epa.gov/hpvis/HPVISlogon}$

NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

NTIS (National Technical Information Service) - http://www.ntis.gov/

NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/

WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical report series/en/

FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/

NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/

FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

Web – perform general search; may find technical data sheets, published reports, etc

Note: ChemPortal can be used to search several of the above databases simultaneously - http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en

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

Dr. Belsito's Team

DR. BELSITO: Okay. Moving on to the next the tissue derived proteins. I guess before we start this, Dan and I had a little side bar conversation at the check in process and he was about to review these and I said that I didn't like the title so I would like these retitled connective tissue because they're not just tissue, they're all connective tissue. Now I have to credit to Dan for coming up as usual with the correct verbiage there.

DR. KLAASSEN: I had the exact same idea.

DR. LIEBLER: While the person at the desk was asking me if I want one or two room keys.

DR. BELSITO: When you said three I wondered why. Yes. Otherwise, I'm not sure I had a lot of comment. So wave two data was all on hydrolyzed collagen and elastin. We got quite a bit of it.

DR. LIEBLER: One thing, Christina, I thought that would be helpful under method of manufacturing PDF 12, I think, you know, this zeros right in on length, typical length distributions of the hydrolyzed proteins. And that's relevant but I actually thought it would be useful to bring in some of the information on the initial steps in the extraction just so readers can get an idea of where these come from between raw bulk material and the ingredients as provided to formulators of cosmetic ingredients. And it looks like you have got that in the wave two data where you have got, you know, some flow charts and information on the ingredients. Maybe you could excerpt some of that just to give a representative look at, you know, some of these are salt extractions, some of these are precipitations, et cetera but just a couple things just to get the reader to know, okay, when do we have protein on our hands as opposed to a bunch of hide.

DR. SNYDER: Christina, in the 2004, 2005 re-review document, there are other tissue derived proteins listed, collagens listed, animal collagen, soluble collagen extract and actin. Are those, why were those not included in this or should they be included in this?

MS. BURNETT: I will have to go back and check why. I'm not sure. I might have either missed that or that was a VCRP designation that I didn't catch or has been dropped from the VCRP because they were not in the dictionary.

DR. SNYDER: Okay.

MS. BURNETT: So I will go back and check on those.

DR. HELDRETH: Okay. Also when we originally put the hydrolyzed proteins and peptides report together we had a very large number of these types of ingredients and at one of the panel meetings we circled out which ones should go into which groups and so we went forward where with the group that the panel had selected for this one. But certainly if you feel there are others that fit in here we are open to whatever you suggest.

DR. SNYDER: Well, I mean, they all fall into that general category of the connective tissue --

DR. BELSITO: Connective tissue.

DR. SNYDER: Yes. Sure.

DR. LIEBLER: I mean, I think that these for the most part fall into that category because these are the most abundant proteins and the most easily accessible starting materials because basically when you get down to peptides, and hydrolyzed stuff protein is protein so this is just a function of abundant starting material and cost effectiveness for manufacturing.

DR. SNYDER: And along the lines of the method manufacturing, so we don't have, it has no sources to derive the ingredients from? We don't list any sources or we --

DR. BELSITO: Wave two.

DR. SNYDER: It's all bovine skin resourced.

DR. BELSITO: Right.

DR. SNYDER: But a lot of our tox data or a lot of our tox studies are based on chicken sternal cartilage, shark skin gelatin, cod fish derived and so I think -- so the wave two --

DR. BELSITO: Do we expect them to be significantly different though?

DR. SNYDER: I don't know. I mean, I wouldn't think so but again there is other issues with regards to impurities or, you know, what else is in there because its cattle aortas, animal protein not always specified, I mean, so when we --

DR. BELSITO: Yes but the skin has been exempt from those, right, I mean, it's only brain tissue where there's concern about the BSE.

DR. LIEBLER: So I think if you are starting with a cod fish skin or a cow skin, and you're going to get elastin out of it or you're going to get, you know, one of these other sort of abundant collagens for example the information in wave two on the manufacturing flow charts and the verbal descriptions of the extraction conditions is probably sufficient and this gets to the point I raised earlier with Christina about adding that information.

And then when get right down to the proteins, collagen for collagen for particular subtype across species it's probably upwards of 70 percent sequence identity if not better. You know, for particular functions so those are pretty well conserved even across, you know --

DR. SNYDER: But I think we just have some minimal language in there that we are that where that's the assumption we are under or that's our understanding because all that second wave was fish scale sourced, AC marine collagen and none of it was bovine sourced. And so -- I just think we need to be, have something in there about how we are considering that.

DR. LIEBLER: I think the information is there, we can bring that in from the tables in wave two.

DR. BELSITO: Okay. And then I guess we have had this discussion before, I just want to be totally clear on this so we are talking about, you know, the sourcing from fish where people can be allergic to fish and it's one of the major food groups that the FDA requires allergen labeling when one or more of the eight major food allergens which include fish are included in food. What did we do with wheat? And what are the requirements when you're using one of the major food allergens as a cosmetic ingredient source?

MS. BURNETT: As far as I understand there is no necessarily no mandate that you put it on the label. I know some companies do.

DR. ANSELL: They, you are required to disclose its presence.

MS. BURNETT: In cosmetics?

DR. ANSELL: Yes.

MS. BURNETT: Or in food?

DR. ANSELL: Well, specific to this discussion cosmetics.

MS. BURNETT: Okay. Because I know it was food.

DR. ANSELL: Our discussion was that we didn't think that we needed to highlight it beyond this disclosure in the ingredients, that we didn't need not bring it up to the front of the label.

MS. BURNETT: Right.

DR. ANSELL: That we concluded that was sufficient to disclose it, the presence.

DR. BELSITO: So is it disclosed just as an ingredient or is there like for instance if you look at some of the, you know, derma smooth FS oil which contains peanut oil, it has it listed not only as an inactive ingredient but then down at the bottom of the package insert there's a sort of a bolding, you know, caution people with peanut allergies.

MS. BURNETT: That's where I think I was thinking because I know when you look at the food package you will still have your ingredient level and then at the very bottom will be the asterisk and it says warning contains peanuts or contains tree nuts or something.

DR. BELSITO: Right.

MS. BURNETT: I don't, I -- is that the same requirements or it's just the listing of the ingredients?

DR. HELDRETH: Yes in the wheat case, that the names had wheat right in them but here for something like collagen it's not going to say fish.

DR. BELSITO: Right.

DR. HELDRETH: In the ingredient list.

DR. KATZ: Well, as of now there are no specific requirements for allergens to be listed unless it is part of the federal register at this point in time. However, given the fact that if it's not readily identifiable and it is a known allergen and it's not going to be denatured in the process then it may behoove you to suggest that a warning be there or in some way highlighted so that someone can find it.

I remember the discussion we had have previously about one of the other nuts with and in our discussions not so much with wheat where its clearly identifiable because it says wheat but with several of the other nut products that I think it was a hazelnut and the issue does that need to be disclosed? And the feeling was from this panel if I remember correctly was that when it was used in a cosmetic because of the way it was processed it was denatured and would no longer be an allergen. If in the processing of this product that the same thing happens in that it's no longer going to be an allergen, just listing it should be sufficient on the ingredient list. But if there's concern that it might actually be a potential allergen because it's not going to be denatured, then I would think you would probably want to identify it so that someone who has an allergy can make sure that they see it, that it's there.

DR. BELSITO: I mean, you know, I'm not an allergist, I'm a dermatologist so, I mean, obviously allergies to fish are due to proteins because that's what causes IgE mediated allergies. I don't know whether they are connective tissues derived proteins or what they are but they must be something in the meat of the fish, that's what you react too right? So yes, I mean, I raised that simply because, you know, as already been pointed out this would just be labeled as hydrolyzed collagen. It wouldn't be hydrolyzed fish collagen and so that was my concern.

DR. BERGFELD: Just broadening the conversation a little bit, collagen, bovine collagen has been reintroduced into dermatology as an injectable for wrinkles coming in as a new product and that requires a skin test before it's used some several weeks ahead so obviously there is a problem somewhere.

DR. BELSITO: Now with the skin test is more for granuloma formation isn't it, for delayed reactions?

DR. BERGFELD: Well, I think that someone had hyper sensitivity to it as well.

DR. BELSITO: Oh. Yes, I mean, but, I mean, the question becomes this would be a new novel approach because it sounds like on wheat we didn't put a specific warning at the end as there are in some of the prescription and OTC

medications causing, you know, in addition to listing inactive ingredients. All we would do is list that this contains collagen. Well, you know, as a consumer I'm not even going to know what collagen is but I'm certainly not going to know that it could be derived from fish and I'm severely allergic to fish.

DR. LIEBLER: So these collagens are listed in fish, I'm just browsing through the wave two data summary. The Atlantic cod is one source of collagen. It looks like the bovine is the major source of collagen.

DR. BELSITO: Yes.

DR. LIEBLER: But the Atlantic cod these are all hydrolyzed collagens. I don't know if people with fish allergies are allergic to collagen proteins from the fish which would be mostly in the skin well, I shouldn't even say that. They could be anywhere in the fish depending on which collagens.

DR. BELSITO: Or scale.

DR. LIEBLER: Allergic to other fish proteins that are not collagens.

DR. BELSITO: Well, sure. Elastins, actins, I mean, its muscle.

DR. LIEBLER: Well or lots of other proteins in there too.

D

R. BELSITO: Right, no I know.

DR. LIEBLER: Shark proteins.

DR. BELSITO: Yes.

DR. LIEBLER: Kinases, you know, whatever so --

DR. BELSITO: I mean, I don't know what (inaudible) they would react to.

DR. LIEBLER: Maybe nobody knows. It's fish.

DR. BELSITO: Yes. I mean, that's my point and so where do we go with that from a labeling standpoint since it's apparent that the rules for cosmetics are not the same as they are for --

DR. ANSELL: Yes but nor is the ingredient the same as the food.

DR. BERGFELD: Non sensitizing.

DR. BELSITO: But then you need to express by non IgE sensitizing but then, I mean, that essentially would eliminate all of these, you know, connective tissue derived proteins being extracted from fish.

DR. SNYDER: I think if we put it in, if we put more information in the method of manufacturer where these are sourced from, I mean, if there are some that are sourced from fish and other things and then we talk about it in the discussion.

DR. BELSITO: What do we say that manufactures of fish derived collagen would be, we would recommend that they alert people buying their products to label them on the, I mean, I don't know where you go with that.

DR. LIEBLER: So people who have fish allergies eat fish that's either raw or cooked. There is no enzymatic acetic basic hydrolysis of the proteins in that. The products we are talking about are collagen from fish scales and that collagen is extensively hydrolyzed to be able to have the properties that would make it useful in a cosmetic ingredient because otherwise it's just insoluble stuff. Its fish scales so that's what makes the scales the scaly scales.

DR. BELSITO: But cod was not just scale.

DR. LIEBLER: It could be skin and scales.

DR. BELSITO: Right.

DR. LIEBLER: Right.

DR. ANSELL: Yes, I think the driver in the nut and wheat discussion was that the food ingredient and the cosmetic ingredient were far enough apart that the allergy was not relevant. I think at least for this is our first look at this, I think it's an interesting question and talk about the processing and whether we think that people are actually being exposed to fish or a highly processed protein or a peptide which is derived from animal origin and whether fish allergies is a relevant discussion. I, you know, it's the first time we have seen this and I think that's an interesting question.

DR. LIEBLER: Yes, my first inclination is to say that the preparation of these ingredients is likely to denature and cleave and otherwise change the epitopes, any epitopes that might be antigenic but I can't prove that without some kind of additional data. I suspect that that is the case because these products are relatively widely used. We would have started encountering problems by now but wow, I don't know that either so if there's a lack of case reports, if there's --

DR. BELSITO: Go ahead, Paul, and point out what you are talking about because I'm not finding it.

DR. SNYDER: Under other related studies under hyposensitivity. There was a large study in which they skin pricked with fish gelatin through acid extraction of cod fish skin --

MS. BURNETT: PDF page 16.

DR. SNYDER: All 30 reacted positive.

DR. BELSITO: Right. No cross reactivity between bovine and fish.

DR. SNYDER: And then they also have tuna derived.

DR. BELSITO: Right. Gelatin.

MS. BURNETT: And then there was a case study or two.

DR. BELSITO: Yes, I highlighted that also. So that nixes that argument.

DR. SNYDER: We need info on the source, more material method stuff.

DR. BELSITO: Well, I mean, I don't know that that is going to help us given these reports, I mean, the question becomes labeling, you know, if it's just labeled gelatin would it create issues on the skin, I don't know. I mean, you know, the only way around it would be to say, you know, we would want -- I don't know what you would want for contact urticaria because it really depends upon how sensitized the individual it is.

You know, its, it was just like the latex epidemic. You had some people with low degrees of sensitivity that just got urticaria under the gloves. You got other people who went into anaphylactic shock wearing gloves. I mean, we are not talking about a little contact dermatitis. The easiest way around it quite honestly, Jay, would be to require labeling on cosmetics when they have major food group allergens in them. And simply say, you know, after you list the ingredients, collagen, actin, whatever it happens to be, gelatin say, you know, sourced from fish.

DR. BERGFELD: Don't you think you should ask first for what is remaining after they prepare the ingredient?

DR. BELSITO: But we have case studies where --

DR. BERGFELD: I know but --

DR. BELSITO: -- where it doesn't matter what's remaining. We have one study skin prick tests, seven out of patients were positive with specific IgE to codfish and then tuna we had three exhibiting reactivity to gelatin, hydrolyzed. One was hydrolyzed and the other was possibly non, two were non hydrolyzed but hydrolyzed caused reactions in one.

DR. HELDRETH: So since we are not regulatory body and can't actually require the manufacturers to do these sort of labelings, should we instead provide instructions to the manufacturers that they must limit these types of potential allergic reactions?

DR. BELSITO: I mean, but we don't know where to set a limit.

DR. ANSELL: Let us think about proposals, I mean, we addressed this in the wheat discussion.

DR. BELSITO: Yes.

DR. ANSELL: And I don't think we are going to be able to draft language right now.

DR. BELSITO: Right. I think it will be interesting to see what the other team -- Linda.

DR. ANSELL: It is an issue -- yes.

DR. KATZ: I just contacted Dr. Luccioli and I will wait to hear back from him. He is our allergist and he does the food allergens and to head of that committee to see what his recommendation would be.

DR. BELSITO: Great. That would be helpful because I think this is a major stumbling block here because it is not like what or oat or soy where it's identifiable simply by reading the label. And I don't know that you can necessarily go with, you know, dose response here so yes, let's hear what the other team has to say and then industry and FDA what information they can get back to us.

The only other issue that I had other than saying I think we can go safe as used once we clarify this whole fish issue was that on page 17 of the PDF it talks about hydrolyzed collagen producing some irritation in an HRIPT and this was summarized from the old report and I guess the question becomes if we do eventually get to a safe as used do we say formulating to be non-irritating because of that data or where do we go with that?

DR. SNYDER: I think we have to.

DR. BELSITO: Okay.

DR. LIEBLER: I mean, normally don't if we have any data that says irritating then we always throw that in?

DR. BELSITO: Okay right. So when we get around to it, Christina, formulated to be non-irritating. That was I think the only other thing I had.

DR. BERGFELD: I would think it would be apt that you would also add non sensitizing if you're going to put non irritating in because of the questions that have risen this morning even though you are going to have some of them answered. At least consider it.

DR. BELSITO: Okay.

DR. ANSELL: There was a question, do we have bovine derived boilerplate?

DR. BERGFELD: We have one on the infectious agents.

DR. BELSITO: Yes, but the skin is exempt, right, I mean, it's just brain and neural tissue that you need to worry about BSE.

DR. SNYDER: Yes, we, that language is in here regarding the hide.

DR. BERGFELD: Prions.

MS. BURNETT: Is it?

DR. SNYDER: Yes.

MS. BURNETT: Yes, I have included --

DR. BELSITO: What page, Christina?

MS. BURNETT: PDF 12 there is the C.F.R. language plus I added language requests from Carol that talks about the World Organization of Animal Health and their recommendations.

DR. BELSITO: All right. Okay. Okie doke.

MS. BURNETT: So I anticipate the discussion section will address the allergen component. Do you have any other things to add to the discussion?

DR. BELSITO: No, I mean, that was my major issue.

MS. BURNETT: The BSE boiler plate?

DR. BELSITO: The BSE is not an issue when its hide right, I mean, basically. That's what I thought. If the World Organization for Animal Health recommends that when authorizing imported transported gelatin collagen prepared exclusively from hides is in skin and any products made from these commodities yada, yada, yada, should not require BSE related conditions.

DR. SNYDER: But we don't have data that says that that is where it is sourced from that's why the method of manufacturing doesn't state where it's sourced from.

DR. ANSELL: Yes except we don't usually put in only legally produced products may be used. I mean, it would be, those are prohibited to be marketed, you know, not a matter of counsel --

DR. BELSITO: I mean, we so you want to put in the BSE boiler plate? I don't have a problem with it, it's just my understanding --

DR. SNYDER: If it's sourced from, if it's sourced, I mean --

MS. BURNETT: We can finesse it so that we say we recognize that while these are not necessarily sourced from materials that are BSE if they happen to be they should not or we can work with the language and have you review it and --

DR. BELSITO: Fine, yes, sure.

MS. BURNETT: And if you don't like it we can remove it.

DR. BELSITO: Sure. Let's see what the other team says too.

DR. SNYDER: That 22 year old female case on the hydrolyzed collagen I highlighted that it just says hydrolyzed animal protein. What does that mean?

DR. BELSITO: Right.

DR. KLAASSEN: I mean, you're not going to hydrolyze a Kansas City steak. And you might take the ligaments and the tendons --

DR. BELSITO: Or the brain.

DR. KLAASSEN: And a lot of the stuff could be coming form.

DR. BELSITO: Or the brain of the animal. Okay well, finesse the language, we will take a look at it and we will see what the other team. Okay. Are we done with this? Okay so.

DR. BERGFELD: So what's your final on it?

DR. BELSITO: Our final is we are going to hear from the FDA about protein allergens. Jay is going to talk with industry about labeling and crafting stuff like that. Christina is going to craft some stuff about BSE and right now here until we hear all about that the feeling was that we could probably go safe as used when formulated to be non-sensitizing and non-irritating.

I'm okay with putting the sensitization in there but I think that what we are really at this point if you say insufficient for further information from FDA, from counsel, but we are not asking for industry to provide us information. We are more asking for regulatory and word something information. Is that a fair assessment?

DR. LIEBLER: Yes. And I don't think we should use insufficient because that connotes --

DR. BELSITO: No I, that's --

DR. LIEBLER: Data from industry so.

DR. BELSITO: Yes. I mean, if worse comes to worse we can table it for further.

DR. BERGFELD: Well, it's an insufficient announcement or you're just --

DR. BELSITO: No, I - if, we are not asking for additional data so if we can't resolve this by tomorrow morning with the other team I would say table it for clarification.

DR. BERGFELD: Okay.

Dr. Marks' Team

DR. MARKS: Exactly. Now, we're going to the tissue derived proteins and peptides. This is the first review of these ingredients. Christina, in her memo, outlines very nicely the background of why we split these up. At any rate, so there are 19 ingredients and my first question would be for Tom, Ron and Ron, do you like all 19?

DR. SHANK: Yes.

DR. MARKS: Is there any outlier?

DR. SHANK: All 19 are fine with me.

DR. MARKS: Good.

DR. HILL: Fine with me too.

DR. MARKS: Okay, great. And then second is comments?

DR. SLAGA: Okay.

DR. MARKS: Do you like the safety data you have? Do we need more?

DR. SLAGA: I think based on the previous reviews we had and some of the overlap, plus the data we have is

sufficient.

DR. MARKS: Ron Shank?

DR. SHANK: We lack, for most of the genotoxicity -- reproductive toxicity, developmental toxicity,

carcinogenicity -- are these ingredients GRAS?

DR. SLAGA: Most of them, probably.

DR. HILL: (Crosstalk)

DR. MARKS: It was mentioned in the content in the --

DR. EISENMANN: Gelatin, I don't think gelatin is GRAS, but it's food. I mean --

DR. SHANK: Yeah.

MS. BURNETT: Yeah.

DR. EISENMANN: -- so, I mean, you don't have to necessarily have to ask if it's GRAS. You should ask if it's

food. I mean, or based from food.

DR. SHANK: I just -- if it's GRAS, makes life simple, but if they're not, we really have to argue --

DR. EISENMANN: Well, another --

DR. SHANK: -- if the whole protein --

DR. EISENMANN: -- thing, I did a search of questioning whether or not you need genotoxicity on proteins and I

found --

DR. SHANK: They don't usually do it.

DR. EISENMANN: -- that a reference that says as long as --

MS. BURNETT: Going to be fine.

DR. EISENMANN: -- as long as it's the standard amino acids and this was looking at drugs that are proteins, as long as it's the standard amino acids, then no, you don't need genotoxicity on proteins in general.

MS. BURNETT: I will note that we did receive, so I do

(crosstalk) ---

MS. EISENMAN: But will you get some, but --

DR. SHANK: Right.

DR. EISENMANN: -- but --

MS. BURNETT: Yeah.

DR. SHANK: Just oncology.

MS. BURNETT: We have some wave two data that had

(inaudible) data for the hydrolysis

DR. MARKS: Oh (inaudible) which didn't we review, so --

DR. SHANK: Well, but these aren't the whole proteins, these are hydraulic seeds. So --

DR. EISENMANN: Still, as long as it's the standard amino acids, this group that got together, recommend that you didn't need genotoxicity in general.

DR. SHANK: Okay and I appreciate that. I think these are all probably safe as used, but we need to deal with the fact that there's considerable lack of data that we usually require and explain why we don't require it. And while we're talking, I'd like to change the title of the report to animal (inaudible), plants or tissues, so tissue doesn't help.

DR. EISENMANN: Animal derived.

DR. SHANK: Animal derived protein (inaudible).

DR. EISENMANN: So have they called extra cellular matrix proteins? That's what we were wondering if that might be the appropriate name.

DR. HILL: Still need something about animal in there.

DR. SHANK: Yeah.

DR. EISENMANN: Okay.

DR. SHANK: Well, tissue doesn't help.

DR. EISENMANN: No.

DR. SHANK: So --

MS. BURNETT: I will give you the heads up. I did not -- the information in the article that I read was not pertinent for a cosmetic use, but apparently, they're working on use -- on deriving collagen from bacterial strains in order --

DR. SHANK: Right.

MS. BURNETT: -- to have a -- what they consider -- considered to be vegetarian or vegan source. It wasn't pertinent for our knowledge, but if we're changing the title, heads up, I don't know if they will use a cosmetically, but --

DR. SHANK: I'm going to bring that up later when we talk about read across in priorities because the microbiome business is going to come up.

MS. BURNETT: Mm-hmm.

DR. HILL: And sponge is interesting because -- although I think sponge is that animal protein in the sponge --

MS. BURNETT: Mm-hmm.

DR. HILL: -- sponge is a symbiote that includes algae as part of its fundamental organismal nature.

DR. MARKS: So, Ron you brought up changing the title. It's gotten more complex very quickly.

DR. HILL: Sorry about that.

DR. MARKS: No, that's okay. I -- the question is, is this the (inaudible), I think there are hazards just limiting it to, I don't know, based on potential bacterial source and then, also sponge, as you --

DR. SLAGA: Yeah, but they said that if it's all of the products were certified and not to have (inaudible).

DR. MARKS: Yeah. Well, I'm not worried about that part of it. It's the title saying that we know at least most and in the future most, it's going to probably be animal derived, unless bacteria overtake it, but how do you want to handle that?

DR. SHANK: Well, we have the same issue with plant derived protein. Plants aren't sterile. They have microorganisms associated with them.

DR. MARKS: Mm-hmm.

DR. SHANK: In life --

DR. MARKS: Yeah.

DR. SHANK: -- and we say nothing about the possibility of microbial protein hydrolysates.

DR. MARKS: Yeah, I guess what Christina and you're implying that the main source of the collagen would be from bacteria, genetically engineered, I guess the --

MS. BURNETT: We're just -- we're just splitting it.

DR. SHANK: And probably not.

MS. BURNETT: They're just looking into it right now. They just -- the conclusion was it could be possible.

DR. MARKS: Mm-hmm.

MS. BURNETT: (Inaudible)

DR. SHANK: And possibly it is --

DR. MARKS: I guess that would warrant reopening the report then to change the title.

MS. BURNETT: (Laughs)

DR. MARKS: So animal, what do you think about that Ron Shank?

DR. SHANK: Well, this is the first time you've seen this.

DR. MARKS: Yeah, I know. I'm talking about 10 years from now.

DR. SHANK: Oh, (laughs).

DR. MARKS: Not 10 months or six months or five months. Ron -- Ron Hill and Tom, what do you think about changing it to animal? I kind of like it actually, but --

DR. SLAGA: Well, more defined for you --

DR. MARKS: Yeah.

DR. SLAGA: -- with all the ingredients from --

DR. HILL: now, yeah, the question is whether you want to constrain it based on this group of ingredients is something like animal, extra cellular matrix proteins. I mean, I know that lengthens the title, but something to think about. So it's not just any old animal proteins here. We're not using a bass-a-matic to grind up the fish. Those of you who know the reference (laughs).

DR. MARKS: So, Tom, do you like animal?

DR. SLAGA: Yeah.

DR. MARKS: Yeah, so do I. Change title to animal

(inaudible). So if I have not, I mentioned that tomorrow, Ron Shank --

DR. SHANK: I will.

DR. MARKS: -- please bring it up.

DR. SHANK: I will.

DR. MARKS: So I'm not sure in my mind. I'm clear, Ron Shank, you brought up we need to explain why with the lack of data we can say genotoxric, repro, et cetera, systemic toxicity is missing. We believe -- I get the sense, we believe they're all foods, but Christina, do you know how in discussion did you get enough direction that how you could explain why it's safe in discussion because obviously, we've got to say that since Ron Shank has brought up the issue of lack of data? And then, Tom, you said in the beginning based on the other proteins and --

DR. SLAGA: (Inaudible)

DR. MARKS: -- peptides we reviewed --

DR. SLAGA: Yeah, they're --

DR. MARKS: -- we felt that there was not an issue, so there could be --

DR. SLAGA: There was overlap --

DR. MARKS: -- even -- yeah, read -- read across --

DR. SLAGA: -- read across other proteins that then hydrolyzed that are -- that we already reviewed.

DR. MARKS: Does that -- Ron Shank, does that sound good to you as addressing this issue?

DR. SHANK: Yes. Yeah, that's going to be all right.

DR. MARKS: And Ron Hill?

DR. HILL: I had a little comment here that just was a rhetorical question that said, do we have all the info we need about or can include in the discussion, molecular weight range for not crosslinking IgE and I noted that the case reports that we have here because I know in some of these, we've looked and said, well, we don't k now any instances where people to react to corn, for example, in the same way that they react to wheat, but here we have some collagen-based case reports. So I wondered if we have everything that we need to at least deal with properly in the discussion, or if that even needs to come into play here. You know?

DR. MARKS: Yeah, I noted that also, Ron. You know and I dealt with it by just as you said, they're case reports and they're rare and so, with that in mind, it wasn't like what we dealt with, with lead.

DR. HILL: That was what I was thinking that you would probably be thinking, but I wasn't sure and that's why I had --

DR. MARKS: Yeah.

DR. HILL: -- if that would --

DR. MARKS: Yeah, that's good.

DR. HILL: The other question that's come up and this is not the first protein group that we've dealt with is, but -- some information as to how, when an enzyme is used to hydrolyze the protein to go down to the molecular weight that they want. What are the general approaches that are used to remove those enzymes from the finished products so that you don't have patients reacting to the presence of the enzyme or fragments of that enzyme protein that they might otherwise be sensitive to. So I guess I -- all of a sudden jumped out on me on this one and I don't know why, but I've been wondering about for several -- several sets of protein ingredients. And I think it should be possible to get some general information about that sort of thing without anybody giving away any trade secrets.

DR. MARKS: Okay, any other comments? If not, then tomorrow I'll be moving that a tentative report be issued with a safe conclusion for these 19 ingredients. We'll change the title to animal derived proteins and peptides. That'll probably generate a little discussion and then we'll deal with the lack of data, one, these are main -- they're foods and that's reassuring and then we use read across data from other protein and peptide reports to substantiate the genotox repro, et cetera. Sound good?

MS. BURNETT: And that's the main part of your specialty?

DR. MARKS: yeah.

MS. BURNETT: Do you have any other special

(inaudible)? Did you want to mention the type one reactions at all in the discussions, or is it sufficient that --

DR. SLAGA: We have in the other one.

DR. MARKS: Yeah.

MS. BURNETT: Okay.

DR. MARKS: Yep. And then obviously, that there would have been what wasn't. There've been reports before with hydrolyzed collagen and it's safe and it was first determined in '85 and --

MS. BURNETT: Mm-hmm.

DR. MARKS: -- reaffirmed in '06 that hydrolyzed collagen is safe. Any others?

DR. SLAGA: Well, the discussion should have something about the BSE --

DR. MARKS: Oh yeah.

DR. SLAGA: (Inaudible) certify --

DR. MARKS: Mm-hmm. Thanks, Tom. Mm-hmm.

DR. HILL: And I was just going to raise again, the issue, so maybe we have more information and I apologize for not having researched this myself, but it's a question I asked previously which was, when you did -- obviously, when you did a search for just collagen in PubMed you got 190,000 hits, so you couldn't read all those. So then you paired down to cosmetic collagen -- and then cosmetic collagen toxicity and again, I'm just wondering based on how the MeSH Tree works in PubMed especially with respect to case reports. Do we think we're getting them all? If you just say toxicity and you've also searched on irritation, but is toxicity getting sensitization, hypersensitivity? I mean, the logic response, those are the terms because I'm not sure it would. That needs to be verified and since case reports here are kind of critical to -- now, again, we have experts that (audio gap) be aware of those sorts of things start showing up, both on our panel and in industry, but I just think we need to verify when you have to pair your searches. Because I routinely read through five or 600 abstracts and titles, or at least start with titles and go to abstracts to make sure I find what I need, but obviously, you can't read through 190 or even 1,400 is a little time-consuming. But if you use -- when you use Scifinder to go after PubMed, it does use a thesaurus of some sort, but I'm not sure what all terms are in there if you use something general like, toxicity.

MS. BURNETT: Well, I will say it was very challenging because collagen --

DR. HILL: I know.

MS. BURNETT: -- is part of the body that --

DR. HILL: Oh, yeah.

MS. BURNETT: -- there is a lot of -- trying to figure out the wording on how to get it just to be applied, not a -- an applied collagen versus something that's already existing in other things acting on the collagen, so --

DR. HILL: And I think you made comment about that somewhere in there.

MS. BURNETT: Yes, and I -- I'm not -- I'm uncertain of the -- a better way and if you have a better way to figure out how to research this, I'd appreciate it (laughs).

DR. HILL: And I also wondered -- yeah, I also wondered in terms of, strictly to cosmetics, whether that would have synonyms in the MeSH Tree pickup, personal care products that are not necessarily thought of as cosmetics. So I think that's a more general question, but this is not the first time this has come up, but I know there is that MeSH Tree in Medline. I know that Scifinder uses some synonyms when you use a bigger terms, but it's not always a complete list because I've seen gaps there in doing searches and again, because our lack of concern about type one which I think we're not even going to end up discussing -- I don't know what anybody else thinks, is a lack of case reports and again, knowing that Dr. Marks, Dr. Belsito, Dr. Bergfeld, might notice if we have a lot of these problems, I think they would probably be aware regardless of our searches, but I just -- I was concerned about that.

DR. MARKS: We actually are going to mention in discussion --

DR. HILL: Okay.

DR. MARKS: -- last (crosstalk) --

DR. HILL: My question was you weren't.

DR. MARKS: No, I think it should be. We mentioned in previous. Okay, any other comments? If not, we'll move on to the next ingredient.

DR. HILL: You all are looking at a lot of other databases, so I'm thinking if it was something significant, I presume it would show up in one of those others, so that adds for me some comfort level, but I think this is something we need to (crosstalk) carefully.

DR. MARKS: I think the data searches are excellent --

DR. HILL: yeah.

DR. MARKS: Because I looked up Biotin to make sure I couldn't find any case reports of allergy to it since that was the reasoning for the first determination of safety and couldn't find any, so -- okay, let me see here. Tissue which will become animal.

Full Panel Meeting

DR. BERGFELD: All right. Moving on to the next ingredient, tissue-derived proteins. Dr. Marks?

DR. MARKS: So this is the first time we've seen these 19 ingredients in this report, and our team felt that all 19 were okay to be reviewed. And the first thing we thought is to be more direct and clarify, we wanted the title to be changed to animal-derived rather than tissue-derived. We had quite a bit of discussion with that. We thought we could move to a tentative report with a safe conclusion, and then we can discuss about the lack of systemic toxicity if we want. But at any rate, the motion is move for a tentative report, safe conclusion for these 19 ingredients. And we changed the name to animal-derived.

DR. BERGFELD: Comment from the Belsito team?

DR. BELSITO: Yeah. We just noted that there was some data suggesting that these could be irritant, and our conclusion was safe when formulated to be nonirritating. I was a little bit surprised by the irritation data. We also felt the title needed to be changed but went a little bit more specific to you to ectodermal tissue-derived proteins because they're not simply animal. They're all ectodermal. But otherwise, safe as used when formulated to be nonirritant.

DR. BERGFELD: Comment?

DR. MARKS: That's fine.

DR. BERGFELD: So to be able to change the motion?

DR. MARKS: Right. And the title, how do you feel, Ron Shank? Ectodermal? Interesting.

DR. BERGFELD: I guess a fish is not an animal.

DR. HILL: A fish is an animal. A sponge is a gray area but fish is --

DR. MARKS: And we also actually got into potentially bacterial-derived that could be in this. So even animal we had discussion back and forth as to what the best title -- we just didn't like tissue-derived at this point. We agree with you with that.

So Ron Shank, you're the one who suggested animal.

DR. SHANK: Yes. Ectodermal is okay. Perhaps not as appealing to the consumer.

DR. MARKS: As opposed to tissue?

DR. MARKS: Well, it's not going to be on the label.

MS. BURNETT: Ecto as in e-c-t-o?

DR. BERGFELD: Mm-hmm.

DR. BELSITO: Yes.

DR. BERGFELD: So there is --

DR. LIEBLER: Ron, how about critter?

DR. BERGFELD: So there's agreement here that we can change it to ectoderm?

DR. MARKS: Correct.

DR. BERGFELD: Okay. And agreement on the conclusions?

DR. MARKS: Correct.

DR. BERGFELD: All right. Any other comments?

DR. MARKS: Yeah. We felt in the discussion to capture several points that it was really a lack of systemic toxicity data in this report, including genotox, repro, and development, but we can explain why we felt that we could move forward with safe but nonirritating conclusion because -- sorry. Did the recorder get any of that?

So discussion. We thought in this report there was a lack of systemic toxic data to support the safe but nonirritating. But we felt because it's food -- it's in foods, we can read-across from other proteins and peptides in previous reports that we were fine with a safe conclusion. There was concern about the type one reactions here also but they were rare. They were just case reports. And also, if you look, we previously had reported on hydrolyzed collagen. Came to a conclusion safe in 1995 and -- or 1985 and reaffirmed that in 2006. And then the only other thing, we thought there should be a BSE boilerplate.

DR. BERGFELD: Any comments from the Belsito team? DR. BELSITO: Yeah, we agree with the BSE boilerplate.

We had a rather length discussion about the urticaria reactions. And I guess our concern, and I think we need to put this in the discussion, was that as opposed to an individual who is allergic to soy or wheat or something like that who can read a label and see that it contains hydrolyzed soy or hydrolyzed wheat, here, if it's derived from fish, there will be no indication that that is the source. It will just be labeled as hydrolyzed collagen or whatever. And it turns out that, you know, the FDA requires allergen labeling when one or more -- the eight major food ingredients, including fish, are in a food substance, but there's no requirement as I understand it for a cosmetic substance. So I think at least in the discussion, we should urge manufacturers who are sourcing their ectodermal-derived proteins from fish to put some type of warning as occasionally occurs in cosmetic products that this contains a potential food allergen and the patients who are allergic or whatever should be cautious. I don't know exactly how the statement usually is worded. There are a number of topical prescription medications that contain peanut oil that have a typical statement in the package insert about that. That was it.

DR. BERGFELD: That was it?

DR. BELSITO: But I think it can go in the discussion that we would recommend that.

DR. BERGFELD: Okay. Ron Hill?

DR. HILL: I had one other sort of big picture issue yesterday I brought up which is -- this is one of a number of reports we've seen where proteins are being hydrolyzed and one of the common strategies is enzymes that are being used to hydrolyze. Without anybody giving away any trade secrets, I'm wondering if we can get, with this report maybe as an example, the general types of strategies that are used to get rid of those enzymes that can be from practically any source, commonly bacterial these days, or yeast, that are used to do the hydrolyses. So I don't know, because if they're left on the product, people could potentially sensitize to those.

DR. BERGFELD: All right. Any other comments?

DR. MARKS: Yeah, Don, I'd like to just go back with a conclusion nonirritating because I didn't have that when I initially reviewed it. Now I'm looking at my notes and in the HRIPTs there was no irritation. Way too many studies. Now, this was with hydrolyzed collagen, nonirritating. I guess I must have missed the studies you picked out that there was some irritation.

DR. BELSITO: Let me go back. I had already moved on to malic acid.

DR. MARKS: Sorry, Don, but --

DR. BELSITO: That's okay.

MS. BURNETT: I think he -- let me check real quick.

DR. MARKS: It was from the prior report.

DR. BELSITO: Oh, the prior report.

MS. BURNETT: In the summery on PDF page 16, under the animal studies for dermal irritation. From the original report it says "primary skin irritation test in rabbits indicated hydrolyzed collagen was nonirritating or minimally irritating when tested up to 100 percent.

DR. MARKS: Yeah. So to me that was not -- yeah, that wasn't an issue. We were using hydrolyzed collagen at 16.5 percent. So it's very, you know, it's a small percentage compared to 100 percent when it says nonirritating or minimally irritating. I didn't get concerned about that. So I just want to be clarified if --

DR. BELSITO: I was looking at page 17 of the PDF.

DR. MARKS: Seventeen?

DR. BELSITO: Where it says on humans, "formulations containing.5 to 28 percent hydrolyzed collagen produced some irritation but no sensitization." And then HRIPT.

DR. MARKS: Yeah. And then the following one was no irritation. And no sensitization. And then wave two just had a whole bunch.

DR. BELSITO: I mean, I don't have a problem. I just was pointing out that there were reports. I mean, it's entirely possible that the irritation was due to other ingredients in the formulation. I mean, it surprised me but --

DR. MARKS: Yeah. If I look a wave two, we have, you know, multiple studies, both in vitro, animal, human, and ocular in vitro with almost universally nonirritating. A couple was slightly irritating.

DR. BELSITO: I mean, my note next to it said "formulated to be nonirritant???" So I'm happy to go without that.

DR. MARKS: Okay.

DR. BERGFELD: So we have a modified conclusion to remove the nonirritating comment?

DR. MARKS: Yes.

DR. BERGFELD: And that's agreeable? All right. You're voting?

All those in favor, please raise your hand. Okay, unanimous again. Thank you much. (The motion passed unanimously.)

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

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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 Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Scientific Analyst/Writer.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 19 ectodermal-derived proteins and peptides, which function mainly as skin and/or hair conditioning agents in cosmetics. The Panel reviewed the relevant data provided and concluded that these ingredients are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The ectodermal-derived proteins and peptides detailed in this report are described in the *International Cosmetic Ingredient Dictionary and Handbook* (Dictionary) to function mainly as skin and hair conditioning agents in cosmetics. ¹ This report assesses the safety of the following 19 ectodermal-derived ingredients:

Ammonium Hydrolyzed Collagen

Atelocollagen

Calcium Hydrolyzed Collagen

Collagen Elastin Fibronectin Gelatin

Hydrolyzed Actin Hydrolyzed Collagen

Hydrolyzed Collagen Extract

Hydrolyzed Elastin Hydrolyzed Fibronectin Hydrolyzed Gelatin Hydrolyzed Reticulin Hydrolyzed Spongin MEA-Hydrolyzed Collagen

Soluble Collagen Soluble Elastin

Zinc Hydrolyzed Collagen

The Panel previously reviewed the ingredient Hydrolyzed Collagen, and concluded that it is safe for use in cosmetics; the report was published in 1985 and the conclusion was reaffirmed in a re-review that was published in 2006. ^{2,3} This ingredient was included in this safety assessment because of the relevance of the information in regards to reviewing the safety of the other ingredients in the report. Summary data from the original safety assessment have been included in this report in *italics*.

Additionally, the safety of several other hydrolyzed proteins as used in cosmetics has been reviewed by the Panel in several previous assessments. The Panel concluded that Hydrolyzed Keratin (finalized in 2016), 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. 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. The CIR is concurrently reviewing the safety of plant-derived and bovine milk-derived proteins, which have tentative conclusions of safe as used, in separate reports. In addition to the review of these other protein-derived ingredients, the Panel has assessed the safety of Ethanolamine (also known as monoethanolamine or MEA) and Ethanolamine Salts and concluded these ingredients are safe when formulated to be nonirritating (rinse-off products only) and should not be used in cosmetic products in which *N*-nitroso compounds may be formed. The panel has assessed the safety of Ethanolamine (also known as monoethanolamine) and should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

Actin, Collagen, Elastin, Fibronectin, Gelatin, and reticulin all are derived from essential components in animal tissues. Much of the available published literature evaluated the effects of pharmaceutical or other agents on these proteins in their naturally occurring tissues. These studies were not considered relevant for assessing the safety of the ectodermal-derived ingredients as used in cosmetics and are not included in this assessment.

The sources for these cosmetic ingredients may be from many different land or marine animals. These differing sources could potentially produce or result in ectodermal-derived proteins with unique properties, which may result in varying compositions and impurities within a single ingredient (e.g., Hydrolyzed Collagen from animals such as cows may have some impurities that are different from Hydrolyzed Collagen obtained from fish).

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/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 ectodermal-derived proteins and peptides, as provided in the Dictionary, are described in Table 1. General and more specific descriptions of these ingredients are found below and in sub-sections, respectively.

Ectodermal protein derivatives form a broad category of materials that are prepared by extraction from animal tissue and partial hydrolysis to yield cosmetic ingredients. Proteins and protein hydrolysates, including those of animal tissue, are used as conditioning agents in hair and skin products. These proteins are present in many types of tissue, including skin.

The most abundant protein in mammals is collagen, making up approximately 30% of all proteins by mass. ^{11,12} The collagen family is comprised of 28 members (named collagen I to collagen XXVIII) that all have at least one triple helix in their structure at varying degrees (see further description below). ¹² The most common are mainly the fibril-forming collagens (types I, II, III, and V) that are found in skin, cartilage, reticulate, and cell surfaces. Most of the other proteins addressed in this report are derivatives of collagen, are co-located with collagen in tissues, or are both. Gelatin, for example, is a product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue, and bones of animals. ¹¹ Reticulin is a type of fiber in connective tissue composed of type III collagen secreted by reticular cells. Actin, elastin, and fibronectin are discrete in structure from collagens, but are commonly co-located with collagen in tissue (e.g., fibronectin commonly provides rigidity on the edges of primarily collagen-based tissues). Spongin, however, is a collagen-like protein found only in marine sponges (constituting the small skeletal elements, or spicules, in the animal).

The preparation of protein hydrolysates can be accomplished via acid, enzyme, or other methodologies. These methodologies, and the degree to which they are utilized, may profoundly affect the size and biological activity of such hydrolysates. In most ingredients in this report, even in ingredients without "hydrolyzed" in the name, the proteins are at least hydrolyzed to some degree as a necessary part of extraction or solubilization. Further steps towards solubilization of these macromolecules are commonly achieved via reaction with an alkaline substance to generate a protein salt (e.g., Calcium Hydrolyzed Collagen).

Actin

Actin is a major protein of muscle and an important component of all eukaryotic cells. ¹¹ α -Actin is found in differentiated muscle cells, while β -actin and γ -actin are in all non-muscle cell types.

Collagen

Collagen is the main constituent of skin (comprising 70% to 80% dry weight of the dermis) and connective tissue, and is the organic substance of bones and teeth. Collagen is primarily responsible for the skin's tensile strength. One Collagen molecule consists of 3 polypeptide chains, each containing approximately 1000 amino acids in a primary sequence that is rich in proline, hydroxyproline, and hydroxylysine. Collagen is not just one discrete, ubiquitous protein sequence, but is a protein superfamily that is diversified across different tissue/function types and source species, including cattle, chicken, and fish. Li, The common structural feature of collagen proteins is the presence of a triple helix. However, the percentage of each protein that this helix makes up can vary across different members of the collagen superfamily from as little as 10% to nearly 100%. The diversity of the Collagen superfamily is further increased by the presence or absence of several α -chains, the existence of several molecular isoforms and supramolecular structures of specific Collagen types, and the use of different methods of extraction/hydrolysis.

Elastin

Elastin is the primary component of the elastic, load-bearing fibers of animal connective tissue.¹¹ It is an insoluble, highly cross-linked hydrophobic protein that is rich in nonpolar amino acid residues, such as valine, leucine, isoleucine, and phenylalanine. There are two types of elastin: Type 1 is derived from bovine neck ligaments, aorta (as reported in 1987), skin, and related tissues; Type 2 is derived from cartilage and its derivatives.¹⁵ In skin, Elastin is the intact elastic fiber network that comprises approximately 2% to 4% of the dermis by volume.¹³

Fibronectin

Fibronectin is a multifunctional glycoprotein found on cell surfaces, in body fluids (especially plasma), in soft connective tissue matrices, and in most basement membranes.¹¹

Gelatin

Gelatin is a heterogeneous mixture of water-soluble proteins of high average molecular weight that are derived from the denaturation and hydrolysis of Collagen. Glycine or alanine accounts for one third to one half of the amino acid residues, while another quarter is composed of proline or hydroxyproline.

Reticulin

Reticulin is a connective tissue protein that occurs wherever connective tissue forms a boundary¹¹

Physical and Chemical Properties

The molecular weight (MW) ranges for some of the ectodermal-derived proteins and peptides are presented in Table 2.

Collagen

Solutions of Collagen for cosmetic use have a pH range of 3.8 to 4.7¹⁴

Hydrolyzed Collagen

Hydrolyzed Collagen may be a powder or solution.² A 10% aqueous solution has a pH of 4.0-6.5.

Elastin

Purified Elastin is a pale yellow color and exhibits a bluish fluorescence in UV light.¹¹ It resists acid and alkaline hydrolysis. It is practically insoluble even in hydrogen-bond-breaking solvents at temperatures up to 100 °C, and is nearly impossible to bring into solution except by using reagents capable of hydrolyzing peptide bonds. Unprocessed or native elastin is reported to be too insoluble for use in cosmetic formulations. ¹⁵

Fibronectin

Fibronectin can be provided in a solution or as a lyophilized powder. ¹⁶

Gelatin

Gelatin is a vitreous, brittle solid that is colorless to faintly yellow. ^{11,17} It is practically odorless and tasteless. When Gelatin granules are immersed in cold water, they hydrate into discrete, swollen particles. When warmed, Gelatin disperses into water. Warm-blooded animal sourced Gelatin has a gel point of 30 to 35 °C, while cold-water ocean fish sourced Gelatin has a gel point between 5 and 10 °C. Gelatin is soluble in aqueous solution of polyhydric alcohols like glycerin and acetic acid and is insoluble in alcohol, chloroform, ether, and most other organic solvents.

Soluble Elastin

Soluble Elastin is reported to be a cream-colored powder that is soluble in water and ethanol.¹⁵

Method of Manufacturing

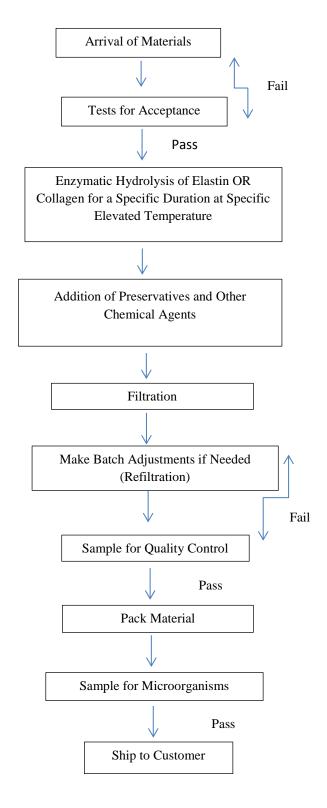
Methods used to manufacture protein hydrolysates typically yield broad MW distributions of peptides, ranging from 500 to 30,000 daltons (Da), equating to 4 to 220 amino acids in length. ^{18,19} Treatment with certain enzymes, such as papain, can routinely yield narrower distributions of 500 to 10,000 Da, equating to 4 to 74 amino acids in length. The available methods of manufacturing for the ectodermal-derived proteins and peptides are summarized in Table 3.

Hydrolyzed Collagen

A representative manufacturing flow chart for Hydrolyzed Collagen is found in Scheme 1. This process may vary slightly between specific products with the elimination of the use of preservatives after hydrolysis and the addition of filtration and concentration of solution before the first quality control.²⁰

A supplier has reported that their Hydrolyzed Collagen products (6 products with MW ranges of 400 to 2000 Da, concentration up to 50% in water) are prepared by acidic, alkalic, and/or enzymatic hydrolysis of bovine gelatin, swine gelatin, or fish scale until the molecular weight reaches the target range.²¹

Scheme 1. Representative manufacturing flow chart for Hydrolyzed Elastin or Hydrolyzed Collagen (bovine and fish sourced)²²⁻²⁶



Soluble Collagen

A representative manufacturing flow chart for Soluble Collagen is found in Scheme 2.

Hydrolyzed Elastin

A representative manufacturing flow chart for Hydrolyzed Elastin is found in Scheme 1. This process may vary slightly between specific products with the use of pH adjustment during hydrolysis.

Gelatin

According to 21 CFR§700.27, Gelatin is "...a product that has been obtained by the partial hydrolysis of collagen derived from hides, connective tissue, and/or bones of cattle and swine. Gelatin may be either Type A (derived from an acid-treated precursor) or Type B (derived from an alkali-treated precursor) that has gone through processing steps that include filtration and sterilization or an equivalent process in terms of infectivity reduction."

Composition

The typical amino acid compositions for Collagen, Soluble Collagen, and Elastin are presented in Table 4.

Impurities

Several of the ingredients in this safety assessment, including Hydrolyzed Collagen, Hydrolyzed Elastin, and Gelatin, may be bovine sourced. Some bovine materials may be considered risk materials for transmission of infectious agents (e.g., bovine spongiform encephalopathy (BSE) prions). According to 21 CFR§700.27, "no cosmetic shall be manufactured from, processed with, or otherwise contain, prohibited cattle materials." Prohibited cattle materials "mean specified risk materials, small intestine of all cattle..., material from non-ambulatory disabled cattle, material from cattle not inspected and passed, or mechanically separated." Prohibited cattle materials do not include Gelatin or hides and hide-derived products. Cosmetic manufacturers must follow record keeping requirements that "demonstrate that the cosmetic is not manufactured from, processed with, or does not otherwise contain prohibited cattle materials."

The World Organization for Animal Health (OIE) recommends that "when authorizing import or transit of...gelatin and collagen prepared exclusively from hides and skins...and any products made from these commodities and containing no other tissues from cattle, veterinary authorities should not require any BSE related conditions [i.e. restrictions], regardless of the BSE risk status of the cattle population of the exporting country, zone, or compartment."²⁸

Collagen

An analysis for 3 different Collagen products found the level of arsenic to be less than 1 ppm. 14

Hydrolyzed Collagen

The maximum concentrations of iron and heavy metals reported in Hydrolyzed Collagen were 3 ppm and 25 ppm, respectively. 2

A supplier reported that their Hydrolyzed Collagen products (6 products with MW ranges of 400 to 2000 Da, concentration up to 50% in water) sourced from bovine gelatin, swine gelatin, and fish scales contain not more than 10 ppm heavy metals and not more than 1 ppm arsenic.²¹

A supplier reported that their Hydrolyzed Collagen products are BSE-free. 29,30

Soluble Collagen

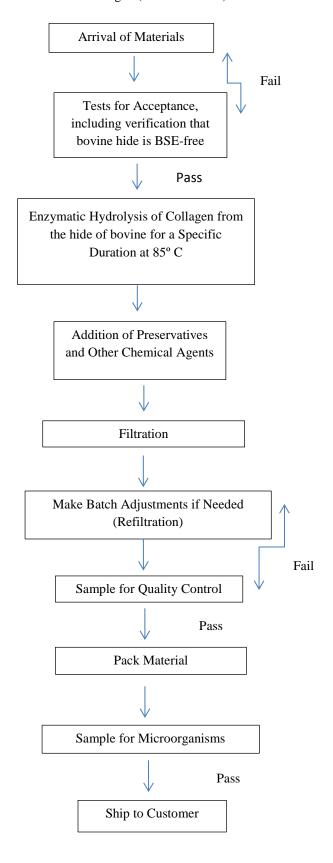
A supplier reported that their Soluble Collagen product is BSE-free.³¹

Elastin and Hydrolyzed Elastin

Impurities in commercial Elastin-based preparations include contamination by lipoid substances from the raw materials and products of Collagen degradations.³²

A supplier certified that their Hydrolyzed Elastin products are BSE-free. 33-35

 $\textbf{Scheme 2}. \ \ \text{Manufacturing flow chart for Soluble Collagen (bovine sourced)}^{27}$



Gelatin

According to the *Food Chemicals Codex*, Gelatin must contain no more than 0.0005% sulfur dioxide, 10 mg/kg chromium, 1.5 mg/kg lead, and 0.3 mg/kg pentachlorophenol.¹⁷

A supplier certified that their Gelatin product is BSE-free.

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, the ingredients with the greatest number of uses are Hydrolyzed Collagen (543 formulations) and Soluble Collagen (425 formulations); the majority of uses are in leave-on skin care products (Table 5 and Table 6).³⁶ Gelatin is used in a total of 334 formulations; the majority of the uses are in rinse-off bath soaps and detergents. The results of the concentration of use survey conducted in 2016 by the Council indicate Collagen has the highest reported maximum concentration of use; it is used at up to 96% in face and neck skin care products.³⁷ Gelatin is used at up to 66% in bath oils, tablets, and salts. The other in-use ingredients are used at much lower concentrations.

Historic and current use data for Hydrolyzed Collagen is reported in Table 6. The number of uses of Hydrolyzed Collagen have declined since the initial safety assessment in 1981 and the re-review in 2002 (923 and 570 uses, respectively^{2,3}). The maximum use concentration of Hydrolyzed Collagen was reported to be 16.5% in hair tonics and dressings in 2016; it was previously reported to be used at concentrations greater than 50% (in rinse-off formulations).^{2,37}

Ingredients with no reported uses in the VCRP or by Council are listed in Table 7.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, Elastin is reported to be used in 46 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, Ammonium Hydrolyzed Collagen was not reported in the VCRP database to be in use, but the industry survey indicated that it is used in several formulations at concentrations up to 0.12%.

Some of these ingredients may be used in products that can come into contact with mucous membranes and the eyes. For example, Gelatin is used in bath oils, tablets and salts at up to 66% and Hydrolyzed Collagen is used in an eyeliner at up to 3.2%. Additionally, some of these ingredients were reported to be used in hair care products, skin care preparations, face powders, and fragrances and could possibly be inhaled. For example, Hydrolyzed Collagen was reported to be used in hair spray at a maximum concentration of 0.28% and Soluble Collagen was reported to be used in face powders at a maximum concentration of 0.0035%. 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. 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. 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.

The ectodermal-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; however, monoalkanolamine ingredients must not have a secondary amine content that exceeds 0.5%, and water-soluble zinc salt ingredients must not have more than 1% zinc in ready for use preparations.⁴⁵

Non-Cosmetic

The FDA determined that the use of peptones as direct food substances is generally recognized as safe (GRAS). These GRAS peptones are defined as "the variable mixture of polypeptides, oligopeptides, and amino acids that are produced by partial hydrolysis of …animal tissue or gelatin…" (21 CFR §184.1553). The FDA requires allergen labeling when one or more of the eight major food allergens, which includes fish, are included in food. ⁴⁶

Collagen

Non-cosmetic uses of Collagen include fibers in sutures, leather substitutes, coatings as a gel in photographic emulsions, and food casings. ¹¹

Gelatin

Non-cosmetic uses of Gelatin include uses in food as a stabilizer, thickener, texturizer, firming agent, surface-active agent, or surface-finishing agent. Gelatin is also used in the manufacturing of rubber substitute, adhesives, cements, lithographic and printing inks, plastic compounds, artificial silk, photographic plates and films, matches, and light filters for mercury lamps. It is also used as a clarifying agent, in hectographic masters, sizing paper and textiles, and for inhibiting crystallization in culture preparations in bacteriology. In pharmaceuticals, Gelatin is a suspending agent, an encapsulating agent, a tablet binder, and a tablet and coating agent.

Gelatin is a category I active ingredient in ophthalmic demulcent over-the-counter (OTC) drug products at up to 0.01% (21CFR §349.12).

TOXICOKINETICS

Gelatin

The bioavailability of Gelatin derived from Nile tilapia scales was determined in an oral pharmacokinetic study in rats. ⁴⁷ Five groups of six female Sprague-Dawley rats received 4000 mg/kg body weight Gelatin intragastrically (i.g.), 400 mg/kg hydroxyproline i.g., 400 mg/kg hydroxyproline intravenously (i.v.), normal saline i.g., or normal saline i.v. Blood plasma was then drawn from the rats at different times over 24 h to determine the hydroxyproline concentration. The bioavailability of the Gelatin was indirectly measured by the bioavailability of hydroxyproline in Gelatin. The relative and absolute bioavailability of Gelatin was 74.12% and 85.97%, respectively. The amino acid profile of plasma showed 41.91% of the digested Gelatin was absorbed from the intestine in di- and tri-peptide form. The authors of this study concluded that Gelatin had high oral bioavailability.

TOXICOLOGICAL STUDIES

Acute

Animal –Dermal

Hydrolyzed Collagen

Hydrolyzed Collagen at up to 2% in formulation was practically nontoxic when administered dermally in acute toxicity studies in rabbits.²

Animal - Oral

Collagen

The safety of a product containing approximately 60% Collagen (type II from chicken sternal cartilage), 20% chondroitin sulfate, and 10% hyaluronic acid was investigated in 5 male and 5 female Sprague-Dawley rats. ⁴⁸ The rats received a single oral dose of 5000 mg/kg body weight and were observed for clinical signs of toxicity for 14 days. All rats survived the observation period and had normal body weight gains. On the 15th day of the study, the rats were killed and underwent macroscopic necropsy: no gross pathological lesions were observed in any of the animals.

Hydrolyzed Collagen

 ${\it Hydrolyzed~Collagen~was~practically~nontoxic~when~administered~orally~(up~to~100\%)~in~acute~toxicity~studies~of~mice~and~rats.}^2$

The oral LD₅₀ of Hydrolyzed Collagen (30% solution in water; fish scale sourced; MW \sim 400 Da) was estimated to be greater than 2500 mg/kg body weight in Sprague-Dawley CD rats. ²¹ This acute toxicity test was performed in accordance to Organization for Economic Co-operation and Development test guideline (OECD TG) 423. A group of 3 female rats were treated orally with the test material at a dose level of 2000 mg/kg body weight, with another group of 3 fasted female rats receiving also receiving the material at the same dose level. No deaths or signs of systemic toxicity were observed during the 14 days of monitoring post-dosing. All animals exhibited expected gains in body weight. No abnormalities were observed at necropsy.

Short-Term Toxicity Studies

Animal – Oral Gelatin

In a rat study of the ability of shark skin Gelatin to increase bone mineral density, no adverse effects were reported.⁴⁹ The female Wistar rats (n=40) were ovariectomized approximately a week after the start of receiving a low-protein diet and then received shark Gelatin as oral doses of 10, 20, or 40 mg/100 g body weight/day for 2 weeks. Control animals were given ovalbumin at 20 mg/100 g body weight/day. No significant differences between experimental groups and the controls were observed in final body weight, feed intake, femoral bone weight, or femoral bone length.

Subchronic Toxicity Studies

Animal – Dermal Hydrolyzed Collagen

Subchronic dermal studies in rabbits and pigs on 2 cosmetic formulations containing 2% Hydrolyzed Collagen were negative for systemic toxicity.²

Animal - Oral Collagen

The safety of a product containing approximately 60% Collagen (type II from chicken sternal cartilage), 20% chondroitin sulfate, and 10% hyaluronic acid was investigated in 40 male and 40 female Sprague-Dawley rats. The rats were divided into groups of 10 animals/sex and received the test material in distilled water at 0, 30, 300, or 1000 mg/kg body weight once daily via gavage for 90 days. Animals were observed twice daily for mortality and detailed observations for clinical signs of toxicity were performed once weekly. Body weight and feed consumption were measured weekly. Hematology samples were collected a week before the end of dosing and the animals were killed at the end of the dosing period. A gross necropsy was performed on all animals and tissues were preserved for histopathological examination.

All animals survived until the end of the dosing period and no adverse effects or clinical signs of toxicity were observed during treatment. No significant findings were observed in changes in average body weights, average body weight gain, or hematology parameters. A small but statistically significant decrease in alkaline phosphatase activity in the 1000 mg/kg/day males was observed, but was not considered adverse. Minimal but statistically significant increases in albumin in 300 mg/kg/day males and in globulin in 1000 mg/kg/day females were not considered to be toxicologically significant since these were not dose-related. Statistically significant, but minimal, changes in average brain weight in the low dose females (higher than controls) and spleen to brain weight ratios in the intermediate dose group males (lower than controls) were also not considered to be toxicologically significant. No treatment-related histopathologic changes or gross abnormalities were observed. The researchers concluded that the test material containing Collagen was tolerated well in this rat study.⁴⁸

Human - Oral

Hydrolyzed Collagen/Gelatin

In a 4-month dietary intake study of Hydrolyzed Collagen (interchangeably reported as Gelatin) for the potential role in enhancing bone remodeling in children, no adverse effects were observed.⁵⁰ The randomized double-blind study divided the children (ages 6-11) in to 3 groups that received placebo (n=18), Hydrolyzed Collagen (n=20), or Hydrolyzed Collagen + calcium (n=22) daily 250 ml dose.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

No published DART studies on ectodermal-derived proteins and peptides were discovered and no unpublished data were submitted.

GENOTOXICITY

In Vitro

Hydrolyzed Collagen

No mutagenicity was observed in an Ames test of Hydrolyzed Collagen (30% solution with water; sourced from fish scales; MW ~400 Da). ²¹ Salmonella typhimurium strains TA 1535, TA1537, TA98, and TA100 and

Escherichia coli strain WP2uvrA were used in this test, which was performed in accordance to OECD TG 471. The dose range was 50 to 5000 µg/ plate, with and without metabolic activation.

In another Ames test performed in accordance to OECD TG 471, Hydrolyzed Collagen (20% solution with water; source from fish scales; MW ~400 Da) was not mutagenic in *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *E. coli* strain WP2uvrA, with or without metabolic activation. The dose range was 50 to 5000 μ g/ plate.

Hydrolyzed Collagen (30% solution with water; sourced from fish scales; MW ~400 Da) was not clastogenic in a Chinese hamster lung (CHL) cell line chromosome aberration test.²¹ The cells were tested with and without metabolic activation.

CARCINOGENICITY

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

OTHER RELEVANT STUDIES

Type 1 Hypersensitivity

Type 1 (i.e., immediate) hypersensitivity reactions can occur in individuals allergic to certain proteins, such as those found in fish. An allergen must have at least 2 IgE-binding epitopes, and each epitope must be at least 15 amino-acid residues long, to trigger a Type 1 hypersensitivity reaction.⁵¹ Type 1 responses can be elicited in sensitized patients when pairs of IgE molecules against a specific allergen are bound to receptors on the surface of mast cells and other cells that mediate immune reactions. The binding of an allergen molecule to two receptor-bound IgE molecules results in the crosslinking of the pair of IgE molecules. The crosslinking of sufficient numbers of IgE pairs bound to the receptors on the surface of a mast cell results in degranulation of the mast cell and the release of vasoactive amines, which are responsible for the Type 1 reaction.

Skin prick tests and histamine release tests of fish Gelatin and codfish were completed in 30 fish-allergic patients (diagnosed in accordance with European Academy of Allergy and Clinical Immunology Guidelines). Codfish-specific IgE was also measured in the patients and they underwent double-blinded, placebo-controlled food challenges with fish Gelatin. The fish Gelatin used for the study was made through acid extraction of codfish skins and had an average molecular weight of 60,000 Da. All 30 patients had positive skin prick tests, histamine release tests, and specific IgE to codfish. Skin prick tests and histamine release tests with fish Gelatin were positive in 3/30 and 7/30 patients, respectively. Oral challenge resulted in two patients reporting mild subjective reactions. One patient had a mild reaction to the placebo but not the fish Gelatin. The proportion of truly sensitive patients was estimated to be 0.03. The study authors concluded that the fish Gelatin in the study presented no risk to fish-allergic patients at doses typically used in foods (3.61 g).

The potential for tuna skin-derived Gelatin to induce allergic reaction in patients with fish allergy or sensitization was investigated using the serum samples of 100 consecutive allergic patients. ⁵³ Serum IgE antibodies were tested against Gelatin and Hydrolyzed Gelatin extracted from yellowfin tuna skin and compared to extracts of yellowfin tuna flesh and skin and bovine or porcine gelatins. Of the 100 samples tested, only 3 exhibited reactivity to tuna skin-derived Gelatin (1 hydrolyzed, 2 non-hydrolyzed). No cross-reactivity was observed between bovine/porcine Gelatin and fish Gelatin.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Dermal irritation studies are presented in Table 8.^{21,54-63} No irritation was predicted in in vitro studies of Hydrolyzed Collagen (bovine sourced; up to 55%), Soluble Collagen (fish and bovine sourced; undiluted), and Hydrolyzed Elastin (fish and bovine sourced; undiluted). No irritation was observed in rabbits or guinea pigs treated with Hydrolyzed Collagen (fish sourced; 30% solution) and Hydrolyzed Elastin (source not reported; tested neat). Hydrolyzed Collagen (bovine, swine, and fish sourced) was not irritating in human studies at concentration up to 50% in water solution.

Animal

Hydrolyzed Collagen

Primary skin irritation tests in rabbits indicated that Hydrolyzed Collagen was nonirritating or minimally irritating when tested at up to 100%.

Human

Hydrolyzed Collagen

Irritation was not observed in human volunteers with healthy skin at concentrations up to 28%, but moderate irritation was observed in volunteers with dermatitis.²

Sensitization

Animal

Hydrolyzed Collagen

Hydrolyzed Collagen was nonsensitizing in guinea pig studies at up to 2%.²

Hydrolyzed Collagen (30% solution in water; fish scale sourced; MW ~400 Da) was considered to be non-sensitizing in a guinea pig maximization test using 15 Hartley guinea pigs and performed in accordance to OECD TG 406.²¹ The animals received 7.5% active ingredient intradermally with Freund's complete adjuvant during the first induction, while undiluted test material was applied to clipped dorsal skin under occlusive 48 h patch during the second induction. The animals were challenged with undiluted test material on clipped flank skin under occlusive 24 h patch. No reactions were observed in any animal 24 h and 48 h post-challenge patching.

Human

Hydrolyzed Collagen

Formulations containing 0.5% to 28% Hydrolyzed Collagen produced some irritation but no sensitization in human repeated insult patch tests (HRIPTs).²

In a HRIPT with 50 subjects, Hydrolyzed Collagen (20% solution in water; fish scale sourced; MW ~400 Da) was not sensitizing. ²¹ The test material (0.2 ml) was applied to infrascapular skin with occlusive patches.

A study of sensitization to protein hydrolysates in hair care products was performed in 3 groups of patients. ⁶⁴ The first group, which comprised 11 hairdressers with hand dermatitis, submitted to scratch and prick tests with 22 trademarked protein hydrolysates, including Soluble Collagen and Hydrolyzed Collagen, as well as quaternized hydrolyzed proteins. The second test group comprised 1260 consecutive adults with suspected allergic respiratory disease: they were subjected to skin prick tests with 1 to 3 of the protein hydrolysates. The third group of patients comprised 28 adults with atopic dermatitis and was also tested with a protein hydrolysate via a skin prick test

Positive reactions were seen in a total of 12 patients (all female with atopic dermatitis) from 3 of the 22 protein hydrolysates. All 12 had reactions to hydroxypropyl trimonium hydrolyzed collagen. Three of the 12 also had a reaction to one trademarked version of Hydrolyzed Collagen (1% solution), while 1 other had a reaction to hydroxypropyl trimonium hydrolyzed milk protein.⁶⁴

Hydrolyzed Elastin

In a HRIPT with 52 subjects, Hydrolyzed Elastin (25% w/v in corn oil; MW = 3000 Da) did not produce dermal irritation or dermal sensitization. ⁶⁵ The test patches were occlusive.

Phototoxicity

Hydrolyzed Collagen

Hydrolyzed Collagen at up to 2% was not phototoxic to guinea pigs and rabbits, nor was it phototoxic or photosensitizing to humans at up to 0.5%. UV-induced erythema was decreased after application of 10% solution of Hydrolyzed Collagen (MW = 1500 Da) onto the skin after irradiation.

OCULAR IRRITATION STUDIES

Ocular irritation studies are presented in Table 9.^{21,54-63} Hydrolyzed Collagen (fish and bovine sourced; up to 55%), Soluble Collagen (fish and bovine sourced; undiluted), and Hydrolyzed Elastin (fish and bovine sourced; undiluted) were predicted to be minimally or non-irritating in in vitro studies. Hydrolyzed Collagen (fish, swine, and bovine sourced; up to 30%) and Hydrolyzed Elastin (source not reported; tested neat) were not irritating in rabbit studies.

Animal

Hydrolyzed Collagen

Hydrolyzed Collagen was minimally irritating to rabbit eyes when tested full-strength.²

CLINICAL STUDIES

Case Reports

Elastin

A 26-year-old woman with a history of fish allergy experienced urticarial eruptions following use of a cosmetic cream containing codfish-derived Elastin. The patient's serum total IgE level was 442 kU/L, and strong radioallergosorbent test (RAST) scores for specific IgE were observed for tuna, salmon, mackerel, flatfish, codfish, horsemackerel, sardine, and salmon roe. No prick-tests were performed because of the patient's history of severe symptoms. Immunoblot analysis revealed that the patient had IgE antibodies against codfish Elastin, parvalbumin, Collagen, and transferrin. The molecular weight range of the proteins that the patient's serum reacted with was 10,000 to 20,000 Da, which corresponded to the range of codfish Elastin. The company that produced the cosmetic cream reported that the Elastin in the cosmetic cream was derived from the skin and soft tissue of codfish.

Atelocollagen and Hydrolyzed Collagen

A 30-year-old woman with a history of atopic dermatitis experienced anaphylaxis twice on separate occasions, once after consuming a fortified yogurt containing fish-sourced Hydrolyzed Collagen and once after consuming a gummy candy containing fish-sourced Hydrolyzed Collagen. Fifteen months prior to the anaphylactic episodes, the patient had been applying a moisturizer containing Atelocollagen derived from fish to her impaired facial skin. The Atelocollagen in the product has a molecular weight of 350,000 Da. Skin prick tests on the patient were positive for fish-sourced Hydrolyzed Collagen in the food products, the moisturizer, Atelocollagen, and fish Gelatin. The tests were negative for Gelatin derived from porcine skin or bovine bone. The patient denied anaphylactic reactions following ingestion of raw or cooked fish. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and IgE western blot analyses showed that the patient's serum reacted with an approximately 140,000 Da protein of Atelocollagen and a 120,000 Da protein of Gelatin from fish Collagen. Weak reactions were observed with bovine bone Gelatin protein and no reactions were observed to porcine skin Gelatin protein or fish-sourced Hydrolyzed Collagen protein. The researchers of this case study speculated that the Atelocollagen (350,000 Da) was degraded on the skin surface by proteases into smaller peptides and induced sensitization, but did not rule out the possibility that intact Collagen or degradation products with greater than 4500 Da were antigens because of the patient's impaired skin.

Hydrolyzed Collagen

A 22-year-old female reported contact urticaria following use of a hair conditioner that contained steartrimonium hydrolyzed animal protein. ⁶⁸ She had a similar, less severe reaction the year before to another hair conditioner that also contained this ingredient. The patient also had a history of hay fever and recurrent hand dermatitis. Prick testing elicited strongly positive wheal and flare response to both hair conditioners, steartrimonium hydrolyzed animal protein, and other hair conditioners that contained protein, including Hydrolyzed Collagen in some products. Negative reactions were observed when the patient was tested with protein-free hair products. Prick tests with the standard series of allergens yielded positive results for grass mix, rye, English plantain, dust mite, cow's milk, soybean, baker's yeast, and wholegrain wheat. Tests with raw meat were negative. The patient's total IgE was 221 kU/L. RASTs were negative to pork, beef, chicken, and mutton.

SUMMARY

This report assesses the safety of 19 ectodermal-derived ingredients, including Hydrolyzed Collagen, which has been previously reviewed by the Panel. Summary information presented in this safety assessment from the previous report is not summarized below.

Ingredients with the greatest number of reported uses in 2017 are Hydrolyzed Collagen (543 formulations) and Soluble Collagen (425 formulations); the majority of uses are in leave-on skin care products. Gelatin is used in a total of 334 formulations; the majority of the uses are in rinse-off bath soaps and detergents. The results of the concentration of use survey conducted in 2016 by the Council indicate Collagen has the highest reported maximum concentration of use; it is used at up to 96% in face and neck skin care products. Gelatin is used at up to 66% in bath oils, tablets, and salts. The other in-use ingredients are used at much lower concentrations.

A toxicokinetics study of fish-derived Gelatin (4000 mg/kg) in rats found that Gelatin has a high oral bioavailability.

A product containing 60% chicken-derived Collagen did not produce acute toxic effects in rats that were given a single oral dose of 5000 mg/kg.

No adverse effects were reported in a 2 week oral study of shark skin-derived Gelatin in ovariectomized rats that received the test material at up to 40 mg/100 g daily.

In subchronic toxicity studies, rats tolerated daily oral dosing of a test material containing 60% Collagen. No adverse effects were reported in a 4 month study of a dietary supplement containing a 250 ml dose of Hydrolyzed Collagen in human children

Gelatin and other ectodermal-derived proteins may be sourced from fish, which is a major food allergen that can produce Type 1 hypersensitivity reactions in sensitized individuals. Researchers have reported a low risk of IgE-mediated reactions to fish Gelatin in individuals with fish allergies.

No dermal irritation was predicted in in vitro studies of Hydrolyzed Collagen (bovine sourced; up to 55%), Soluble Collagen (fish and bovine sourced; undiluted), and Hydrolyzed Elastin (fish and bovine sourced; undiluted). No dermal irritation was observed in rabbits or guinea pigs treated with Hydrolyzed Collagen (fish sourced; 30% solution) and Hydrolyzed Elastin (source not reported; tested neat). Hydrolyzed Collagen (bovine, swine, and fish sourced) was not irritating in human dermal studies at concentration up to 50% in water solution.

A guinea pig maximization test found Hydrolyzed Collagen (fish sourced; 30% solution in water) to be non-sensitizing. In HRIPT studies, Hydrolyzed Elastin (25% w/v in corn oil) and Hydrolyzed Collagen (fish sourced; 20% solution in water) did not produce dermal irritation or dermal sensitization. Hydrolyzed Collagen produced positive results in skin prick tests of dermatitic patients.

Hydrolyzed Collagen (fish and bovine sourced; up to 55%), Soluble Collagen (fish and bovine sourced; undiluted), and Hydrolyzed Elastin (fish and bovine sourced; undiluted) were predicted to be minimally or non-irritating in ocular in vitro studies. Hydrolyzed Collagen (fish, swine, and bovine sourced; up to 30%) and Hydrolyzed Elastin (source not reported; tested neat) were not irritating in rabbit ocular studies.

Case reports of dermal sensitization to cosmetics containing Elastin, Atelocollagen, and Collagen derived from fish have been described in the published literature. Reactions to Hydrolyzed Collagen have been reported as well.

No relevant published DART or carcinogenicity studies on ectodermal-derived proteins and peptides were identified in a literature search for these ingredients, and no unpublished data were submitted.

DISCUSSION

These proteins and peptides, which are similar to the other proteins and peptides reviewed by the Panel, 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. The Panel also found that the earlier assessments of Hydrolyzed Collagen supported the safety of these ingredients in cosmetic products. The Panel noted a general lack of systemic toxicity data (i.e. reproductive and developmental toxicity and carcinogenicity data); however, they did not believe that these proteins and peptides would cause adverse systemic effects in the general population.

The Panel noted that fish proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. The Panel expressed concern that sensitized individuals would not easily recognizes cosmetic products containing fish-derived collagen based on the current naming conventions used in the ingredient lists on product labels (e.g., Collagen and Hydrolyzed Collagen may be sourced from fish, though "fish" is not in the ingredient name). The Panel strongly urged manufacturers to place a warning on the label of products that may contain fish-derived ingredients so that sensitive individuals may avoid exposure.

The Panel was also concerned about the inherent risks of using animal-derived ingredients in cosmetic products, namely the potential for transmission of infectious agents. While Gelatin and Collagen prepared exclusively from hides and skins do not have the propensity to carry disease, the Panel stressed that these ingredients must be free of detectible infectious pathogens (i.e., BSE) if these materials are derived from other bovine materials. Raw material suppliers and formulators of these ingredients must assure that these ingredients are free from pathogenic viruses and other infectious agents.

The Panel discussed the issue of incidental inhalation exposure from hair care products, skin care preparations, face powders, and fragrances. There were no inhalation toxicity data available. Although the Panel noted that droplets/particles from spray and loose-powder cosmetic products would not be respirable to any appreciable amount, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the

lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The Panel concluded that the 19 ectodermal-derived proteins and peptides listed below are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Ammonium Hydrolyzed Collagen

Atelocollagen

Calcium Hydrolyzed Collagen*

Collagen Elastin Fibronectin Gelatin Hydrolyzed Actin

Hydrolyzed Collagen

Hydrolyzed Collagen Extract*

Hydrolyzed Elastin Hydrolyzed Fibronectin Hydrolyzed Gelatin* Hydrolyzed Reticulin Hydrolyzed Spongin* MEA-Hydrolyzed Collagen

Soluble Collagen Soluble Elastin*

Zinc Hydrolyzed Collagen*

^{*}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

Ingredient CAS No.	Definition	Function
Ammonium Hydrolyzed	Ammonium Hydrolyzed Collagen is the ammonium salt of Hydrolyzed	hair conditioning agents; skin-
Collagen	Collagen.	conditioning agents-misc.
68951-88-2 [generic to		
ammonium hydrolyzed proteins]		
Calcium Hydrolyzed Collagen	Calcium Hydrolyzed Collagen is the calcium salt of Hydrolyzed Collagen.	nail conditioning agents; skin- conditioning agents-misc.
MEA-Hydrolyzed Collagen	MEA-Hydrolyzed Collagen is the monoethanolamine salt of Hydrolyzed Collagen.	hair conditioning agents; skin- conditioning agents-misc.
Zinc Hydrolyzed Collagen	Zinc Hydrolyzed Collagen is the zinc salt of Hydrolyzed Collagen.	hair conditioning agents; skin- conditioning agents-misc.
Hydrolyzed Collagen 73049-73-7 [generic to animal peptones] 92113-31-0	Hydrolyzed Collagen is the hydrolysate of animal or fish collagen derived by acid, enzyme or other method of hydrolysis. It is characterized by a significant level of hydroxyproline residues.	hair conditioning agents; nail conditioning agents; skin-conditioning agents-misc.
Hydrolyzed Collagen Extract	Hydrolyzed Collagen Extract is the extract of Hydrolyzed Collagen.	skin protectants
Soluble Collagen	Soluble Collagen is a non-hydrolyzed, native protein derived from the connective tissue of animals. It consists essentially of a mixture of the precursors of mature collagen. It has a triple helical structure and is predominantly not cross-linked.	hair conditioning agents; skin- conditioning agents-misc.
Collagen 9007-34-5	Collagen is the protein found in cartilage and other connective tissues in animals.	hair conditioning agents; skin- conditioning agents-misc.
Atelocollagen 55963-88-7	Atelocollagen is the protein obtained when the telopeptides are enzymatically removed from collagen.	hair conditioning agents; skin- conditioning agents-misc.
Gelatin 9000-70-8	Gelatin is a product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals.	binders; hair conditioning agents; lytic agents; oral health care drugs; skin-conditioning agents-misc.; viscosity increasing agents-aqueous
Hydrolyzed Gelatin 68410-45-7 [specific to enzymatic digest product]	Hydrolyzed Gelatin is the hydrolysate of Gelatin derived by acid, enzyme or other method of hydrolysis.	skin-conditioning agents-misc.
Hydrolyzed Reticulin 73049-73-7 [generic to animal peptones] 99924-37-5	Hydrolyzed Reticulin is the hydrolysate of the reticulin portion of animal connective tissue derived by acid, enzyme or other method of hydrolysis. [Reticulin is a type of fiber in connective tissue composed of type III collagen secreted by reticular cells]	hair conditioning agents; skin- conditioning agents-misc.
Hydrolyzed Actin 73049-73-7 [generic to animal peptones]	Hydrolyzed Actin is the hydrolysate of actin derived by acid, enzyme or other method of hydrolysis.	hair conditioning agents; skin-conditioning agents-misc.
Elastin 9007-58-3	Elastin is a fibrous protein found in the connective tissue of animals.	hair conditioning agents; skin- conditioning agents-misc.
Soluble Elastin	Soluble Elastin a water soluble non-hydrolyzed, native protein derived from Elastin.	skin-conditioning agents-misc.
Hydrolyzed Elastin 100085-10-7 73049-73-7 [generic to animal peptones] 91080-18-1	Hydrolyzed Elastin is the hydrolysate of elastin derived by acid, enzyme or other method of hydrolysis.	hair conditioning agents; skin- conditioning agents-emollient; skin-conditioning agents-misc.
Fibronectin 98725-78-1	Fibronectin is a glycoprotein found in connective tissues, basement membranes, in plasma and other body fluids.	hair conditioning agents; skin- conditioning agents-misc.
Hydrolyzed Fibronectin 100085-35-6 73049-73-7 [generic to animal peptones]	Hydrolyzed Fibronectin is the hydrolysate of Fibronectin derived by acid, enzyme or other method of hydrolysis.	hair conditioning agents; skin- conditioning agents-misc.
Hydrolyzed Spongin	Hydrolyzed Spongin is the hydrolysate of spongin derived by acid, enzyme or other method of hydrolysis. [Spongin is a collagen-type protein, common to marine sponges]	skin-conditioning agents-misc.

Table 2. Reported molecular weights of ectodermal-derived proteins^{2,11,15,21,32,69-71}

Table 2: Reported morecular v	Table 2: Reported molecular weights of ectoderman derived proteins					
Ingredient	Molecular Weight (Da) Range					
Collagen (native)	130,000 to > 1,000,000					
Soluble Collagen	30,000 - 40,000, but may be up to an average of 300,000					
Hydrolyzed Collagen	400 to 25,000					
Hydrolyzed Actin	58.4% < 5000; 41.4% > 5000 and < 30,000					
Hydrolyzed Elastin	500 to 150,000					
Fibronectin	> 200,000					

Table 3. Method of manufacturing

Ingredient	Source	Procedure	Reference
Collagen	Not reported	Prepared by dissolving the mineral part of bones with phosphoric acid.	11
Hydrolyzed Collagen	Bovine or fish	Prepared by alkaline hydrolysis followed by enzymatic hydrolysis to the desired molecular weight	2,3
Hydrolyzed Collagen (MW = 2000 Da)	Bovine	Prepared by combination of alkaline and enzymatic hydrolysis	71
Elastin	Farm animals such as cattle or goats	Prepared from cattle aortas through extraction with sodium hydroxide at 100° C and filtration (which both may be repeated several times), precipitation, neutralization with hydrochloric acid, and washing to remove residual salt. The resultant extract may then be purified by autoclaving or by amylase pretreatment.	15
Elastin	Collagen (unspecified)	Elastin may be a byproduct of the purification of Collagen	15
Hydrolyzed Elastin (MW=1000-4000 Da)	Codfish skin or bovine neck tendons	Prepared by washing and purifying to remove soil and other residual material and then dried. Dried material is then hydrolyzed for several hours until the target molecular weight is reached. The final product is a solution, with the bovine source material being concentrated to a 30% active content.	72,73
Hydrolyzed Elastin (MW = 3000-4000 Da)	Numerous sourced animal ligaments or hides	Prepared by enzymatic hydrolysis (by pancreatic elastase, ficin, pepsin or trypsin) or acid hydrolysis at high temperatures (70-100° C, depending on acid) at several 1 hour intervals.	15
Hydrolyzed Elastin (MW=2000-4000 Da)	Not reported	Manufactured by enzymatic hydrolysis for a specific duration of time and at an elevated temperature (details not provided). Resultant hydrolyzed protein composed of di- and tri-peptides.	62
Gelatin	Collagen (unspecified)	Prepared by the acid, alkaline or enzymatic hydrolysis of Collagen. Type A Gelatin is produced by the acid processing of collagenous raw materials and exhibits an isoelectric point between pH 7 and pH 9. Type B Gelatin is produced by the alkaline or lime processing of collagenous raw materials and exhibits an isoelectric point between pH 4.6 and pH 5.2.	17
Soluble Collagen	Bovine dermal tissues, bony fish skins, or tropical fish swim bladders	Extracted by neutral salt solutions	74
Soluble Elastin	Cattle ligaments	Obtained by acid treatment at 80° C and a pH less than 4, followed by filtration, grinding, enzymatic treatment at pH 9/13 (alkaline proteases in the presences of urea), and finally neutralizing enzymes at 90° C.	15

Table 4. Amino acid residue profile of Collagen, soluble Collagen, and Elastin (residues per 1000). 14,15,75

Amino Acid	Collagen	Soluble Collagen	Elastin
Hydroxyproline	73-98	95.9-105.8	7.1
Aspartic acid	42-48	43.9-48.3	7.3
Threonine	17-19	15.2-21.1	10.1
Serine	22-31	28.3-44.1	9.0
Glutamic acid	73-80	68.3-86.1	17.4
Proline	121-125	115.6-144.8	125.4
Glycine	325-347	310.3-324.0	316.2
Alanine	112-114	88.2-107.3	223.3
Cysteine	not determined	not determined	not determined
Valine	19-26	not determined	134.0
Methionine	not determined	3.9-8.3	not detected
Isoleucine	11-14	11.8-13.0	26.6
Leucine	24-31	25.5-29.3	64.7
Tyrosine	1-7	1.8-3.3	6.1
Phenylalanine	13-16	10.7-16.3	33.6
Histidine	4-6	4.8-6.5	0.5
Hydroxylysine	not determined	8.3-9.8	not detected
Lysine	26-31	25.8-27.7	3.6
Arginine	50-55	46.5-52.0	6.0
Tryptophan	not determined	not determined	not determined

Table 5. Frequency (2017) and concentration of use (2016) according to duration and type of exposure for ectodermal-derived proteins and peptides. ^{36,37}

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	
·	Ammonium	Hydrolyzed Collagen	Atelocollagen			Collagen		Elastin	
Totals [†]	NR	0.03-0.12	118	0.0000001-0.099	299	0.00005-96	46	NR	
Duration of Use									
Leave-On	NR	0.1-0.12	114	0.0000001-0.005	241	0.0001-96	40	NR	
Rinse Off	NR	0.03-0.05	4	0.0000001-0.099	58	0.00005-1.3	6	NR	
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR	
Exposure Type									
Eye Area	NR	NR	17	0.0000022	31	0.00012-0.2	2	NR	
Incidental Ingestion	NR	NR	39	0.0004	5	0.0035-0.05	NR	NR	
Incidental Inhalation-Spray	NR	NR	19 ^b ; 18 ^c	0.0000001 ^b	55 ^b ; 94 ^c	0.00095^{b}	11 ^b ; 11 ^c	NR	
Incidental Inhalation-Powder	NR	0.1ª	1; 18 ^c	0.000022; 0.00002- 0.000033 ^a	94°	0.0018-96 ^a	11°	NR	
Dermal Contact	NR	0.03-0.12	66	0.0000001-0.099	240	0.00005-96	42	NR	
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR	
Hair - Non-Coloring	NR	0.05	1	NR	39	0.00095-1.3	4	NR	
Hair-Coloring	NR	NR	NR	NR	1	NR	NR	NR	
Nail	NR	NR	NR	NR	4	NR	NR	NR	
Mucous Membrane	NR	NR	39	0.0004	8	0.0035-0.67	NR	NR	
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR	

	Fibi	ronectin		Gelatin	Hyd	rolyzed Actin	Ну	drolyzed Elastin
Totals [†]	2	NR	334	0.000052-66	20	0.00075-1.6	278	0.00000035-5
Duration of Use								
Leave-On	2	NR	33	0.0003-37.8	18	1.6	211	0.0000035-5
Rinse Off	NR	NR	301	0.000052-9.5	2	0.00075	67	0.0000035-2.5
Diluted for (Bath) Use	NR	NR	NR	0.21-66	NR	NR	NR	NR
Exposure Type								_
Eye Area	NR	NR	NR	0.5-1	5	1.6	10	0.00035-0.5
Incidental Ingestion	NR	NR	3	NR	NR	NR	2	0.00035-0.15
Incidental Inhalation-Spray	2°	NR	19 ^b ; 6 ^c	0.03; 0.009-0.095 ^b ; 0.016 ^c	7 ^b ; 6 ^c	NR	57 ^b ; 88 ^c	0.00031-0.42; 0.002-0.24 ^b
Incidental Inhalation-Powder	2°	NR	1; 6 ^c	0.016°; 0.03-37.8°	6°	NR	88°; 2ª	0.0000035; 0.00025-5 ^a
Dermal Contact	2	NR	286	0.0003-66	10	NR	227	0.00000035-5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	12	0.000052-0.5	7	0.00075	48	0.00031-2.5
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	33	0.001-0.02	NR	NR	NR	NR
Mucous Membrane	NR	NR	257	0.0011-66	NR	NR	5	0.00035-0.15
Baby Products	NR	NR	NR	NR	NR	NR	4	NR

Table 5. Frequency (2017) and concentration of use (2016) according to duration and type of exposure for ectodermal-derived proteins and peptides. 36,37

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%
-	Hydrol	yzed Fibronectin	Hydr	Hydrolyzed Reticulin		MEA-Hydrolyzed Collagen		ible Collagen*
Totals [†]	10	0.025-0.05	NR	0.025-0.05	NR	0.03-0.12	425	0.0000005-0.7
Duration of Use								
Leave-On	9	0.05	NR	0.05	NR	0.1-0.12	368	0.0000005-0.7
Rinse Off	1	0.025	NR	0.025	NR	0.03-0.06	57	0.000025-0.014
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	0.000035-0.005
Exposure Type								
Eye Area	1	NR	NR	NR	NR	NR	51	0.00003-0.05
Incidental Ingestion	NR	NR	NR	NR	NR	NR	6	0.00035-0.01
Incidental Inhalation-Spray	4 ^b ; 3 ^c	NR	NR	NR	NR	NR	104 ^b ; 141 ^c	0.000005-0.0035; 0.00035-0.0035 ^b
Incidental Inhalation-Powder	3°	NR	NR	NR	NR	0.1 ^a	141°	0.0035; 0.0001-0.7 ^a
Dermal Contact	10	0.025-0.05	NR	0.025-0.5	NR	0.03-0.12	379	0.000005-0.7
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	0.06	15	0.00001-0.014
Hair-Coloring	NR	NR	NR	NR	NR	NR	1	0.000025-0.0005
Nail	NR	NR	NR	NR	NR	NR	NR	0.0000005-0.01
Mucous Membrane	NR	NR	NR	NR	NR	NR	9	0.000035-0.01
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Soluble	Collagen Extract‡	
Totals [†]	2	NR	
Duration of Use			
Leave-On	2	NR	
Rinse Off	NR	NR	
Diluted for (Bath) Use	NR	NR	
Exposure Type			
Eye Area	NR	NR	
Incidental Ingestion	NR	NR	
Incidental Inhalation-Spray	1 ^b ; 1 ^c	NR	
Incidental Inhalation-Powder	1 ^c	NR	
Dermal Contact	2	NR	
Deodorant (underarm)	NR	NR	
Hair - Non-Coloring	NR	NR	
Hair-Coloring	NR	NR	
Nail	NR	NR	
Mucous Membrane	NR	NR	
Baby Products	NR	NR	

NR = Not reported. Data highlighted is new since the Panel's last review.

[†] 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 powders, but it is not specified whether the reported uses are powders.

^{b.} It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

^c Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^{*} Includes 25 uses listed in the VCRP as "soluble animal collagen".

‡ Not listed in the Dictionary, possibly the same as Collagen Extract.

Table 6. Historic and current frequency and concentration of use according to duration and type of exposure for Hydrolyzed Collagen. 36,37

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	1981 uses/concentrations		2002 uses	/2004 concentrations	2017 use	s/2016 concentrations
Totals [†]	923	<u><0.1 - >50</u>	570 ^d	0.000004-6	543	0.00003-16.5
Duration of Use						
Leave-On	284	≤0.1 - ≤50	245	0.000004-6	365	0.00003-16.5
Rinse Off	633	<u>≤</u> 0.1 - >50	321	0.007-0.2	177	0.00003-3
Diluted for (Bath) Use	6	>0.1-5	4	NR	1	NR
Exposure Type						
Eye Area	40	<u><</u> 0.1 - <u><</u> 5	21	0.000004-3	23	0.001-3.2
Incidental Ingestion	15	<u>≤</u> 1	7	1	5	0.01-0.1
Incidental Inhalation-Spray	7; 96 ^a ; 46 ^b	$<1;>0.1 ->50^a; \le 10^b$	3; 108 ^a ; 38 ^b	0.000004-1 ^a ; 0.06-6 ^b	116 ^a ; 139 ^b	0.0017-0.28; 0.0092-16.5 ^a
Incidental Inhalation-Powder	5; 46 ^b	$\leq 1; \leq 10^{b}$	4; 38 ^b	$0.5; 0.06-6^{b}$	3; 139 ^b ; 2 ^c	0.0015-5°
Dermal Contact	207	<u>≤</u> 0.1 - <u>≤</u> 25	210	0.000004-6	401	0.0003-5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	609	>0.1 ->50	331	0.02-0.2	121	0.0003-16.5
Hair-Coloring	46	≤0.1 - ≤5	4	NR	3	0.15-1.2
Nail	18	≤0.1 - ≤50	9	NR	7	0.00003-0.01
Mucous Membrane	24	>0.1-5	28	0.1-1	22	0.0024-0.1
Baby Products	1	<u>≤</u> 0.1	NR	NR	4	NR

NR = Not reported.

Table 7. Ingredients not reported in use.
Calcium Hydrolyzed Collagen
Zinc Hydrolyzed Collagen
Hydrolyzed Collagen Extract
Hydrolyzed Gelatin
Soluble Elastin
Hydrolyzed Spongin

[†] 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. Majority of the uses were categorized as "Hydrolyzed Animal Protein" in the VCRP database.

Table 8. Dermal irritation studies of Hydrolyzed Collagen, Soluble Collagen, and Hydrolyzed Elastin.

Ingredient	Concentration	Method	Result	Reference
		In Vitro		
Hydrolyzed Collagen (MW ~ 2000 Da; source = bovine)	25, 50, 75, 100, or 125 μl	Irritection® dermal model	Predicted to be non-irritating	54
Hydrolyzed Collagen (source = bovine)	55% solution, undiluted	EpiDerm TM Assay	Predicted to be non-irritating	57
Soluble Collagen (source = Atlantic cod)	25, 50, 75, 100, or 125 μl	Irritection® dermal model	Predicted to be non-irritating	56
Soluble Collagen (source = bovine)	Undiluted	EpiDerm TM Assay	Predicted to be non-irritating	61
Hydrolyzed Elastin (MW ~4000 Da; source = fish)	Concentration not reported	EpiDerm TM Assay	Predicted to be non-irritating	62
Hydrolyzed Elastin (MW ~4000 Da; source not reported)	Concentration not reported	EpiDerm TM Assay	Predicted to be non-irritating	62
Hydrolyzed Elastin (source = Atlantic cod)	Undiluted	EpiDerm TM Assay	Predicted to be non-irritating	58
Hydrolyzed Elastin (source = young cattle)	25, 50, 75, 100, or 125 μ1	Irritection® dermal model	Predicted to be non-irritating	55
Hydrolyzed Elastin (source = cow skin)	Undiluted	EpiDerm TM Assay	Predicted to be non-irritating	60
Hydrolyzed Elastin (source = cow skin)	Undiluted	EpiDerm TM Assay	Predicted to be non-irritating	59
		Animal		
Hydrolyzed Collagen (MW ~400 Da; source = fish scale)	30 % solution in water, tested neat	Primary skin irritation test in 3 New Zealand White rabbits; occluded 2.5 cm ² patches with 0.5 ml test material; test	Very slight erythema noted in one treated skin 1 h post- patch removal; primary irritation index was 0.0; test	21
W 1 1 1 1 0 11 0 11 0 11 0 11 11	20.0%	performed in accordance to OECD TG 404	material non-irritating and not corrosive	21
Hydrolyzed Collagen (MW ~400 Da; source = fish scale)	30 % solution in water, tested neat	Cumulative skin irritation test in 3 male and 3 female Hartley guinea pigs; once daily treatments for 14 days to 2.0 cm ² clipped dorsal skin	Non-irritating	
Hydrolyzed Elastin (MW ~3000 Da; source not reported)	Tested neat	Draize primary dermal irritation study in 6 New Zealand white rabbits; test sites occluded for 24 h	Not a primary irritant; primary irritation index was 0.38	63
H I I I C II ANV	50% solution in water,	Human	NT ' ' '	21
Hydrolyzed Collagen (MW ~400 Da; source = bovine gelatin)	tested neat	24 h occlusive patch test in 60 subjects (50 healthy, 10 allergic); 0.5 ml applied to left front arms	Non-irritating	
Hydrolyzed Collagen (MW ~400 Da; source = bovine gelatin)	30% solution in water, tested neat	24 h occlusive patch test in 60 subjects (50 healthy, 10 allergic); 0.5 ml applied to left front arms	Non-irritating	21
Hydrolyzed Collagen (MW ~1000 Da: source = swine gelatin)	30% solution in water, tested neat	24 h occlusive patch test in 60 subjects (50 healthy, 10 allergic); 0.5 ml applied to left front arms	Non-irritating	21
Hydrolyzed Collagen (MW ~2000 Da; source = swine gelatin)	30% solution in water, tested neat	24 h occlusive patch test in 60 subjects (50 healthy, 10 allergic); 0.5 ml applied to left front arms	Non-irritating	21
Hydrolyzed Collagen (MW ~400 Da; source = fish scale)	30% solution in water, tested neat	24 h occlusive patch test in 21 healthy subjects; 0.03 g applied to backs	Non-irritating	21
Hydrolyzed Collagen (MW ~400 Da; source = fish scale)	20% solution in water, tested neat	24 h occlusive patch test in 20 healthy subjects	Slight erythema in one subject; non-irritating	21

Table 9. Ocular irritation studies of Hydrolyzed Collagen, Soluble Collagen, and Hydrolyzed Elastin

Ingredient	Concentration	Method	Result	Reference
		In Vitro		54
Hydrolyzed Collagen (MW ~ 2000 Da; source = bovine)	25, 50, 75, 100, or 125 μ1	Irritection® ocular model	Predicted to be a minimal irritant	
Hydrolyzed Collagen (MW ~400 Da; source = fish scale)	10% active in purified water	BCOP in accordance to OECD TG 437	Predicted to be non-irritating	21
Hydrolyzed Collagen (source = bovine)	55% solution, undiluted	EpiOcular TM Assay	Predicted to be non-irritating	57
Soluble Collagen (source = Atlantic cod)	25, 50, 75, 100, or 125 μl	Irritection® ocular model	Predicted to be a minimal irritant	56
Soluble Collagen (source = bovine)	Undiluted	EpiOcular TM Assay	Predicted to be non-irritating	61
Hydrolyzed Elastin (source = Atlantic cod)	Undiluted	EpiOcular TM Assay	Predicted to be non-irritating	58
Hydrolyzed Elastin (source = young cattle)	25, 50, 75, 100, or 125 μ1	Irritection® ocular model	Predicted to be a minimal irritant	55
Hydrolyzed Elastin (source = cow skin)	Undiluted	EpiOcular TM Assay	Predicted to be non-irritating	60
Hydrolyzed Elastin (source = cow skin)	Undiluted	EpiOcular TM Assay	Predicted to be non-irritating	59
Hydrolyzed Elastin (MW = 2000-4000 Da; 2 products, one source = fish, other source not reported)	Concentration not reported	EpiOcular™ Assay	Predicted to be non-irritating	62
Toponeu)	Ocular	- Animal		
Hydrolyzed Collagen (MW ~400 Da; source = bovine gelatin)	25% active diluted by 1%, 5%, 15%, 25%, and 50% v/v in saline	Ocular irritation study in 15 male rabbits; test material instilled in one eye while other eye served as control; eyes observed at instillation, 1 h and 24 h post	Non-irritating	21
Hydrolyzed Collagen (MW ~400 Da; source = bovine gelatin)	15% active diluted by 1%, 5%, 15%, 25%, and 50% v/v in saline	Ocular irritation study in 15 male rabbits; test material instilled in one eye while other eye served as control; eyes observed at instillation, 1 h and 24 h post	Non-irritating	21
Hydrolyzed Collagen (MW ~1000 Da; source = swine gelatin)	3% active diluted by 0.1%, 0.5%, 1%, 5%, and 10% v/v in saline	Ocular irritation study in 15 male rabbits; test material instilled in one eye while other eye served as control; eyes observed at instillation, 1 h and 24 h post	Non-irritating	21
Hydrolyzed Collagen (MW ~2000 Da; source = swine gelatin)	15% active diluted by 1%, 5%, 15%, 25%, and 50% v/v in saline	Ocular irritation study in 15 male rabbits; test material instilled in one eye while other eye served as control; eyes observed at instillation, 1 h and 24 h post	Non-irritating	21
Hydrolyzed Collagen (MW ~400 Da; source = fish scale)	30% active, tested neat	Ocular irritation study in 3 New Zealand White rabbits; test performed in accordance with OECD TG 405	Maximum group mean score was 4.0; minimally irritating	21
Hydrolyzed Elastin (MW = 3000 Da; source not reported)	tested neat	Draize ocular irritation study in 6 New Zealand white rabbits; treated eye was not rinsed	Not a primary irritant	63

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2017 FDA VCRP RAW DATA

03D - Eye Lotion	COLLAGEN	9
03E - Eye Makeup Remover	COLLAGEN	1
03F - Mascara	COLLAGEN	10
03G - Other Eye Makeup Preparations	COLLAGEN	11
05A - Hair Conditioner	COLLAGEN	13
05C - Hair Straighteners	COLLAGEN	1
05E - Rinses (non-coloring)	COLLAGEN	1
05F - Shampoos (non-coloring)	COLLAGEN	10
05G - Tonics, Dressings, and Other Hair Grooming	COLLAGEN	8
Aids		
05I - Other Hair Preparations	COLLAGEN	6
06D - Hair Shampoos (coloring)	COLLAGEN	1
07C - Foundations	COLLAGEN	3
07E - Lipstick	COLLAGEN	5
07I - Other Makeup Preparations	COLLAGEN	4
08C - Nail Creams and Lotions	COLLAGEN	1
08E - Nail Polish and Enamel	COLLAGEN	1
08G - Other Manicuring Preparations	COLLAGEN	2
10A - Bath Soaps and Detergents	COLLAGEN	1
10E - Other Personal Cleanliness Products	COLLAGEN	2
11A - Aftershave Lotion	COLLAGEN	1
11E - Shaving Cream	COLLAGEN	1
12A - Cleansing	COLLAGEN	7
12C - Face and Neck (exc shave)	COLLAGEN	79
12D - Body and Hand (exc shave)	COLLAGEN	15
12F - Moisturizing	COLLAGEN	26
12G - Night	COLLAGEN	15
12H - Paste Masks (mud packs)	COLLAGEN	20
12I - Skin Fresheners	COLLAGEN	4
12J - Other Skin Care Preps	COLLAGEN	39
13A - Suntan Gels, Creams, and Liquids	COLLAGEN	2
01B - Baby Lotions, Oils, Powders, and Creams	HYDROLYZED COLLAGEN	2
01C - Other Baby Products	HYDROLYZED COLLAGEN	2
02A - Bath Oils, Tablets, and Salts	HYDROLYZED COLLAGEN	1
03D - Eye Lotion	HYDROLYZED COLLAGEN	4
03F - Mascara	HYDROLYZED COLLAGEN	6
03G - Other Eye Makeup Preparations	HYDROLYZED COLLAGEN	13
04C - Powders (dusting and talcum, excluding	HYDROLYZED COLLAGEN	3
aftershave talc)	LIVEROLVZED COLLACEN	40
05A - Hair Conditioner	HYDROLYZED COLLAGEN	48
05C - Hair Straighteners 05D - Permanent Waves	HYDROLYZED COLLAGEN HYDROLYZED COLLAGEN	2
05E - Rinses (non-coloring)	HYDROLYZED COLLAGEN HYDROLYZED COLLAGEN	1
05E - Rinses (non-coloring) 05F - Shampoos (non-coloring)	HYDROLYZED COLLAGEN HYDROLYZED COLLAGEN	42
05G - Tonics, Dressings, and Other Hair Grooming	I I I DNOLIZED COLLAGEN	42

Aids		
05H - Wave Sets	HYDROLYZED COLLAGEN	3
05I - Other Hair Preparations	HYDROLYZED COLLAGEN	14
06A - Hair Dyes and Colors (all types requiring	HYDROLYZED COLLAGEN	1
caution statements and patch tests)		
06G - Hair Bleaches	HYDROLYZED COLLAGEN	1
06H - Other Hair Coloring Preparation	HYDROLYZED COLLAGEN	1
07C - Foundations	HYDROLYZED COLLAGEN	5
07D - Leg and Body Paints	HYDROLYZED COLLAGEN	1
07E - Lipstick	HYDROLYZED COLLAGEN	3
07F - Makeup Bases	HYDROLYZED COLLAGEN	1
07I - Other Makeup Preparations	HYDROLYZED COLLAGEN	5
08A - Basecoats and Undercoats	HYDROLYZED COLLAGEN	1
08E - Nail Polish and Enamel	HYDROLYZED COLLAGEN	4
08G - Other Manicuring Preparations	HYDROLYZED COLLAGEN	2
09B - Mouthwashes and Breath Fresheners	HYDROLYZED COLLAGEN	2
10A - Bath Soaps and Detergents	HYDROLYZED COLLAGEN	5
10E - Other Personal Cleanliness Products	HYDROLYZED COLLAGEN	11
12A - Cleansing	HYDROLYZED COLLAGEN	10
12C - Face and Neck (exc shave)	HYDROLYZED COLLAGEN	128
12D - Body and Hand (exc shave)	HYDROLYZED COLLAGEN	11
12F - Moisturizing	HYDROLYZED COLLAGEN	88
12G - Night	HYDROLYZED COLLAGEN	10
12H - Paste Masks (mud packs)	HYDROLYZED COLLAGEN	48
12I - Skin Fresheners	HYDROLYZED COLLAGEN	3
12J - Other Skin Care Preps	HYDROLYZED COLLAGEN	46
13A - Suntan Gels, Creams, and Liquids	HYDROLYZED COLLAGEN	1
13B - Indoor Tanning Preparations	HYDROLYZED COLLAGEN	2
13C - Other Suntan Preparations	HYDROLYZED COLLAGEN	1
-		
05F - Shampoos (non-coloring)	SOLUBLE ANIMAL COLLAGEN	1
07F - Makeup Bases	SOLUBLE ANIMAL COLLAGEN	22
12D - Body and Hand (exc shave)	SOLUBLE ANIMAL COLLAGEN	1
12J - Other Skin Care Preps	SOLUBLE ANIMAL COLLAGEN	1
03D - Eye Lotion	SOLUBLE COLLAGEN	18
03F - Mascara	SOLUBLE COLLAGEN	24
03G - Other Eye Makeup Preparations	SOLUBLE COLLAGEN	9
05A - Hair Conditioner	SOLUBLE COLLAGEN	4
05F - Shampoos (non-coloring)	SOLUBLE COLLAGEN	4
05G - Tonics, Dressings, and Other Hair Grooming	SOLUBLE COLLAGEN	5
Aids		
05H - Wave Sets	SOLUBLE COLLAGEN	1
06G - Hair Bleaches	SOLUBLE COLLAGEN	1
07C - Foundations	SOLUBLE COLLAGEN	11
07E - Lipstick	SOLUBLE COLLAGEN	6
07F - Makeup Bases	SOLUBLE COLLAGEN	1
07G - Rouges	SOLUBLE COLLAGEN	1
07I - Other Makeup Preparations	SOLUBLE COLLAGEN	7

10A - Bath Soaps and Detergents	SOLUBLE COLLAGEN	3
11A - Aftershave Lotion	SOLUBLE COLLAGEN	2
12A - Cleansing	SOLUBLE COLLAGEN	25
12C - Face and Neck (exc shave)	SOLUBLE COLLAGEN	110
12D - Body and Hand (exc shave)	SOLUBLE COLLAGEN	30
12F - Moisturizing	SOLUBLE COLLAGEN	75
12G - Night	SOLUBLE COLLAGEN	21
12H - Paste Masks (mud packs)	SOLUBLE COLLAGEN	18
12I - Skin Fresheners	SOLUBLE COLLAGEN	3
12J - Other Skin Care Preps	SOLUBLE COLLAGEN	21
12D - Body and Hand (exc shave)	SOLUBLE COLLAGEN EXTRACT	1
12F - Moisturizing	SOLUBLE COLLAGEN EXTRACT	1
03D - Eye Lotion	ELASTIN	1
03G - Other Eye Makeup Preparations	ELASTIN	1
05A - Hair Conditioner	ELASTIN	1
05F - Shampoos (non-coloring)	ELASTIN	1
05I - Other Hair Preparations	ELASTIN	2
07I - Other Makeup Preparations	ELASTIN	1
11A - Aftershave Lotion	ELASTIN	1
12A - Cleansing	ELASTIN	3
12C - Face and Neck (exc shave)	ELASTIN	9
12D - Body and Hand (exc shave)	ELASTIN	2
12F - Moisturizing	ELASTIN	7
12G - Night	ELASTIN	2
12H - Paste Masks (mud packs)	ELASTIN	1
12I - Skin Fresheners	ELASTIN	1
12J - Other Skin Care Preps	ELASTIN	12
13A - Suntan Gels, Creams, and Liquids	ELASTIN	1
01B - Baby Lotions, Oils, Powders, and Creams	HYDROLYZED ELASTIN	2
01C - Other Baby Products	HYDROLYZED ELASTIN	2
03D - Eye Lotion	HYDROLYZED ELASTIN	2
03F - Mascara	HYDROLYZED ELASTIN	1
03G - Other Eye Makeup Preparations	HYDROLYZED ELASTIN	7
05A - Hair Conditioner	HYDROLYZED ELASTIN	21
05F - Shampoos (non-coloring)	HYDROLYZED ELASTIN	16
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROLYZED ELASTIN	11
07C - Foundations	HYDROLYZED ELASTIN	4
07E - Lipstick	HYDROLYZED ELASTIN	2
07F - Makeup Bases	HYDROLYZED ELASTIN	22
07I - Makeup Bases 07I - Other Makeup Preparations	HYDROLYZED ELASTIN	2
10E - Other Personal Cleanliness Products	HYDROLYZED ELASTIN	3
11A - Aftershave Lotion	HYDROLYZED ELASTIN	1
12A - Cleansing	HYDROLYZED ELASTIN	20
12C - Face and Neck (exc shave)	HYDROLYZED ELASTIN	59
12D - Body and Hand (exc shave)	HYDROLYZED ELASTIN	29
122 Dody and Hand (one share)	51.051.255 251.01114	23

12F - Moisturizing	HYDROLYZED ELASTIN	34
12G - Night	HYDROLYZED ELASTIN	10
12H - Paste Masks (mud packs)	HYDROLYZED ELASTIN	7
12J - Other Skin Care Preps	HYDROLYZED ELASTIN	21
13B - Indoor Tanning Preparations	HYDROLYZED ELASTIN	2
3 1		
12C - Face and Neck (exc shave)	FIBRONECTIN	2
03G - Other Eye Makeup Preparations	HYDROLYZED FIBRONECTIN	1
12C - Face and Neck (exc shave)	HYDROLYZED FIBRONECTIN	2
12D - Body and Hand (exc shave)	HYDROLYZED FIBRONECTIN	1
12F - Moisturizing	HYDROLYZED FIBRONECTIN	2
12G - Night	HYDROLYZED FIBRONECTIN	2
12H - Paste Masks (mud packs)	HYDROLYZED FIBRONECTIN	1
12J - Other Skin Care Preps	HYDROLYZED FIBRONECTIN	1
05A - Hair Conditioner	GELATIN	3
05E - Rinses (non-coloring)	GELATIN	1
05F - Shampoos (non-coloring)	GELATIN	1
05G - Tonics, Dressings, and Other Hair Grooming	GELATIN	4
Aids 05H - Wave Sets	GELATIN	1
05I - Other Hair Preparations	GELATIN	2
07B - Face Powders	GELATIN	1
07C - Foundations	GELATIN	2
08E - Nail Polish and Enamel	GELATIN	6
08F - Nail Polish and Enamel Removers	GELATIN	27
09B - Mouthwashes and Breath Fresheners	GELATIN	3
10A - Bath Soaps and Detergents	GELATIN	248
10E - Other Personal Cleanliness Products	GELATIN	6
12A - Cleansing	GELATIN	10
12C - Face and Neck (exc shave)	GELATIN	4
12D - Body and Hand (exc shave)	GELATIN	2
12F - Moisturizing	GELATIN	12
12H - Paste Masks (mud packs)	GELATIN	1
acto macho (maa pacho)		-
03D - Eye Lotion	HYDROLYZED ACTIN	1
03F - Mascara	HYDROLYZED ACTIN	3
03G - Other Eye Makeup Preparations	HYDROLYZED ACTIN	1
05A - Hair Conditioner	HYDROLYZED ACTIN	1
05F - Shampoos (non-coloring)	HYDROLYZED ACTIN	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROLYZED ACTIN	5
12C - Face and Neck (exc shave)	HYDROLYZED ACTIN	6
12F - Moisturizing	HYDROLYZED ACTIN	1
12G - Night	HYDROLYZED ACTIN	1
03D - Eye Lotion	ATELOCOLLAGEN	2
03F - Mascara	ATELOCOLLAGEN	12

03G - Other Eye Makeup Preparations	ATELOCOLLAGEN	3
05F - Shampoos (non-coloring)	ATELOCOLLAGEN	1
07A - Blushers (all types)	ATELOCOLLAGEN	1
07B - Face Powders	ATELOCOLLAGEN	1
07C - Foundations	ATELOCOLLAGEN	12
07E - Lipstick	ATELOCOLLAGEN	39
07I - Other Makeup Preparations	ATELOCOLLAGEN	4
12A - Cleansing	ATELOCOLLAGEN	3
12C - Face and Neck (exc shave)	ATELOCOLLAGEN	17
12D - Body and Hand (exc shave)	ATELOCOLLAGEN	1
12F - Moisturizing	ATELOCOLLAGEN	14
12G - Night	ATELOCOLLAGEN	3
12J - Other Skin Care Preps	ATELOCOLLAGEN	3
13B - Indoor Tanning Preparations	ATELOCOLLAGEN	2



TO: COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.

Industry Liaison to the CIR Expert Panel

DATE: June 15, 2017

SUBJECT: Updated Concentration of Use by FDA Product Category: Animal Tissue (Ectoderm)

Proteins

Concentration of Use by FDA Product Category – Collagen, Hydrolyzed Collagen and Related Proteins*

Ammonium Hydrolyzed Collagen Soluble Elastin

Collagen Soluble Collagen Hydrolyzed Elastin

Calcium Hydrolyzed Collagen Gelatin Fibronectin

MEA-Hydrolyzed Collagen Hydrolyzed Gelatin Hydrolyzed Fibronectin
Zinc Hydrolyzed Collagen Hydrolyzed Reticulin Hydrolyzed Spongin

Hydrolyzed Collagen Hydrolyzed Actin

Hydrolyzed Collagen Extract Elastin

Ingredient	Product Category	Maximum
		Concentration of Use
Ammonium Hydrolyzed	Hair conditioners	0.05%
Collagen		
Ammonium Hydrolyzed	Face and neck products	
Collagen	Not spray	0.1%
Ammonium Hydrolyzed	Moisturizing products	
Collagen	Not spray	0.12%
Ammonium Hydrolyzed	Night products	
Collagen	Not spray	0.12%
Ammonium Hydrolyzed	Paste masks and mud packs	0.03%
Collagen		
MEA-Hydrolyzed Collagen	Hair conditioners	0.06%
MEA-Hydrolyzed Collagen	Face and neck products	
	Not spray	0.1%
MEA-Hydrolyzed Collagen	Moisturizing products	
	Not spray	0.12%
MEA-Hydrolyzed Collagen	Night products	
	Not spray	0.12%
MEA-Hydrolyzed Collagen	Paste masks and mud packs	0.03%
Hydrolyzed Collagen	Eyebrow pencils	0.001%
Hydrolyzed Collagen	Eyeliners	0.001-3.2%
Hydrolyzed Collagen	Eye lotions	0.0029-0.1%
Hydrolyzed Collagen	Mascara	0.001-0.25%
Hydrolyzed Collagen	Other eye makeup preparations	0.02%
Hydrolyzed Collagen	Hair conditioners	0.038-3%
Hydrolyzed Collagen	Hair sprays	
	Aerosol	0.28%
	Pump spray	0.0017-0.038%
Hydrolyzed Collagen	Hair straighteners	0.2%
Hydrolyzed Collagen	Permanent waves	0.15-0.19%
Hydrolyzed Collagen	Rinses (noncoloring)	0.1-0.15%
Hydrolyzed Collagen	Shampoos (noncoloring)	0.0003-0.5%
Hydrolyzed Collagen	Tonics, dressings and other hair grooming aids	0.01-16.5%
	Not spray	0.01-0.55%
	Aerosol	0.0095%
Hydrolyzed Collagen	Wave sets	0.039%

Hydrolyzed Collagen	Other hair preparations (noncoloring)	0.015%
Hydrolyzed Collagen	Hair dyes and colors	1.2%
Hydrolyzed Collagen	Hair tints	0.15%
Hydrolyzed Collagen	Hair lighteners with color	0.25%
Hydrolyzed Collagen	Hair bleaches	0.25%
Hydrolyzed Collagen	Foundations	0.0003-0.05%
Hydrolyzed Collagen	Lipstick	0.01-0.1%
Hydrolyzed Collagen	Nail polish and enamel	0.00003-0.01%
Hydrolyzed Collagen	Nail polish and enamel removers	0.00003%
Hydrolyzed Collagen	Bath soaps and detergents	0.0024-0.048%
Hydrolyzed Collagen	Other personal cleanliness products	
, ,	Hand wash	0.06%
Hydrolyzed Collagen	Skin cleansing (cold creams, cleansing lotions,	0.029%
	liquids and pads)	
Hydrolyzed Collagen	Face and neck products	
	Not spray	0.0029-5%
Hydrolyzed Collagen	Body and hand products	
	Not spray	0.0015-1.5%
	Spray	0.029%
Hydrolyzed Collagen	Moisturizing products	
	Not spray	0.0005-0.1%
Hydrolyzed Collagen	Night products	
	Not spray	0.0024%
Hydrolyzed Collagen	Paste masks and mud packs	0.05-0.5%
Hydrolyzed Collagen	Other skin care preparations	0.5%
Hydrolyzed Collagen	Indoor tanning preparations	0.0092-0.21%
Collagen	Eyebrow pencils	0.2%
Collagen	Eyeliners	0.2%
Collagen	Eye shadows	0.00018-0.2%
Collagen	Eye lotions	0.00012-0.00088%
Collagen	Mascara	0.02%
Collagen	Hair conditioners	1.3%
Collagen	Shampoos (noncoloring)	1.3%
Collagen	Tonics, dressings and other hair grooming aids	
	Not spray	0.00095%
Collagen	Blushers	0.2%
Collagen	Foundations	0.0004-0.2%
Collagen	Lipstick	0.0035-0.05%
Collagen	Bath soaps and detergents	0.67%
Collagen	Aftershave lotions	0.0075%
Collagen	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00005%
Collagen	Face and neck products	
	Not spray	0.0018-96%
Collagen	Moisturizing products	
	Not spray	0.001%

Collagen	Night products	
Conagen	Not spray	0.0001%
Soluble Collagen	Bath oils, tablets and salts	0.000035%
Soluble Collagen	Bubble baths	0.005%
Soluble Collagen	Eyeliners	0.00003%
Soluble Collagen	Eye shadows	0.000035%
Soluble Collagen	Eye lotions	0.002-0.011%
Soluble Collagen	Mascara	0.002-0.011%
Soluble Collagen	Other eye makeup preparations	0.0033-0.03%
Soluble Collagen	Other fragrance preparations Other fragrance preparations	0.000005%
Soluble Collagen	Hair conditioners	0.00005-0.001%
Soluble Collagen		0.00005-0.001%
Soluble Collagen	Hair sprays Aerosol	0.000095%
		0.000095%
Calubla Callagan	Pump spray	0.00035%
Soluble Collagen	Rinses (noncoloring)	_
Soluble Collagen	Shampoos (noncoloring)	0.00005-0.014%
Soluble Collagen	Tonics, dressings and other hair grooming aids	0.00035-0.0035%
C.I. I.I. C.II.	Not spray	0.000052%
Soluble Collagen	Hair dyes and colors	0.000025-0.0005%
Soluble Collagen	Blushers	0.000035%
Soluble Collagen	Face powders	0.0035%
Soluble Collagen	Foundations	0.0001-0.0035%
Soluble Collagen	Lipstick	0.00035-0.01%
Soluble Collagen	Makeup bases	0.005-0.008%
Soluble Collagen	Rouges	0.0035%
Soluble Collagen	Other makeup preparations	0.0001%
Soluble Collagen	Nail creams and lotions	0.0000005-0.01%
Soluble Collagen	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00074-0.0035%
Calubla Callagan	Face and neck products	
Soluble Collagen	•	0.0001.0.79/
	Not spray	0.0001-0.7% 0.0035%
Calubla Callagan	Spray Reduced band products	0.0055%
Soluble Collagen	Body and hand products	0.0001-0.02%
	Not spray	0.0001-0.02%
Soluble Collagen	Spray Maisturizing products	0.0003370
Soluble Collagen	Moisturizing products Not spray	0.002-0.035%
Soluble Collagen	Night products	
Consider Consider.	Not spray	0.002-0.0069%
Soluble Collagen	Paste masks and mud packs	0.00035-0.002%
Soluble Collagen	Skin fresheners	0.0006%
Soluble Collagen	Other skin care preparations	0.000035-0.002%
Soluble Collagen	Suntan products	
Ŭ	Not spray	0.0001-0.00035%
Gelatin	Bath oils, tablets and salts	3.7-66%
Gelatin	Other bath preparations	0.21%

Gelatin	Eyeliners	0.5%
Gelatin	Eye lotions	1%
Gelatin	Other fragrance preparations	0.03%
Gelatin	Hair conditioners	0.000052-0.1%
Gelatin	Rinses (noncoloring)	0.5%
Gelatin	Shampoos (noncoloring)	0.5%
Gelatin	Tonics, dressings and other hair grooming aids	0.009-0.095%
Gelatin	Blushers	0.0011%
Gelatin	Makeup bases	0.01%
Gelatin	Basecoats and undercoats (manicuring	0.001%
	preparations)	
Gelatin	Nail creams and lotions	0.02%
Gelatin	Nail polish and enamel	0.001%
Gelatin	Bath soaps and detergents	0.0011-0.008%
Gelatin	Other personal cleanliness products	0.0015-0.009%
Gelatin	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0023-2%
Gelatin	Face and neck products	
Gelatiii	Not spray	1-2%
Gelatin	Body and hand products	1 2/0
Gelatin	Not spray	0.03-37.8%
Gelatin	Foot products	0.016%
Gelatin	Moisturizing products	0.01070
Gelatin	Not spray	0.0003-0.14%
Gelatin	Paste masks and mud packs	9.5%
Hydrolyzed Reticulin	Moisturizing products	
, ,	Not spray	0.05%
Hydrolyzed Reticulin	Paste masks and mud packs	0.025%
Hydrolyzed Actin	Mascara	1.6%
Hydrolyzed Actin	Hair conditioners	0.00075%
Hydrolyzed Actin	Shampoos (noncoloring)	0.00075%
Hydrolyzed Elastin	Eyebrow pencils	0.2%
Hydrolyzed Elastin	Eyeliners	0.2%
Hydrolyzed Elastin	Eye shadows	0.2%
Hydrolyzed Elastin	Eye lotions	0.00035-0.06%
Hydrolyzed Elastin	Eye makeup removers	0.01%
Hydrolyzed Elastin	Other eye makeup preparations	0.5%
Hydrolyzed Elastin	Hair conditioners	0.0015-2.5%
Hydrolyzed Elastin	Hair sprays	
	Pump spray	0.00031-0.42%
Hydrolyzed Elastin	Permanent waves	0.001%
Hydrolyzed Elastin	Rinses (noncoloring)	0.0015-0.0083%
Hydrolyzed Elastin	Shampoos (noncoloring)	0.0015-0.83%
Hydrolyzed Elastin	Tonics, dressings and other hair grooming aids Aerosol	0.002-0.24% 0.005%
Hydrolyzed Elastin	Blushers	0.2%
TIYATOIYZCA EIASIIII	Diagricia	0.270

Hydrolyzed Elastin	Face powders	0.0000035%
Hydrolyzed Elastin	Foundations	0.0000035-0.2%
Hydrolyzed Elastin	Lipstick	0.00035-0.15%
Hydrolyzed Elastin	Makeup bases	0.0000035%
Hydrolyzed Elastin	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0000035-0.06%
Hydrolyzed Elastin	Face and neck products	
	Not spray	0.00025-5%
Hydrolyzed Elastin	Body and hand products	
	Not spray	0.008-0.06%
Hydrolyzed Elastin	Moisturizing products	
	Not spray	0.001-0.1%
Hydrolyzed Elastin	Night products	
	Not spray	0.06%
Hydrolyzed Elastin	Paste masks and mud packs	0.06%
Hydrolyzed Elastin	Skin fresheners	0.06%
Hydrolyzed Elastin	Other skin care preparations	0.5%
Hydrolyzed Fibronectin	Moisturizing products	
	Not spray	0.05%
Hydrolyzed Fibronectin	Paste masks and mud packs	0.025%

^{*}Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2015-2016
Table prepared February 11, 2016

Updated June 5, 2017: Soluble Collagen: Suntan products 0.00035% added high concentration



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: July 6, 2017

SUBJECT: Concentration of Use by FDA Product Category: Atelocollagen

Concentration of Use by FDA Product Category – Atelocollagen

Product Category	Maximum Concentration of Use
Eye shadows	0.0000022%
Blushers	0.0000022%
Face powders	0.000022%
Foundations	0.000099-0.00022%
Lipstick	0.0004%
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0000001-0.099%
Face and neck products	
Not spray	0.00002-0.000033%
Moisturizing products	
Not spray	0.00017-0.0002%
Skin fresheners	0.000001%
Other skin care preparations	0.0011-0.005%

Information collected in 2017 Table prepared: July 6, 2017



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 Tissue-Derived Proteins and

Peptides as Used in Cosmetics (draft prepared for the June 12-I3, 2017 CIR

Expert Panel Meeting)

Introduction - Please add bovine to describe the milk-derived protein report, and it should be added that this report has a tentative conclusion of safe as used.

Since Gelatin is produced from Collagen, it should not be called "naturally occurring". Definition, Elastin - It would be helpful to note that the reference (10) reporting that Elastin is derived in part from bovine aortas was published in 1987, just at the start of the BSE crisis.

Method of Manufacture, Gelatin - It would be helpful to include the definition of Gelatin from 21CFR700.27. "Gelatin means a product that has been obtained by the partial hydrolysis of collagen derived from hides, connective tissue, and/or bones of cattle and swine. Gelatin may be either Type A (derived from an acid-treated precursor) or Type B (derived from an alkali-treated precursor) that has gone through processing steps that include filtration and sterilization or an equivalent process in terms of infectivity reduction."

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:

July 7, 2017

SUBJECT:

Tentative Report: Safety Assessment of Ectodermal-Derived Proteins and

Peptides as Used in Cosmetics

Key Issues

The report title change to "Ectodermal-Derived" is not appropriate. Although many of these ingredients can be derived from skin which originates from the ectoderm, nervous system tissue also originates from the ectoderm, and these ingredients are not derived from nervous system tissue. In addition, many of these ingredients may be derived from bone and other connective tissues, which originate from the mesoderm. A more appropriate name would be "Skin and Connective Tissue-Derived" Proteins and Peptides.

Type 1 Hypersensitivity - It would be helpful if this section also noted that to cause a Type 1 reaction a protein must be greater than a certain size (about 3500 Daltons as stated in the report on Hydrolyzed Wheat Protein). The following reference would be a helpful addition to this section.

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

Discussion - The Discussion should state that manufacturers of cosmetic products should know the source and size (molecular weight and/or number of amino acids) of proteins added to cosmetic products. A warning should be recommended if the ingredient is made from fish and has a molecular weight large enough to interact with IgE.

Additional Considerations

Summary - It should also be noted that there is a case report of someone reacting to Atelocollagen from fish in a cosmetic product.

Table 2 - As Table 8 and 9 include studies of a Hydrolyzed Collagen with a molecular weight of about 400 Da (reference 20), the molecular weight range shown in Table 2 should be expanded to "400 to 25,000".

TO:

Bart Heldreth, Ph.D., Interim Director

COSMETIC INGREDIENT REVIEW (CIR)

FROM:

CIR Science and Support Committee of the Personal Care Products Council

DATE:

August 14, 2017

SUBJECT:

Tentative Report: Safety Assessment of Ectodermal (Tissue)-Derived Proteins and

Peptides as Used in Cosmetics

We appreciate the opportunity to comment on the tentative report, Safety Assessment of Ectodermal (Tissue)-Derived Proteins and Peptides as Used in Cosmetics.

Although we agree that the source of potential Type 1 allergenic ingredients derived from major food allergens should be included on the label of a cosmetic product, we are concerned about the current recommendation that a "warning" be placed on the label of products "that may contain fish-derived ingredients." Consistent with the CIR report on Hydrolyzed Wheat Protein, proteins less than 3500 Daltons (approximately 30 amino acids or less) are not a concern for Type 1 allergy no matter the source. We suggest that additional information be added to the Type 1 hypersensitivity section of the CIR report on ectodermal (tissue) proteins to indicate that proteins less than 3500 Daltons (approximately 30 amino acids or less) are not a concern for Type 1 allergy. The discussion of the CIR report should then recommend that if a protein is obtained from fish, (which is a major food allergen as defined by FDA) and is greater than 3500 Daltons, the source of the protein should be stated on the label of the cosmetic product.

We will work with the INCI Committee to consider solutions to identify the source of proteins greater than 3500 Daltons when they are made from FDA food allergens (egg, milk, soy, wheat, peanut, tree nuts, fish and shellfish).