
Safety Assessment of Bovine Milk Proteins and Protein Derivatives 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, Senior Scientific Analyst/Writer.



Cosmetic
Ingredient
Review

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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 Bovine Milk Proteins and Protein Derivatives

Enclosed is the Draft Final Report of the Safety Assessment of Bovine Milk Proteins and Protein Derivatives as Used in Cosmetics. (It is identified as *mlkpro092017rep* in the pdf document).

In April 2017, the CIR Expert Panel (Panel) issued a Tentative Report with the conclusion that the 16 bovine milk proteins and protein-derived ingredients are safe in the present practices of use and concentration.

Data received since the April meeting include the results of the concentration of use survey on Lactoglobulin: no uses were reported. The 2017 FDA VCRP data indicate this ingredient has 1 reported use in a face and neck skin care preparation. Comments received from the Council prior to the April meeting and on the tentative report have been considered. The data and the comments are identified as *mlkpro092017data* and *mlkpro092017pcpc1-pcpc2*, 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.

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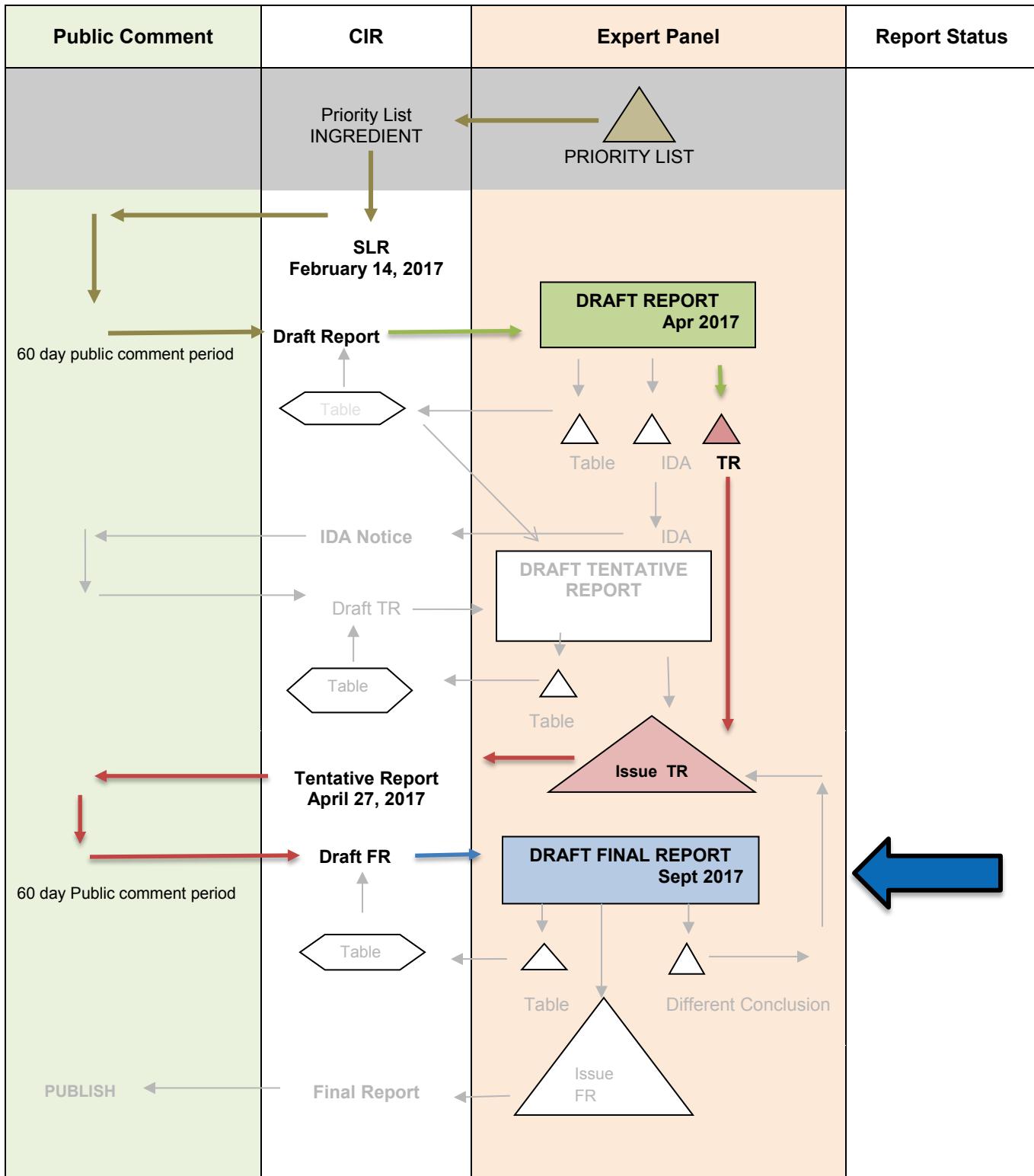
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INGREDIENT/FAMILY Milk Proteins and Protein Derivatives

MEETING Sept 2017



Milk Proteins and Protein Derivatives

February 2017 – Scientific Literature Review announced.

April 2017 - The Panel issued a tentative report with the conclusion that the 16 bovine milk proteins and protein derivatives are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

While the maximum reported use concentration of Sodium Caseinate is 96.9%, this concentration is in bath oils, tablets, and salts, which are diluted in water prior to use. The maximum concentration of use reported in the casein-derived ingredients is 2% in leave-on products. Safety test data of Hydrolyzed Casein were negative at concentrations up to 30%. These observations supported the Panel's safe as used conclusion for Sodium Caseinate at the concentrations in diluted bath products.

The Panel noted that bovine milk proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. The Panel reviewed studies showing no relevant ocular irritation and no dermal irritation or sensitization in animals and human subjects. Additionally, no reported cases of Type I immediate hypersensitivity reactions from cosmetic use were reported in the literature and the Panel has not found such reactions to bovine milk products in their clinical experience. Thus, the Panel concluded that the induction of Type I sensitivity to bovine milk proteins in cosmetics is not likely.

Milk Proteins and Protein Derivatives 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	Clinical/Case Studies
Ammonium Caseinate		X			X											
Calcium Caseinate		X			X											
Casein	X	X	X	X	X					X						
Casein Extract																
Hydrolyzed Casein	X		X	X	X		X					X	X			
Hydrolyzed Lactalbumin																
Hydrolyzed Milk Protein	X	X	X	X		X					X	X	X	X	X	
Hydrolyzed Whey Protein	X								X							
Hydrolyzed Yogurt Protein	X										X		X			
Lactoglobulin	X															
Milk Protein	X															
Milk Protein Extract	X															
Potassium Caseinate			X			X										
Sodium Caseinate	X	X			X											
Sodium Hydrolyzed Casein																
Whey Protein	X				X	X				X						

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

Search Strategy for Milk Protein and Protein Derivatives
(Performed by Christina Burnett)

- SciFinder

- December 2016 - Search for ingredients by “toxicity of milk protein”, 26 hits for close association = 0 relevant to cosmetic use. Most concerned milk allergy from consumption. When the 16 ingredients and available CAS# were entered in substance identifier search, returns were found for Hydrolyzed Milk Protein, Whey Protein, Milk Protein, Potassium Caseinate, Hydrolyzed Casein, Lactoglobulin, Sodium Caseinate, Calcium Caseinate, Ammonium Caseinate, and Casein. References on “adverse events, including toxicity” were only found for Hydrolyzed Casein (20 hits) and were similar to those found in the PubMed search.

Search Terms	TOXLINE Hits (excluding PUBMED)	PUBMED Hits	SCCS/SCCP Opinion	ECHA Hits	NICNAS Assessment
ammonium caseinate OR 9005-42-9	0	4; 0 retrieved	No	No	No
calcium caseinate OR 9005-43-0	5; 0 retrieved	76; 3 retrieved	No	No	No
casein	1981; limited w/ “dermal” = 3; 0 retrieved	30440; limited w/ “toxicity” = 693; limited w/ “toxicity and dermal” = 1; 0 retrieved	No	No	Tier 1 assessment; low concern for human health
casein extract	79; limited w/ “dermal” = 0	800; limited w/ “toxicity” = 20; 0 retrieved	No	No	No
hydrolyzed casein	122; limited w/ “dermal” = 0	739; limited w/ “toxicity” = 14; 0 retrieved	No	No	No
hydrolyzed lactalbumin	3; 0 retrieved	58; 0 retrieved	No	No	No
hydrolyzed milk protein	1; 0 retrieved	823; limited w/ “toxicity” = 7; 0 retrieved	No	No	No
hydrolyzed whey protein	4; 0 retrieved	310; 0 retrieved	No	No	No
hydrolyzed yogurt protein	0	6; 0 retrieved	No	No	No
lactoglobulin	165; limited w/ “dermal” = 0	3990; limited w/ “toxicity” = 41; 1 retrieved	No	No	No
milk protein	2150; limited w/ “dermal” = 3; 0 retrieved	53092; limited w/ “toxicity” = 1028; limited w/ “toxicity and dermal” = 2; both retrieved	No	No	No
milk protein extract	83; limited w/ “dermal” = 0	815; limited w/ “toxicity NOT thistle” = 38; 0 retrieved	No	No	No
potassium caseinate	3; 0 retrieved	19; 1 retrieved	No	No	No

Search Terms	TOXLINE Hits (excluding PUBMED)	PUBMED Hits	SCCS/SCCP Opinion	ECHA Hits	NICNAS Assessment
sodium caseinate	1958; limited w/ “dermal” = 3; 0 retrieved	15020; limited w/“toxicity” = 308; 0 retrieved	No	No	No
sodium hydrolyzed casein	2; 0 retrieved	91; 1 retrieved	No	No	No
whey protein	52; 2 retrieved	15639; limited w/ “toxicity” = 267; 6 retrieved	No	No	No

Total references ordered or downloaded: 16

Searches updated July 2017: 0 relevant studies found.

Bovine Milk-Derived Proteins and Peptides
April 10-11, 2017

Dr. Belsito's Team

DR. BELSITO: Yeah. So this milk and protein derivatives, this is the first time we're looking at these 16 milk and proteins. They were originally in that hydrolyzed source protein, and then taken out and looked at as a group. And then in addition to what we originally got in the report, we got a huge amount of data dumped on us and waved to as well that is incorporated into this. And --

DR. SNYDER: So I had a global question. So the INCI, how does it define milk, because we have almond milk, coconut milk.

DR. HELDRETH: Bovine source.

SPEAKER: Bovine --

DR. BELSITO: Bovine --

SPEAKER: -- source.

DR. BELSITO: -- source.

SPEAKER: But we probably need to have that in here because we're not talking about --

DR. BELSITO: It is.

SPEAKER: I believe it's in there.

DR. BELSITO: It is there.

SPEAKER: (Inaudible) in the title. Assessment of milk proteins.

SPEAKER: Yeah.

MS. BURNETT: Bovine milk proteins.

DR. BELSITO: Bovine source.

DR. SNYDER: And then, where does yogurt come in? Because we have, now, yogurt data, and so is that just a -- is it under milk or is it under yogurt in the dictionary? So is this a milk --

DR. BELSITO: But it's similar -- I mean, I think we've decided that it's like everything else. It can be (inaudible).

DR. SNYDER: But it has different properties because of the -- to make it --

DR. LIEBLER: Well, it just depends. I think you're asking how is it organized in the dictionary.

SPEAKER: Yeah, yeah.

DR. LIEBLER: Because we know it comes from bovine milk.

DR. SNYDER: Right, yeah. I'm not questioning that. But it's just a matter of --

SPEAKER: Because all of a sudden we got a bunch of yogurt data and yogurt proteins which would then also have proteins from, I would assume, some of the --

MS. BURNETT: Bacteria?

SPEAKER: -- bacteria that are used to ferment it. So, is that appropriate? I mean, so --

DR. BELSITO: Oh, the grouping.

SPEAKER: Yeah, so it's, like, hmm. Because it seemed like it extended beyond just bovine sourced milk proteins.

MS. BURNETT: If you don't feel that it belongs in this group you can go ahead and take it out.

DR. BELSITO: Did you have a problem with it, Paul?

DR. SNYDER: No, I didn't. No, I just -- it was just a matter of questioning the grouping and curious as to how --

DR. BELSITO: So yogurt protein would have the milk protein plus the bacteria protein.

SPEAKER: Correct.

DR. BELSITO: If there were any issues with the safety of any of the bacterial proteins from these cultures, then that would be (inaudible), because these are protein extracts, so all the other stuff from bacteria doesn't count.

DR. SNYDER: I mean, we got dermal and ocular information on a hydrolyzed milk protein and a hydrolyzed yogurt protein.

DR. BELSITO: Right.

DR. SNYDER: Yeah.

DR. LIEBLER: I would be inclined to say that the amount of bacteria protein mass versus milk protein mass in yogurt is probably very small.

DR. BELSITO: And they make the use concentrations - -

SPEAKER: Yeah, it wasn't that I was --

DR. BELSITO: -- pretty low.

SPEAKER: It wasn't that I was throwing up already red flags or anything. I was just about to --

DR. LIEBLER: And if you have the safety data on it, I think, you know, the level of confidence is better.

JAY ANSELL: If the yogurt in high concentrations relative to the cosmetic applications are okay, the fact that bacteria don't induce any toxicity would be -- could be derived from that. I mean, if it's not causing any toxicity, the additional stuff in there is also not causing any problems.

DR. BELSITO: All right, I was okay with it.

DR. LIEBLER: I'm particularly okay with it because it's a protein that's hydrolyzed. Not only is it a protein, it's further hydrolyzed. So you got kind of an extra level of

(inaudible).

DR. SNYDER: I mean, there's certainly allergic reactions to casing and things like that, but --

DR. BELSITO: Yeah, but I mean, we've dealt with that. There's a, you know, and we talk about and there are allergic reactions to soy, and we talk about, you know, people should be careful if they are known to be soy sensitive, so I mean, that (inaudible) goes in our discussion. So the biggest issue for me was the 96.9% sodium caseinate in the bath preparation. And, you know, we don't have that -- the data that will go that high, but it's a bath preparation, and we do have data for casing in that 30%, so I was okay with it. But I just wanted to point that out that it has that very high level (inaudible) of use. And so I thought that could go in the discussion along with the respiratory boilerplate, and safe as used was what I thought here.

DR. LIEBLER: I agree.

DR. BELSITO: Paul? You have questions?

DR. SNYDER: No, no, no. It's just the -- I wanted to ask why we added this figure of the molecular weight range. Was that because of the hydrolyzed protein issue and sensitization we had previously with --

DR. BELSITO: Wheat.

DR. SNYDER: Wheat? So is that why we -- what's the context of why we have that figure in there?

SPEAKER: Figure one.

DR. SNYDER: Yeah.

MS. BURNETT: So, remember, these were all part of a larger report, and I was -- I had received data that was -- we had presented in different histograms like this, and so it's just residual picture I have from that original report, and I don't need to include it.

DR. LIEBLER: Yeah, I just felt this figure was kind of useless, excuse me, better summarized at distributions for the hydrolyzed proteins on the table.

MS. BURNETT: All right.

DR. LIEBLER: Because you've got a lot of that in the text, already.

MS. BURNETT: Right.

DR. SNYDER: I'm just more cautious about setting a precedent when we start putting in that kind of stuff.

DR. BELSITO: Right.

MS. BURNETT: Okay.

DR. SNYDER: I think it's good. Thank you.

DR. BELSITO: Anything else? Okay.

SPEAKER: I (inaudible).

DR. BELSITO: Okay, save the milk.

Dr. Marks' Team

DR. MARKS: Okay. Next, is the milk-derived proteins. So, this is a continuing saga of protein ingredients, and Christina will probably ask you to

(inaudible). So, --

MS. BURNETT: Did they have milk in their coffee this morning?

DR. MARKS: This is the first review that we've seen, the milk proteins and protein derivatives. Yes, move that. No, that's okay. I didn't know you were going to be over here so quickly. Let me put this over here.

MS. BECKER: I just want to get ready for next time. Sorry.

DR. MARKS: No, that's okay. Excuse me while I rearrange my workspace. So, the first thing, Ron and Tom, are the 16 ingredients that are milk protein and protein derivatives. Do they all look okay to you as being grouped together?

DR. SHANK: Yes, they do.

DR. HILL: Yes.

DR. MARKS: Okay. Good. And, then the next question, of course, is what are our needs for these 16 ingredients, or can we move on to a safe?

DR. SLAGA: Safe as used.

DR. SHANK: We can move on to conclusion safe as used.

DR. MARKS: Okay. Ron Hill, safe. Tom, I have irritation and sensitization is okay for two of them. I guess we can expand that as a read-across for the others, the casein, hydrolyzed casein, the hydrolyzed milk protein. Refresh my memory on the type 1 reactions. We set a limit, right?

MS. BURNETT: You restricted the molecular weight.

DR. MARKS: Yes. And, in --

MS. BURNETT: (Inaudible) molecule.

DR. MARKS: And, did we do the same with the second protein group?

MS. BURNETT: That was the only one that you restricted --

DR. MARKS: Okay.

MS. BURNETT: -- due to molecular weight due to all the case studies that we had on the reactions.

DR. MARKS: Right.

MS. BURNETT: There were no case studies from cosmetic ingredients causing any type 1 reactions.

DR. MARKS: Yes, that's what I have. No topical cases reported. We obviously know type 1 reactions of ingested milk is a significant issue, particularly for children, and it's usually the lactoglobulin and the -- lactalbumin is the main culprit in the sources we have. But, obviously, that doesn't exclude others.

But, my feeling was, with no topical cases reported we could move on and say it is safe like you recommended, Ron Shank, and just note in the discussion that we considered the type 1 reactions, but since there are no reported ones, then we feel, to cosmetics, that we could consider this to be safe, without any restrictions of molecular weight. Other comments?

DR. HILL: So, I didn't really quite know how to think about this when I just was going to redistill what we learned from wheat. Because, we've discussed this in several other additional groups, as it was a situation where the way they were hydrolyzing was modifying protein side chains apparently in a similar way that could also occur in cooking.

So, it was using that soap product exposure to mucus membranes in the eyes over a period of 2 to 3 years when they started seeing the reactions, and then somebody reacting after a big meal of, I guess, the wheat baked in a particular way. So, --

DR. MARKS: So, then reacting to the topical. They weren't reacting to the (inaudible).

DR. HILL: My understanding was that they were sensitizing to the soap but then they were reacting to ingestion. That's not --

SPEAKER: Other way around?

DR. HILL: No, it wasn't. Or, it was --

DR. EISENMANN: There was some topical reaction in some -- just like exercise-induced also.

DR. HILL: Yes, okay. Right. I remember the exercise-induced. So, they were reacting after the use of a soap or the exercises. Yes. I remember it was some combination of that, and then they traced it down to these modified amino acids being at least long enough to -- the peptide chunks -- at least long enough to cross-link IgE, and that's why we set that molecular weight limit.

So, on that basis I had no idea how to think about this milk report and I'm letting it go. But, I just wanted to make sure I understood what we captured from the wheat lesson.

DR. MARKS: Yes, that's why I brought it up.

DR. HILL: Because, --

DR. MARKS: Because, I didn't want us to ignore that problem with the wheat-derived proteins and --

DR. HILL: Because, in a couple of other protein- ingredient groups (inaudible), as I remember it was in between. We said, well, we don't have similar observations of dietary sensitization to the wheat. So, I don't know what's the story here with the milk.

I mean, that's something that a larger percentage of children react to. Most of them outgrow it, certainly not 100 percent. Knowing what I know about the pharmacogenetics of sensitization to drugs these days, there's almost certainly a genetic component. And, I don't know how we grapple with that until everybody has their genome.

DR. MARKS: I had the same concerns you did, Ron, until I saw there were no topical case reports of type 1 allergy. So, to me, I would have expected that would have come in the literature. And, Christina did, I thought, a good job at summarizing type 1 reactions to ingested milk protein.

So, our team will second tomorrow. Sounds like we're satisfied with moving forward with a safe conclusion, having a discussion about type 1 reactions and why we feel the use of milk proteins and protein derivatives are safe as far as type 1 reactions also. We're going to comment. I think I read that.

DR. SADRIEH: Yes. I was just going to mention that, you know, foods that contain milk-derived proteins obviously have a requirement to have a statement on it. You know, I didn't know whether that was something that -- you know, people may not recognize the ingredients as being potentially milk derived and that there might be some sort of statement --

DR. MARKS: I think that is --

DR. SADRIEH: -- that might be needed. Well, --

MS. BURNETT: I capture that there's required labeling for the food.

DR. SADRIEH: Right. But, I'm saying for the cosmetics, though. What I'm saying is that people who may have an allergy to dairy products, they may want to have the choice to not use something that could (inaudible) dairy products, because they may have a potential reaction. So, I'm saying that the cosmetics that contain milk-derived proteins might need to have some sort of statement on it to make people, you know, aware of the fact that there is potential.

DR. JONAS: My thought is that because there is full disclosure on the ingredient label it's already there, so I would hope that people that are sensitive would be reading the label as is.

DR. MARKS: I guess, I think it could be handled in the discussion. I agree with you that it would be on the label, but would the lay public translate caseinate to milk and whey protein, perhaps. So, you know, when it says really the only one of the ingredients, which it's clear it's milk by the label, is milk protein. Everything else has other names - - lactoglobulin, hydrolyzed yogurt protein. Perhaps they would know that. But, I think we can include that in the discussion. And, then I think the manufacturers have to decide how they want to proceed with it, whether they want to put in (milk-derived ingredient), something like that.

DR. BERGFELD: I don't think we've done that before. Have we done that before, have cautionary labeling?

DR. MARKS: Do you mean in terms of discussion recommending it?

DR. BERGFELD: Yes. Is there another way of doing that? Not that I disagree with you, but I just --

DR. MARKS: Yes. Do you have any suggestions? Would the FDA be the one implementing a mandatory labeling, or should be --

DR. SADRIEH: I mean, that would be a regulation, and so, --

DR. MARKS: Yes, exactly.

DR. SADRIEH: -- you know, it takes a while. Not in this environment it's not going to happen, so.

DR. MARKS: The other is we could handle it by -- hmm.

DR. HILL: The other question I had in here -- and I guess it relates back to the wheat -- the problem only occurred with the wheat, that cosmetic ingredient in the soap, because it was acid hydrolysis generating a particular molecular weight fraction. And, what I guess I didn't get a great confidence on here is that there must be now -- in fact, there's a little bit of it -- a big body of science that I felt inadequately familiar with, I guess.

As to exactly why do people that do react to the milk -- because it's clearly down to a subset of people, the ones that outgrow it. That's something a little different going on than the -- what is it -- 3-5 percent of the people who don't outgrow it of that subset. So, it's a smallish amount, but then they never outgrow it. And, do we know exactly what the mechanisms are so that you can say when the manufacturer is generating -- I guess, in terms of knowing what to put in the discussion.

Because, in thinking about the labeling, any of these aren't necessarily going to cause the problem. It would be certain ones of them manufactured in a certain way, I think, which, as he says, they're not seeing out there right now on the market, as we can tell.

So, does the consumer really need to be concerned, you know, based on what's there. And, I don't feel clear at all. I don't get clarity from what we've got in the report, even though it's a good -- it's a well-assembled report. And, I don't know if we can, without having a little more science, to figure out which things are they reacting to and what's known about the mechanisms.

DR. MARKS: I think in Christina's discussion she mentioned that the proteins that predominantly cause the problem, the lactoglobulin and the other one that -- but, that's only -- again, there's a subset that react to other proteins, not just those two. Ron Shank, what do you think about the cautionary statement, since this would be precedent setting, it sounds like, in the discussion? We do caution other things in the discussions.

DR. SLAGA: We have to be careful.

SPEAKER: (Inaudible) suggest labeling.

DR. MARKS: Yes.

DR. SLAGA: The majority of these were part of a report back in 2013, so whatever we do here, you know, we need to carry it back, or otherwise, you know, we're disrupting --

DR. MARKS: You probably weren't here in 2013, were you?

DR. SADRIEH: Not here.

DR. MARKS: Yes, exactly. So, you would tend to not include it as a labeling caution.

DR. SLAGA: I don't think we need it, but --

DR. MARKS: Okay.

DR. SLAGA: -- at some time we have to consider the 2013 report.

DR. GILL: I would just suggest that -- and we can open this to the full panel discussion tomorrow -- that we're clear on the science when recommending the statement, because I think we're going to be asked to justify it so that we don't cause undue alarm in the public about milk. So, if there's a justifiable reason amongst the panel members why we should raise that, then we do it. Otherwise, they're only going to come back and say justify why you guys think it should be on.

MS. BURNETT: And, to the earlier point, I mean, we've already done the wheat and the soy which also are known food allergens. We didn't mention that kind of language in the previous discussions. Then, you would be opening up having to go re-examine those reports.

DR. MARKS: Yes, that's Tom's point. Yes. Ron Shank, how do you feel?

DR. SHANK: Yes, I don't think it's necessary to put any warning with the cosmetic.

DR. MARKS: Okay.

DR. SHANK: I did have one. Since yogurt contains bacteria, should be in the discussion point out that there are bacterial proteins associated, at least with the cosmetics that contain yogurt protein. You say that in the manufacture somewhere there are other proteins besides milk proteins.

MS. BURNETT: Right, right.

DR. SHANK: But, the bacterial proteins from yogurt are not specifically mentioned. Should we mention that in either the chemistry section or the discussion?

MS. BURNETT: And, not the (inaudible).

DR. SHANK: Not for a toxicological reason but just for chemical identity.

MS. BURNETT: If we were to mention it in the discussion and, say, the panel has no concern about these proteins or --

DR. SHANK: Yes, that's correct.

DR. BERGFELD: Excuse me. Why don't we have a concern if we don't know what they are?

DR. SHANK: Usage.

DR. BERGFELD: Usage? There's no reported adverse events?

DR. SHANK: Correct.

DR. BERGFELD: We ought to probably add that.

DR. SHANK: Pardon me?

DR. BERGFELD: We probably ought to add that.

DR. MARKS: Any other comments? So, tomorrow presumably I will be seconding a motion that a tentative report be issued with a safe conclusion. Team, sound good?

DR. SHANK: Yes.

DR. MARKS: Okay. And, then I'm sure we'll get in a discussion of the type 1 reactions tomorrow, and I'll bring up the reason we feel comfortable with no topical cases reported and also no need for a caution on the label, that our team feels. We'll see how that goes tomorrow. Any other discussion with the milk proteins and protein-derivatives?

DR. SADRIEH: I just have a question. When you said no cases reported, you mean from, like, none of the companies have received any adverse events? Or, when you say no cases report, what does that mean?

MS. BURNETT: In the published literature there are no case studies reported.

DR. HILL: Yes, because this caused me, while you were talking, to go back and look about the yogurt again, because we don't have anything about method of manufacture. So, I was sitting here pondering, do we know there are no prominent lipopolysaccharides in there that somebody might react to. So, that's the question. We don't have a method of manufacture for yogurt product in here that I can find.

MS. BURNETT: We did receive data on yogurt in the way of two -- I can't remember offhand if it included --

DR. HILL: Okay. Maybe that's --

MS. BURNETT: -- in (inaudible) manufacture or not.

DR. HILL: I should have it captured as summary, at least. Yes, we did. Sorry. I missed that.

MS. BURNETT: I believe --

DR. HILL: I was looking at the main report, but yes.

MS. BURNETT: Do you for sure have ocular and dermal irritation in vitro studies on it?

DR. HILL: Yes. Well, okay, but then you're looking for regular -- I mean, not type 1 in that context.

DR. MARKS: Oh, absolutely. That's what I said in that we have irritation and sensitization for the prime ingredients and feel safe about that. And, I was concerned about the type 1 allergy, but I was reassured by the lack of any reports of allergy after topical application, which I would have expected we would find.

DR. HILL: So, in the adverse events reporting system, do we pick up anything cosmetic these days? I thought this was just drugs, pharmaceuticals, and the like at the moment.

DR. SADRIEH: Well, there's an adverse event reporting system for cosmetics as well.

DR. HILL: Yes, that's been initiated in the last -- or, it's been in existence for a long time, because it seems like we don't mind that routinely in preparing our reports, I guess, is what I'm driving at.

DR. EISENMANN: Because, it's product based, --

DR. HILL: Yes.

DR. EISENMANN: -- we (inaudible) know the ingredients in the products.

DR. SADRIEH: Right. But, I mean, you know, if there's a reaction to a product that contains, you know, milk- derived proteins and it's a hypersensitivity reaction, then one could think that it might be because of that.

DR. HILL: And, since the issue on the table for me right now is mainly the yogurt, because somebody raised -- other than milk proteins in there -- specifically a possibility of bacteria, which there's, depending on the yogurt, quite a bit. It might be worth questioning. I don't remember us ever mining that system, but it would be possible to look for anything yogurt-derived and see if anything showed up. I mean, this would be a new thing from my time on the panel.

I mean, that system is noisy and that's the biggest problem about ever getting anything out of it, but yet progress is being made on figuring out how to get past that noise. And, in this case, yogurt is something that could be searched on. It wouldn't be that difficult to at least see what's there.

MS. BURNETT: When the report it on the system, when it says -- because it's product-based -- I don't know if they list the ingredients when they say the product. So, the problem there is I won't be able to search it. So, unless I would go and look at every product label to go see, you know, it's --

DR. HILL: I get it.

MS. BURNETT: Yes.

DR. HILL: But, no, the FDA doesn't maintain an index of that, so you wouldn't have any way to cross-index.

DR. SADRIEH: We do go to the, you know, product's sort of web page to get information on the products
(inaudible) purchase products to get labeling. So, we, you know, do pay attention to -- we try to find out if there's, you know, ingredients in there. And, you know, it's not like there aren't any types of hypersensitivity reactions that are already in our database for products that contain milk proteins.

MS. BURNETT: I should also note that there's only five reported uses on the VCRP for this ingredient.

DR. SADRIEH: Yes, but VCRP is not, you know, --

MS. BURNETT: It's voluntary.

DR. SADRIEH: Yes.

MS. BURNETT: I recognize that, but.

DR. HILL: So, the VCRP just gives the category, right? That's all you get out of the VCRP.

DR. MARKS: No, you get the ingredient.

DR. HILL: By the ingredient.

MS. BURNETT: The ingredient and the category that it belongs to.

DR. HILL: All right. So, if there's only four or five, that would narrow it down a lot in trying to do a search to see if there have been anything showing up in the adverse events reporting system. But, I don't know who should do that search.

DR. SADRIEH: Well, I can tell you I got one last week, so. (chuckles)

DR. MARKS: So, I think we'll have more time obviously to mine this more. This is just the first review. Even if I second the issuing of a tentative report with a conclusion that's safe tomorrow, we still will have time to delve into that.

DR. BERGFELD: Jim, what do you know about the American Contact Dermatitis Group and their patch testing reporting? Every include the milk proteins? I've never seen it in there.

DR. MARKS: No. And, actually, if I were testing milk protein, I'd be much more interested in an immediate reaction. So, you can do contact urticaria, both by percutaneous exposure, percutaneous with a scratch in the skin, and a prick in the skin, to see if they're type 1 reactions.

There are not many dermatologists, actually, in the U.S. who do that, because of the potential of anaphylaxis, but it's routinely done in Europe in patch-test clinics. So, I obviously felt reassured without any reports of topical cases of type 1 allergy, that this was safe. And, obviously, with the wheat protein it was really the series of cases that were reported in Japan that alert us to this concern from topical exposure.

So, I would expect a similar type of reports. Even individual case reports would have appeared in the literature if there had been significant reactions. So, that was reassuring. Actually, that was the number one thing, no topical cases reassured me.

DR. SADRIEH: I had a question. In the patch- testing studies that are done, you know, people who have allergies, are they excluded from the studies, actually, or are they -- you know, I mean, are they done in people -- is that part of the exclusion criteria for not selecting somebody for a patch-test study, because they actually don't have -- because, how would you find out that they actually have an allergy if you actually select to not have those people with those sensitivities.

And, then if you know that they have an allergy, then how do you actually do a study ethically, exposing them to the allergen? So, I just was wondering, the lack of data seems, to me, to be basically a self-fulfilling prophecy. You're selecting to not test those people.

DR. MARKS: Not really. Because, I was referring to case reports, not HRIPT studies. In the HRIPT, you would have to look at the criteria. But, even if they did have a history of type 1 allergy, unless they anaphylax, you wouldn't know it, because you put the patch on and then you read it a day or two later, take it off a day or two later, and contact urticaria would have already occurred and disappeared.

So, when you test for that, if you do it under a patch, you have to take the patch off in, like, a half an hour and see if there's a reaction. And, that's not typically done on an HRIPT. As far as the criteria, you'd have to go back -- we would have to go back and look at it. But, they're done in adults. More than likely if they had a history of milk allergy as a child, I doubt that they were excluded, but I don't know that for sure.

DR. HILL: And, then the other thing is with that soap. I mean, with the wheat deal, once again, was people were getting the soap in their eyes. The mucus membrane was the only way, and so a normal patch test, unless you do the skin prick, you shouldn't be seeing protein responses.

DR. MARKS: Correct.

DR. SADRIEH: I mean, I'm not talking about a question of risk here so much as basically people being aware so that they, you know, if they choose to not use a product because they may have --

DR. MARKS: Right.

DR. SADRIEH: -- a concern. It's more for an individual concern rather than a sort of general public safety concern --

DR. MARKS: Right.

DR. SADRIEH: -- that I'm talking about here.

DR. MARKS: Yes. No, we understand that, and our team felt that we had no need for a cautionary statement on the label at this point.

DR. BERGFELD: Well, also, those people who have skin reactions, we don't include in patch testing if they have a generalized dermatitis, until they're clear and off most medications. I myself had a milk allergy as a kid and was covered in eczema and outgrew it, but the truth is, in clinical practice we would probably pick these people up, because we would not be testing those with dermatitis. Would we?

DR. MARKS: Right. Okay. Any other comments? This was a robust discussion, which was good. Yeah. So, tomorrow, just to review, this is our first look at the milk proteins and protein derivatives. Presumably, I'm going to second a motion that a tentative report be issued with a safe conclusion, and then we'll talk about the type 1 allergy in the discussion. Okay. We'll see what the Belsito team moves.

Full Panel Meeting

DR. BERGFELD: Then we're moving on to the reports advancing. And the first one in that group is the milk derived proteins Dr. Belsito.

DR. BELSITO: So this is the first time we're looking at the 16 milk derived proteins and protein derivatives that function as skin and hair conditioning agents. First and foremost is, we're told that they're all bovine source. So we thought we should change the title of the Safety Assessment to the Safety Assessment of Bovine Derived or Bovine Sourced. Since they're either milks like soy and rice that might be misinterpreted here in looking at that. And then, having said that, we came to a conclusion that all of these were safe as used.

DR. MARKS: Second. If that's a motion.

DR. BELSITO: Yes.

DR. BERGFELD: Okay.

DR. MARKS: That we would issue a tentative report with a safe conclusion.

DR. BERGFELD: Any discussion then? Any comment?

DR. BELSITO: Yeah. The respiratory boilerplate --

DR. BERGFELD: Okay.

DR. BELSITO: -- that the sodium caseinate is used at 96.9 percent in a bath preparation. But, given the negative leave on data for casein at 30 percent, we were not concerned about that discrepancy in the concentrations. All of the others are used at quite low concentrations. And we recommended that the figure be deleted, since it's essentially summarized in the text in the table.

DR. MARKS: Did -- our team discuss the type 1 reactions at some length that occur with ingested milk protein. Lactoglobulin and lacto albumin being the main culprits. But, because of no topical cases of type 1 reactions to this bovine milk derived in protein ingredients, we felt that, obviously, that we could go with a safe conclusion. As recalled when we talked about wheat, there were reports of type 1 reactions with topical exposure. But since we have seen none with this bovine milk proteins, we felt it could be safe. We wanted that in the discussion. And it also came up, should there be a cautionary statement on the label of products that contain these ingredients? And we felt no.

DR. BERGFELD: Is that agreeable to include that in the discussion?

DR. BELSITO: Yes.

DR. BERGFELD: Thank you. Ron Hill.

DR. HILL: What about the yogurt discussion that we had related to bacteria?

DR. SHANK: Bacteria protein.

DR. MARKS: Go ahead Ron Hill.

DR. HILL: I wasn't the one that raised the issue initially. I thought it was Dr. Shank. But anyway, we talked about under -- we didn't have method of manufacture that there are high concentrations of bacteria in yogurt under the conditions. And the way that the products are produced from that, do we have to worry about contamination with bacterial proteins? I guess, hypothetically, lipopolysaccharides. But, we were really just talking about bacterial proteins from the yogurt, lacking method of manufacture.

DR. BERGFELD: Any comments?

DR. BELSITO: We had the same discussion. Let me let Dan answer it. He figured out that the amount would be so low it would be negligible.

DR. HILL: That was my initial thought.

DR. LIEBLER: Yeah.

DR. HILL: And I think it still is.

DR. LIEBLER: I can't point to data on yogurt, to say that. But we've -- on other topics, we've been engaged periodically in the analysis of human tissues that result from various types of infections. And the amount of host protein relative to pathogen derived protein. I mean, you can't even detect the pathogen derived proteins. It's very hard. I realize it's a different situation. But, that gave me a little bit more confidence in my sort of gut reaction. No pun intended (Laughter) to this yogurt issue. You know, it doesn't take much bacteria to create this product. And I think that the amount of bacterial protein present in the protein extracts that we'd be talking about, would be very small. So.

DR. BERGFELD: Would that be put in the discussion or comment on that?

DR. LIEBLER: I think it's reasonable to add to the discussion. Certainly.

DR. BERGFELD: Okay.

DR. LIEBLER: I mean, it's something that we've thought about too, you know. So.

DR. BERGFELD: Okay. So we'll add that.

DR. SHANK: How about just putting it in the definition? We mentioned that the -- in page 9, under Chemistry, the definition, we're talking about proteins and the protein hydro lysates.

DR. BERGFELD: Okay.

DR. SHANK: And it just says, at the very last sentence.

DR. BELSITO: Page 9.

DR. SHANK: Or somewhere in there. That the yogurt contains, in addition to milk proteins, bacterial proteins. That's all. Just so it shows we did recognize that.

DR. BELSITO: Yeah. That's fine.

DR. BERGFELD: It looks like we have concurrence.

DR. SHANK: Yeah.

DR. BERGFELD: Everyone agrees. Okay. Are you also advocating putting it in the discussion?

DR. SHANK: No.

DR. BERGFELD: Or just in that (inaudible). Okay. Is that up for discussion? You want to comment on that?

DR. LIEBLER: I think that's fine.

DR. BERGFELD: Fine. Okay,

DR. LIEBLER: I think Ron's suggestion is the right way to handle it.

DR. BERGFELD: Good. Any other points of discussion or comments? Then I'll move the question. All those in favor of a safe conclusion, indicate by raising your hand. Unanimous.

Safety Assessment of Bovine Milk Proteins and Protein Derivatives 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, Senior Scientific Analyst/Writer.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 16 bovine milk proteins and protein-derived ingredients, which function mainly as skin and hair conditioning agents in personal care products. The Panel reviewed relevant data provided in this safety assessment, and concluded that these ingredients are safe in the present practices of use and concentration.

INTRODUCTION

Milk and dairy products, especially bovine (cow) sourced, are considered vital sources of nutrition for billions of people around the world.¹ Milk proteins and protein derivatives form a broad category of materials that are prepared by extraction from bovine milk and partial hydrolysis to yield cosmetic ingredients. The Food and Drug Administration (FDA) defines the term “protein” to mean any α -amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.² The bovine milk proteins and protein derivatives detailed in this report are described by the *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)* to function mainly as skin and hair conditioning agents in personal care products.³ This report assesses the safety of the following 16 milk-derived ingredients:

Ammonium Caseinate	Hydrolyzed Yogurt Protein
Calcium Caseinate	Lactoglobulin
Casein	Milk Protein
Casein Extract	Milk Protein Extract
Hydrolyzed Casein	Potassium Caseinate
Hydrolyzed Lactalbumin	Sodium Caseinate
Hydrolyzed Milk Protein	Sodium Hydrolyzed Casein
Hydrolyzed Whey Protein	Whey Protein

The safety of various 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 Collagen (published in 1985, re-review published in 2006) Hydrolyzed Soy Protein (finalized in 2015), Hydrolyzed Silk (finalized in 2015), Hydrolyzed Rice Protein (published in 2006), and Hydrolyzed Corn Protein (published in 2011) are safe for use in cosmetics.⁴⁻¹⁰ Additionally, the Panel concluded that Hydrolyzed Wheat Gluten and Hydrolyzed Wheat Protein are safe for use in cosmetics when formulated to restrict peptides to a weight-average MW of 3500 Da or less.¹¹ The CIR is concurrently reviewing the safety of plant-derived proteins and peptides and tissue-derived proteins and peptides, in separate reports.

While relevant data on the cosmetic ingredient Hydrolyzed Lactalbumin could not be identified in the published literature, information on the unprocessed protein, lactalbumin, was discovered and has been incorporated into this report to aid in the review of safety.

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

CHEMISTRY

Definition

The definitions and functions of the milk proteins and protein derivatives are described in Table 1. Bovine milk proteins are synthesized in the mammary epithelial cells and are only produced by the mammary gland.¹² There are numerous milk proteins, but the most prevalent are caseins (~79% of all milk proteins; the gelatinous material of the curd), and whey; whey is primarily lactalbumin (~4%) and lactoglobulin (~10%).¹³ While other proteins exist in milk (e.g., enzymes, antibodies, and growth factors; all together comprising the other ~7%), the ingredients in this report predominantly comprise casein, lactalbumin, and/or lactoglobulin proteins.

Protein hydrolysates can be prepared via acid hydrolysis, enzymatic hydrolysis, or other methodologies. The methodology selected and the conditions and duration of the hydrolysis may profoundly affect the size and reactivity of the hydrolysates. Most of the ingredients in this report, even those without “hydrolyzed” in the name,

are hydrolyzed to some degree as necessary for extraction or solubilization. Further steps towards solubilization of these macromolecules commonly include reaction with an alkaline substance to produce a protein salt (e.g., Calcium Caseinate).

Milk proteins in yogurt are partially hydrolyzed by proteolytic enzymes in lactic acid bacteria during fermentation.¹⁴ However, the levels of hydrolyzed bacterial proteins in yogurt are expected to be insignificant compared to the levels of hydrolyzed milk protein after processing to produce hydrolyzed yogurt protein.

Physical and Chemical Properties

Casein and Caseinate Salts

Casein is described as an off-white to cream-colored granular or fine powder. It is insoluble in water and alcohol, but can be dissolved by aqueous alkalis to form caseinate salts.¹⁵ Caseinate salts are white to cream-colored granules or powders that are soluble or dispersible in water. The amino acid sequence of β -casein contains 209 residues with an approximate molecular weight (MW) of 23,600 daltons (Da).¹⁶

Hydrolyzed Casein

A supplier has reported that the molecular weight of a Hydrolyzed Casein product is approximately 600 Da.¹⁷

Hydrolyzed Milk Protein

A Hydrolyzed Milk Protein product was described as a cream colored powder with a slight, characteristic odor and a pH of 5.0 to 7.0.¹⁸

A supplier has reported that the molecular weight of Hydrolyzed Milk Protein is ~1000 Da.¹⁹ Another supplier has reported the molecular weight distribution of 3 batches of Hydrolyzed Milk Protein yielded 58.4% of the MW to be below 5000 Da and 41.4% of the MW to be greater than 5000 Da and less than 30,000 Da.²⁰

At 25° C, Hydrolyzed Milk Protein is soluble in water, partially soluble in 75/25 and 50/50 water/ethanol, and insoluble in 25/75 water/ethanol, 200 proof ethanol, mineral oil, glycerin, and propylene glycol.¹⁸

Hydrolyzed Lactalbumin

α -Lactalbumin (non-hydrolyzed) is described as a homogenous, free-flowing, semi-hygroscopic, light cream-colored powder.¹⁵ Physical and chemical properties on Hydrolyzed Lactalbumin were not found.

Method of Manufacturing

Methods used to manufacture protein hydrolysates typically yield broad molecular weight distributions of peptides, ranging from 500 to 30,000 Da.²¹ However, certain enzymes, such as papain, can routinely produce narrower distributions of 500 to 10,000 Da. For example, if the average molecular weight of an amino acid is 135 Da, then, under the broader distribution figures (i.e., 500 to 30,000 Da), these ingredients are approximately 4 to 220 amino acids in length (and approximately 4 to 74 amino acids in length under the narrower distribution, i.e., 500 to 10,000 da).²²

Casein

Casein is derived from the coagulum formed by treating skim milk with a food-grade acid (acid casein), enzyme (rennet casein), or other food-grade precipitating agent.¹⁵ After precipitation, Casein is separated from the soluble milk fraction, washed and dried. Casein is a mixture of at least 20 electrophoretically distinct phosphoproteins, with the main fractions being α -casein, β -casein, and κ -casein.

Hydrolyzed Casein

A supplier reported that a Hydrolyzed Casein product (MW = 600 Da; 30% solution in water) is prepared by acidic, alkaline, and/or enzymatic hydrolysis of bovine milk until the molecular weight reached the target range.¹⁷

Hydrolyzed Lactalbumin

α -Lactalbumin (non-hydrolyzed) is isolated from either bovine milk or from whey.¹⁵ A method of manufacture for the hydrolysis of lactalbumin (specifically) to Hydrolyzed Lactalbumin was not found.

Hydrolyzed Milk Protein

A supplier reported that Hydrolyzed Milk Protein is produced from milk intended for human consumption.²³ The milk solids are separated and hydrolyzed with a protease for 2 hours. When the target molecular weight is achieved, the enzyme is inactivated by heating the solution to 140°C for 30 minutes. The inactivation step is repeated if gelatin mixed with a sample loses viscosity, indicating the presence of active protease.

Another supplier reported that Hydrolyzed Milk Protein is manufactured by enzymatic hydrolysis for a specific duration and at an elevated temperature (details not provided).²⁴ The resultant hydrolyzed proteins have molecular weights in the 2000-4000 Da range and all contain di- and tri-peptides.

Whey Protein

Whey is the liquid obtained by separating the coagulum from milk, cream, and/or skim milk (usually in cheese making).¹⁵ Acid-type whey is produced by converting a significant amount of lactose to lactic acid or by direct acidification of milk. Sweet-type whey is derived from a process in which there is insignificant conversion of lactose to lactic acid. Whey protein concentrate is a liquid or dry product that is obtained by the removal of sufficient non-protein constituents from whey so that the finished dry product contains not less than 25.0% protein, while whey protein isolate is a liquid or dry product that is obtained by removing sufficient non-protein constituents from whey so that the finished dry product contains not less than 90% protein. Whey protein concentrate and whey protein isolate are produced by physical separation techniques such as precipitation, filtration, dialysis and/or ion exchange.

Composition

Casein

Casein is reported to have all the amino acids considered to be essential for human nutrition.¹⁵

Hydrolyzed Milk Protein

The amino acid distribution in a Hydrolyzed Milk Protein product is presented in Table 2. A Hydrolyzed Milk Protein (MW = 1250 Da) raw material produced by enzymatic hydrolysis was reported to be 81.0 to 93.8% pure.²⁵ Sodium chloride content was ≤ 10% and moisture content was ≤ 5%.

Impurities

The ingredients in this safety assessment are bovine sourced; however, the FDA does not consider milk or processed milk ingredients as risk materials for transmission of infectious agents (i.e. bovine spongiform encephalopathy) in cosmetic products (21 CFR §700.27).

The World Organization for Animal Health (OIE) recommends that “when authorizing import or transit of [milk and milk products] 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.”²⁶

The *Food Chemicals Codex*, a compendium of internationally recognized standards published by the United States Pharmacopeia (USP) for the purity and identity of food ingredients, states that the acceptable lead limit for Casein and caseinate salts is no more than 1 mg/kg.¹⁵ Acid casein should contain not less than 90% protein calculated on a dry basis. The acceptable lead limit in α-lactalbumin (non-hydrolyzed form of Hydrolyzed Lactalbumin) is no more than 0.5 mg/kg on the dried basis, and the acceptable phosphorus limit is no more than 700µg/g. α-Lactalbumin may also contain β-lactoglobulin (no more than 6.5% calculated on total protein basis), lactose (no more than 1.0%), and lipids (no more than 1.0%). Whey, whey protein concentrate, and whey protein isolate may contain no more than 0.5 mg/kg lead calculated on the dried basis. Whey protein isolate should contain not less than 90% protein calculated on a dry basis.

Hydrolyzed Casein

A supplier reported that a Hydrolyzed Casein product (MW = 600 Da, 30% solution in water) did not contain more than 5 ppm heavy metals and not more than 0.5 ppm arsenic.¹⁷

Hydrolyzed Milk Protein

A Hydrolyzed Milk Protein product was reported to have a maximum microbiological count of 500 organisms per gram (opg), with yeast and molds being < 100 opg.¹⁸

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. FDA and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys conducted by the Personal Care Products Council (Council) of maximum reported use concentrations by product category.

According to 2017 VCRP data, Hydrolyzed Milk Protein is used in 189 formulations; the majority of uses are in leave-on products (Table 3).²⁷ Whey Protein has the second greatest number of overall uses reported, with a total of 67; the majority of the uses are in leave-on formulations. The results of the concentration of use survey conducted in 2016 by the Council indicate Sodium Caseinate has the highest reported maximum concentration of use; it is used at up to 96.9% in bath oils, tablets, and salts.^{28,29} The highest reported maximum concentration of use in a leave-on formulation for this ingredient is 0.1% in a face and neck skin care product. Casein has the highest reported maximum concentration of use in a leave-on product and is used at up to 2% in makeup preparations. Ingredients with neither reported uses in the VCRP nor by Council are listed in Table 4.

In some cases, reports of use were received from the VCRP, but no concentration of use data were provided. For example, Milk Protein Extract is reported to be used in 4 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, Casein was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 2% in makeup preparations. It should be presumed that Casein is used in at least one cosmetic formulation for each category for which it is reported to be used.

Some of these ingredients may be used in products that can come into contact with mucous membranes and the eyes. For example, Sodium Caseinate is used in bath oils, tablets, and salts at up to 96.9% and Milk Protein is used in eye makeup preparations at up to 0.5%.²⁸ Additionally, some of these ingredients were reported to be used in spray deodorants, hair sprays, face powders, face and neck sprays, body and hand sprays, and fragrances and could possibly be inhaled. For example, Casein was reported to be used in a spray deodorant at 0.013% and Milk Protein was reported to be used in face powders at 0.0002%. 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.³⁰⁻³³ 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.^{30,32} There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.³² However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. 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.³⁴⁻³⁶

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

Non-Cosmetic

According to the U.S. FDA, bovine milk is considered generally recognized as safe (GRAS) as it is a substance used in food prior to January 1, 1958, through experience based on common use in food (21 CFR§170.30). The FDA has also determined that the use of peptones as direct food substances is GRAS. These GRAS peptones are defined as “the variable mixture of polypeptides, oligopeptides, and amino acids that are produced by partial hydrolysis of casein...or lactalbumin (whey protein) (21 CFR §184.1553). Additionally, Casein is GRAS as substances migrating to food from paper and paperboard products (21CFR §182.90). Sodium Caseinate is GRAS for human and animal consumption (21CFR§182.1748, 21CFR§582.1748). Whey is GRAS for human consumption (21CFR§184.1979). Labeling requirements for milk-related ingredients and hydrolyzed proteins in food that is GRAS for human consumption are defined in 21CFR101.4 and 21CFR102.22.

Calcium Caseinate and Sodium Caseinate are used in over the counter (OTC) weight control drug products, but these active ingredients do not have adequate data available to be generally recognized as safe and effective for these specified uses (21 CFR§ 310.545). These casein salts and whey protein, in mixtures with other substances, are also being investigated for use as drug coatings and topical drug delivery systems, respectively.³⁸⁻⁴⁰

The FDA requires allergen labeling when one or more of the eight major food allergens, such as milk, are included in food.⁴¹

Casein and caseinate salts, α -lactalbumin, whey, whey protein concentrate, and whey protein isolate are all listed in the *Food Chemicals Codex*.¹⁵ Casein and caseinate salts are described as binders, extenders, clarifying agents, emulsifiers, and stabilizers in food. α -Lactalbumin is described as a nutrient and a source of tryptophan. Whey and whey protein concentrate are described as texturizers and nutrients, with the concentrate also used as an emulsifier, water-binding aid, and gelling agent in foods. Whey protein isolate is considered a source of high-quality protein that may also be used as a gelling agent, water-binding aid, foaming or whipping aid, emulsifier, and an edible coating used as a moisture barrier.

TOXICOKINETICS

Hydrolyzed Milk Protein

While no experimental data were available for the dermal absorption of Hydrolyzed Milk Protein, it was noted that gastro-intestinal absorption allows for substantially greater bioavailability than dermal absorption.⁴² In worst-case scenarios of oral exposures greater than 2000 mg/kg, no signs of systemic toxicity were observed and, therefore, it was concluded that no systemic toxicity would occur with cutaneous exposure.

TOXICOLOGICAL STUDIES

Bovine milk, milk proteins, and milk protein derivatives are GRAS food substances, and daily exposures from food use would result in much greater systemic exposures than those resulting from use in cosmetic products. Consequently, systemic toxicity potential for these ingredients is not addressed further in this report. The safety assessment focuses on the potential for irritation and sensitization from topical exposure to these milk ingredients.

GENOTOXICITY

Hydrolyzed Casein

The mutagenic potential of a Hydrolyzed Casein product (MW = 600 Da, 30% solution in water) was studied in an Ames test using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and *Escherichia coli* strain WP2uvrA, with and without S9 metabolic activation.¹⁷ Concentrations were tested up to 5000 μ g/plate. The test material did not induce reverse mutations with or without S9. It was concluded that Hydrolyzed Casein was not mutagenic.

Hydrolyzed Milk Protein

The potential of Hydrolyzed Milk Protein to induce gene mutation was studied in *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 with and without S9 metabolic activation.⁴² Concentrations were tested up to 5000 μ g/plate. The test material did not induce reverse mutations with or without S9. It was concluded that Hydrolyzed Milk Protein was not mutagenic.

CARCINOGENICITY

Tumor Suppression

Several studies have investigated the carcinogenic effects of milk and its related proteins and protein derivatives in the diet, and the results indicated that these substances may suppress tumor formation.⁴³⁻⁴⁵ Review articles of the role of milk proteins and hydrolyzed proteins on cancer reported that Casein and casein peptides have antimutagenic properties, and that animal models for colon and mammary tumorigenesis (like the study described below) showed that Hydrolyzed Whey Protein suppressed tumor development.⁴⁶⁻⁴⁸ The tumor suppression observed in studies with Hydrolyzed Whey Protein has been attributed to the high content of cystine/cysteine and γ -glutamylcyst(e)ine dipeptides in the milk proteins, which are efficient substrates for synthesizing glutathione, an important cellular antioxidant.

An example of tumor suppression is the effect of milk proteins on the ability of dimethylbenzanthracene (DMBA) to induce mammary tumors in pregnant Sprague-Dawley rats.⁴⁵ The rats (number not reported) were fed diets that included 20% Casein, Hydrolyzed Casein, Whey Protein, or Hydrolyzed Whey Protein starting on gestation day 4. The offspring of these rats were fed the same diet. At 50 days, the female offspring (44-49 rats/group) were dosed by gavage with sesame oil containing 80 mg/kg DMBA and were killed 62 days post-treatment. The rats that were fed Hydrolyzed Whey Protein had an adenocarcinoma incidence of 17% compared to rats fed Casein (34%), Hydrolyzed Casein (33%), and Whey Protein (36%) ($P < 0.001$). The median palpable tumor latency for rats fed Hydrolyzed Whey Protein (61 days, $P < 0.001$) was greater compared to those fed Casein (44

days), Hydrolyzed Casein (42 days), or Whey Protein (45 days). When compared to rats fed Casein and Hydrolyzed Casein, tumor multiplicity was lower in rats fed Hydrolyzed Whey Protein (1.5 vs 3.0, $P < 0.05$). The authors of the study concluded that dietary intake of Hydrolyzed Whey Protein reduced DMBA-induced mammary tumor formation.

OTHER RELEVANT STUDIES

Type 1 Hypersensitivity

Bovine milk protein is a major food allergen that can produce Type 1 (immediate) reactions in sensitized individuals, including up to 8% of children.^{49,50} The allergy to bovine milk protein usually occurs in infancy and childhood and is often outgrown by age 5, but approximately 15% to 20% of allergic children remain allergic into adulthood with increased levels of immunoglobulin E (IgE), especially bovine-specific IgE. The IgE-mediated reaction may include cutaneous, respiratory, and gastrointestinal reactions that may on rare occasions result in systemic anaphylaxis.^{1,49,50} Non-IgE-mediated reactions may also occur, but these are not as well characterized.⁵⁰ While the reactions may be to any of the proteins found in milk, reactions are most commonly linked to α -lactalbumin, β -lactoglobulin, and casein.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation and Sensitization

Dermal irritation and sensitization studies are presented in Table 5 and Table 6, respectively.^{17,24,42,51-58} The results of in vitro assays predicted no potential for irritation to Hydrolyzed Milk Protein or Hydrolyzed Yogurt Protein when tested undiluted. Hydrolyzed Milk Protein was not irritating to rabbits or humans when tested at up to 25% and 5%, respectively. Hydrolyzed Casein (MW = 600 Da) was not irritating to humans when tested in a 30% solution in water. No irritation or sensitization was observed in a guinea pig maximization study of 5% (v/v) Hydrolyzed Milk Protein in water. Hydrolyzed Casein (MW = 600 Da) and Hydrolyzed Milk Protein (MW = 1250 Da) were not sensitizing in a human repeated insult patch test (HRIPT) when tested in a 30% solution in water or at up to 0.01% in formulation, respectively.

Phototoxicity

Phototoxicity studies are presented in Table 7.⁴² Hydrolyzed Milk Protein was not a photoirritant or a photosensitizer in human subjects when tested at 5%.

OCULAR IRRITATION STUDIES

In vitro and animal ocular irritation studies are presented in Table 8.^{17,24,42,52,53,59,60} No irritation was predicted to Hydrolyzed Milk Protein (undiluted), Hydrolyzed Casein (1.5% active ingredient), or Hydrolyzed Yogurt Protein (undiluted) in in vitro assays. Hydrolyzed Milk Protein was not irritating to rabbit eyes when tested at up to 25%.

CLINICAL STUDIES

Hydrolyzed Milk Protein

A study of sensitization to protein hydrolysates in hair care products was performed in 3 groups of patients.⁶¹ Eleven hairdressers with hand dermatitis comprised the first group, which submitted to scratch and prick tests with 22 trademarked protein hydrolysates, including Hydrolyzed Milk Protein, as well as quaternized hydrolyzed proteins. The second test group included 1260 consecutive adults with suspected allergic respiratory disease; they were subjected to skin prick tests with 1 to 3 of the protein hydrolysates (only 1232 patients in this group were tested with Hydrolyzed Milk Protein). The third group of patients included 28 adults with atopic dermatitis and was also tested with 1 to 3 protein hydrolysates via a skin prick test.

Of all 3 groups tested, positive reactions were seen in a total of 12 patients (all female with atopic dermatitis) from exposure to 3 of the 22 protein hydrolysates. All 12 had reactions to hydroxypropyl trimonium hydrolyzed collagen. One of the 12 also had a reaction to hydroxypropyl trimonium hydrolyzed milk protein (not an ingredient in this report) while 3 others had a reaction to one trademarked version of hydrolyzed collagen. No adverse reactions to Hydrolyzed Milk Protein were observed in the 1271 patients tested.⁶¹

SUMMARY

Hydrolyzed Milk Protein is used in 189 formulations; the majority of uses are in leave-on products. Whey Protein has the second greatest number of overall uses reported, with a total of 67; the majority of the uses are in leave-on formulations. Sodium Caseinate has the highest reported maximum concentration of use; it is used at up to 96.9% in bath oils, tablets and salts. The highest reported maximum concentration of use in a leave-on formulation for this ingredient is 0.1% in a face and neck skin care product. Casein has the highest reported maximum concentration of use in a leave-on product and is used at up to 2% in makeup preparations.

Bovine milk, milk proteins, and milk protein derivatives are GRAS, and daily exposures from food use would result in much greater systemic doses than those resulting from use in cosmetic products. The safety assessment focuses on the potential for irritation and sensitization from topical exposure to these milk ingredients.

Hydrolyzed Milk Protein and Hydrolyzed Casein were not mutagenic at concentration up to 5000 µg/plate in Ames assays.

Casein and casein peptides are reported to have antimutagenic properties, and animal models for colon and mammary tumorigenesis have shown that Whey Protein and Hydrolyzed Whey Protein suppressed tumor development. The tumor suppression observed in studies with Hydrolyzed Whey Protein have been attributed to the high content of cystine/cysteine and γ -glutamylcyst(e)ine dipeptides in the milk proteins, which are efficient substrates for synthesizing glutathione, an important cellular antioxidant.

Bovine milk protein is a major food allergen that can produce Type 1 reactions in sensitized individuals, especially children. The IgE-mediated reaction may include cutaneous, respiratory, and gastrointestinal reactions that may, on rare occasions, result in systemic anaphylaxis. While the reactions may be to any of the proteins found in milk, reactions are most commonly linked to α -lactalbumin, β -lactoglobulin, and casein.

Hydrolyzed Milk Protein (concentration not reported) was negative in an in vitro dermal irritation assay. Hydrolyzed Milk Protein was not irritating to rabbits or humans when tested at up to 25% and 5%, respectively. Hydrolyzed Casein (MW = 600 Da) was not irritating to humans when tested in a 30% solution in water.

No dermal sensitization was observed in a guinea pig maximization study of Hydrolyzed Milk Protein at up to 100%. No sensitization was observed in a study of Hydrolyzed Milk Protein in sensitized patients (concentration not reported). Hydrolyzed Casein (MW = 600 Da) was not sensitizing in a HRIPT when tested in a 30% solution in water.

Hydrolyzed Milk Protein was not a photoirritant or a photosensitizer in human subjects when tested at 5%.

No ocular irritation was predicted to Hydrolyzed Milk Protein (concentration not reported) or Hydrolyzed Casein (1.5% active ingredient) in in vitro assays. Hydrolyzed Milk Protein was not irritating to rabbit eyes when tested at up to 25%.

No adverse effects from cosmetic use of milk protein or protein-derived ingredients were discovered in the published literature.

DISCUSSION

The bovine milk protein ingredients in this assessment are found in foods, and daily exposures from the consumption of foods can be expected to yield much larger systemic exposures to these ingredients than those from use in cosmetic products. Bovine milk and bovine milk proteins are GRAS in foods and animal feeds. The Panel did acknowledge that bovine milk proteins are known food allergens that can elicit Type I hypersensitivity reactions when ingested by sensitized individuals. However, no relevant ocular irritation and no dermal irritation or sensitization were reported in animals or human subjects, and no reported cases of Type I hypersensitivity reactions from cosmetic use were found in the published literature. Additionally, according to their collective knowledge in treating patients with Type 1 hypersensitivity, the Panel clinicians have not experienced responses to bovine milk protein via dermal exposures. Thus, the Panel was not concerned that Type I reactions would be induced by dermal exposure to bovine milk proteins in cosmetics.

The Panel noted that Sodium Caseinate has use concentrations reported up to 96.9%; however, this concentration is in bath oils, tablets, and salts, which are diluted in water prior to use. In leave-on products, the maximum concentration of use reported in the Casein-derived ingredients is 2%. Safety test data of Hydrolyzed Casein were negative at up to 30%. Because of these factors, the Panel was not concerned with the use of Sodium Caseinate at such a high concentration in bath products that are intended to be diluted for use.

The Panel discussed the issue of incidental inhalation exposure in spray deodorants, hair sprays, face powders, face and neck sprays, body and hand sprays, 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 16 bovine milk proteins and protein derivatives listed below are safe in the present practices of use and concentration.

Ammonium Caseinate*	Hydrolyzed Yogurt Protein
Calcium Caseinate*	Lactoglobulin
Casein	Milk Protein
Casein Extract*	Milk Protein Extract
Hydrolyzed Casein	Potassium Caseinate*
Hydrolyzed Lactalbumin*	Sodium Caseinate
Hydrolyzed Milk Protein	Sodium Hydrolyzed Casein*
Hydrolyzed Whey Protein	Whey Protein

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

TABLES**Table 1.** Definitions and functions of the ingredients in this safety assessment.³

Ingredient CAS No.	Definition	Function
Casein 9000-71-9	Casein is a mixture of phosphoproteins obtained from cow's milk.	hair conditioning agents; skin-conditioning agents-misc.
Casein Extract	Casein Extract is the extract of Casein.	not reported
Calcium Caseinate 9005-43-0	Calcium Caseinate is the calcium salt of Casein.	binders; bulking agents; hair conditioning agents; skin-conditioning agents-misc.
Ammonium Caseinate 9005-42-9	Ammonium Caseinate is the ammonium salt of Casein.	hair conditioning agents; skin-conditioning agents-misc.
Sodium Caseinate 9005-46-3	Sodium Caseinate is the sodium salt of Casein.	hair conditioning agents; skin-conditioning agents-misc.
Potassium Caseinate 68131-54-4	Potassium Caseinate is the potassium salt of Casein.	hair conditioning agents; skin-conditioning agents-misc.
Hydrolyzed Casein 65072-00-6 73049-73-7	Hydrolyzed Casein is the hydrolysate of Casein derived by acid, enzyme or other method of hydrolysis.	hair conditioning agents; skin-conditioning agents-misc.
Sodium Hydrolyzed Casein	Sodium Hydrolyzed Casein is the sodium salt of Hydrolyzed Casein.	hair conditioning agents; skin-conditioning agents-misc.
Hydrolyzed Lactalbumin 68458-87-7 73049-73-7	Hydrolyzed Lactalbumin is the hydrolysate of milk albumins derived by acid, enzyme, or other method of hydrolysis. [Lactalbumin is a member of the whey protein family.]	skin-conditioning agents-misc.
Milk Protein 91053-68-8	Milk Protein is a mixture of proteins obtained from cow's milk.	hair conditioning agents; skin-conditioning agents-misc.
Milk Protein Extract	Milk Protein Extract is the extract of Milk Protein.	not reported
Hydrolyzed Milk Protein 92797-39-2	Hydrolyzed Milk Protein is the hydrolysate of milk protein derived by acid, enzyme or other method of hydrolysis.	hair conditioning agents; skin-conditioning agents-misc.
Whey Protein 84082-51-9	Whey Protein is a polypeptide obtained from the fluid part of Milk after separation from curds.	hair conditioning agents; skin-conditioning agents-misc.
Hydrolyzed Whey Protein	Hydrolyzed Whey Protein is the hydrolysate of Whey Protein derived by acid, enzyme or other method of hydrolysis.	skin-conditioning agents-misc.
Lactoglobulin	Lactoglobulin is a globular protein isolated from milk. [Lactoglobulin is a member of the whey protein family.]	hair conditioning agents; skin-conditioning agents-misc.
Hydrolyzed Yogurt Protein	Hydrolyzed Yogurt Protein is the hydrolysate of yogurt protein derived by acid, enzyme or other method of hydrolysis.	hair conditioning agents; skin-conditioning agents-misc.

Table 2. Amino acid distribution for a Hydrolyzed Milk Protein produced by enzymatic hydrolysis.¹⁸

alanine	2.9
arginine	3.6
aspartic acid	6.5
cysteine	0.4
glutamic acid	20.5
glycine	1.8
histidine	2.7
isoleucine	5.8
leucine	8.8
lysine	7.0
methionine	2.7
phenylalanine	4.7
proline	10.4
serine	5.9
threonine	3.8
tryptophan	1.2
tyrosine	5.1
valine	0.5

Table 3. Frequency and concentration of use according to duration and type of exposure for milk proteins and protein derivatives.²⁷⁻²⁹

Table 3. Frequency and concentration of use according to duration and type of exposure for milk proteins and protein derivatives.²⁷⁻²⁹

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Sodium Caseinate		Whey Protein					
Totals[†]	3	0.0005-96.9	67	0.0001-0.5				
Duration of Use								
Leave-On	NR	0.1	62	0.0001-0.5				
Rinse Off	3	2.5	4	0.0075-0.25				
Diluted for (Bath) Use	NR	96.9	1	0.0065				
Exposure Type								
Eye Area	NR	0.001	16	0.05-0.5				
Incidental Ingestion	NR	NR	NR	NR				
Incidental Inhalation-Spray	NR	0.0005; 0.05 ^a	22 ^a ; 13 ^b	0.0001-0.0075; 0.026-0.2 ^a				
Incidental Inhalation-Powder	NR	0.001-0.1 ^c	13 ^b	0.0001-0.5 ^c				
Dermal Contact	3	0.0005-96.9	66	0.0001-0.5				
Deodorant (underarm)	NR	NR	NR	0.0075 ^d				
Hair - Non-Coloring	NR	0.05-2	1	0.0075-0.032				
Hair-Coloring	NR	NR	NR	NR				
Nail	NR	NR	NR	NR				
Mucous Membrane	NR	0.1-96.9	1	0.0065-0.012				
Baby Products	NR	NR	NR	NR				

NR = Not reported.

[†] Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.^a It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.^b Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.^c It is possible these products may be powders, but it is not specified whether the reported uses are powders.^d Use reported in an aerosol deodorant.**Table 4.** Ingredients not reported in use.^{27,28}

Ammonium Caseinate
Calcium Caseinate
Casein Extract
Hydrolyzed Lactalbumin
Potassium Caseinate
Sodium Hydrolyzed Casein

Table 5. Dermal irritation studies for milk proteins and protein derivatives.

Ingredient	Concentration	Method	Results	Reference
<i>In Vitro</i>				
Hydrolyzed Milk Protein (MW = 2000-4000 Da)	In solution, concentration not reported	EpiDerm™ assay	Non-irritating	²⁴
Hydrolyzed Milk Protein (MW = 2000-4000 Da)	Undiluted	EpiDerm™ Assay	Predicted to be non-irritating	⁵³
Hydrolyzed Yogurt Protein (MW = 2000-4000 Da)	Undiluted	EpiDerm™ Assay	Predicted to be non-irritating	⁵²
<i>Animal</i>				
Hydrolyzed Milk Protein (MW = 1500 Da)	10% (v/v) aqueous dilution, pH 6.7	Dermal irritation study performed under OECD* Guideline 404 in 6 White New Zealand rabbits; semi-occluded for 24 h	Non-irritating	⁴²
Hydrolyzed Milk Protein (MW = 1500 Da)	25% w/v in water	Primary skin irritation study in 6 female New Zealand White rabbits, occluded for 24 h	Primary irritation index = 1.3. Not a primary irritant.	⁵¹
<i>Human</i>				
Hydrolyzed Casein (MW = 600 Da)	30% solution in water	24-hpatch test in 20 female subjects using Finn Chambers (occluded)	No irritation	¹⁷

* OECD = Organisation for Economic Co-operation and Development

Table 6. Dermal sensitization studies for milk proteins and proteins derivatives.

Ingredient	Concentration	Method	Results	Reference
Hydrolyzed Milk Protein	5% v/v in water	Animal Guinea pig maximization study using male and female Pirbright white guinea pigs (number not reported); induced intracutaneously with 5% of the test material in adjuvant and water and epicutaneously with 100% of the test material; challenged with 100% of the test material	No irritation or sensitization	⁴²
Hydrolyzed Casein (MW = 600 Da)	30% solution in water	Human HRIPT with 0.2 mL of the test material applied using an occlusive patch on the infrascapular region of 50 subjects	No sensitization	¹⁷
Hydrolyzed Milk Protein (MW = 1250 Da)	0.011% in a hair styling product	HRIPT in 102 subjects; applied neat with occlusive patches; positive (1% SLS) and negative control patches (distilled water) applied	12% of subjects had cutaneous reactions in the induction phase (total cumulative irritation score 70.3); 5 and 2 subjects had cutaneous reactions of "1" at the 48 h and 96 h challenge observations, respectively. Study concluded product did not induce allergic contact dermatitis and is not predicted to be a skin irritant.	⁵⁷
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a hair conditioning product	HRIPT in 102 subjects; applied neat with occlusive patches; positive (1% SLS) and negative control patches (distilled water) applied	24% of subjects had cutaneous reactions in the induction phase (total cumulative irritation score 179.2); 8 and 4 subjects had cutaneous reactions of "1" or "1P" at the 48 h and 96 h challenge observations, respectively. Study concluded product did not induce allergic contact dermatitis and is not predicted to be a skin irritant.	⁵⁵
Hydrolyzed Milk Protein (MW = 1250 Da)	0.0102% in a hair styling product	HRIPT in 109 subjects; applied neat with occlusive patches; positive (0.2% SLS) and negative control patches (distilled water) applied	63% of the subjects had transient, barely-perceptible to mild responses (specific or nonspecific) during the induction and/or challenge phases; reactivity was not considered to be clinically meaningful irritation or sensitization. The total cumulative irritation score was 172.5. Study concluded product did not induce allergic contact dermatitis and is not predicted to be a skin irritant.	⁵⁶
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a shampoo	HRIPT in 109 subjects; 1% solution tested; positive (0.2% SLS) and negative control patches (distilled water) applied; patch type not reported	Total cumulative irritation score was 325. No reactions observed during the challenge phase. Study concluded product did not induce allergic contact dermatitis and is not predicted to be a skin irritant.	⁵⁸
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a hair conditioning product	HRIPT in 100 subjects; 10% solution tested with occlusive patches; positive (0.2% SLS) and negative control patches (distilled water) applied	Total cumulative irritation score was 14. No reactions observed during the challenge phase. Study concluded product did not induce allergic contact dermatitis and is not predicted to be a skin irritant.	⁵⁴

Table 7. Phototoxicity/Photosensitization studies in humans for Hydrolyzed Milk Protein.

Ingredient	Concentration	Method	Results	Reference
Hydrolyzed Milk Protein	5% aq. dilution, v/v	Photoirritation study in 10 subjects; occluded. After 24 h exposure, 1 treated site irradiated with UVA (320-400 nm) for 15 min, other site was control.	Not a photoirritant	42
Hydrolyzed Milk Protein	5% dilution in water, v/v	Photosensitization study in 29 subjects; 3 weeks of 6 induction patches in duplicate. After 24 h exposure, 1 treated site irradiated with UV (260-400 nm) for 15 min, other site was control. After 2 week rest, challenge on virgin irradiated and non-irradiated sites.	Not a photosensitizer	42

Table 8. Ocular irritation studies for Hydrolyzed Milk Protein.

Ingredient	Concentration	Method	Results	Reference
<i>In Vitro</i>				
Hydrolyzed Casein (MW = 600 Da)	1.5% active ingredient	HET-CAM assay	Non-irritating	¹⁷
Hydrolyzed Milk Protein (MW = 2000-4000 Da)	In solution, concentration not reported	EpiOcular™ assay	Non-irritating	²⁴
Hydrolyzed Milk Protein (MW = 2000-4000 Da)	Undiluted	EpiOcular™ Assay	Predicted to be non-irritating	⁵³
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a hair styling product	Chorioallantoic Membrane Vascular Assay (CAMVA)	RC50 (%): 3.1 (95% CI 1.4-6.7); not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a hair conditioning product	CAMVA	RC50 (%): > 100 (95% CI not determined); not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.011% in a hair styling product	CAMVA	RC50 (%): 12 (95% CI 7.9-18); not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.011% in a hair styling product	CAMVA	RC50 (%): 16 (95% CI 9.2-27); not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a hair conditioning product	CAMVA	RC50 (%): > 30 (95% CI not reported); not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a hair styling product	Bovine Corneal Opacity and Permeability Test (BCOP)	In vitro score: 11.72; not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a hair conditioning product	BCOP	In vitro score: 0.48; not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.011% in a hair styling product	BCOP	In vitro score: 1.11; not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.011% in a hair styling product	BCOP	In vitro score: 1.70; not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Milk Protein (MW = 1250 Da)	0.01% in a hair conditioning product	BCOP	In vitro score: 3.0; not predicted to be an ocular irritant	⁶⁰
Hydrolyzed Yogurt Protein (MW = 2000-4000 Da)	Undiluted	EpiOcular™ Assay	Predicted to be non-irritating	⁵²
<i>Animal</i>				
Hydrolyzed Milk Protein	10% aq. dilution at pH 6.7	Ocular irritation study performed under OECD guideline 405 using 6 albino White New Zealand rabbits	Not irritating	⁴²
Hydrolyzed Milk Protein (MW = 1500 Da)	25% in distilled water	Ocular irritation study in 6 female New Zealand White rabbits; unrinSED eyes	Not irritating	⁵⁹

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2017 FDA VCRP Raw Data – Milk Proteins

03E - Eye Makeup Remover	CASEIN HYDROLYSATE	1
03G - Other Eye Makeup Preparations	CASEIN HYDROLYSATE	1
05A - Hair Conditioner	CASEIN HYDROLYSATE	1
12D - Body and Hand (exc shave)	CASEIN HYDROLYSATE	1
12F - Moisturizing	CASEIN HYDROLYSATE	5
12G - Night	CASEIN HYDROLYSATE	1
12J - Other Skin Care Preps	CASEIN HYDROLYSATE	1
<hr/>		
02A - Bath Oils, Tablets, and Salts	HYDROLYZED MILK PROTEIN	1
02B - Bubble Baths	HYDROLYZED MILK PROTEIN	2
02D - Other Bath Preparations	HYDROLYZED MILK PROTEIN	3
03D - Eye Lotion	HYDROLYZED MILK PROTEIN	1
03E - Eye Makeup Remover	HYDROLYZED MILK PROTEIN	1
03G - Other Eye Makeup Preparations	HYDROLYZED MILK PROTEIN	3
05A - Hair Conditioner	HYDROLYZED MILK PROTEIN	7
05F - Shampoos (non-coloring)	HYDROLYZED MILK PROTEIN	8
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROLYZED MILK PROTEIN	4
05I - Other Hair Preparations	HYDROLYZED MILK PROTEIN	2
07E - Lipstick	HYDROLYZED MILK PROTEIN	3
10A - Bath Soaps and Detergents	HYDROLYZED MILK PROTEIN	14
10B - Deodorants (underarm)	HYDROLYZED MILK PROTEIN	2
10E - Other Personal Cleanliness Products	HYDROLYZED MILK PROTEIN	12
12A - Cleansing	HYDROLYZED MILK PROTEIN	5
12C - Face and Neck (exc shave)	HYDROLYZED MILK PROTEIN	6
12D - Body and Hand (exc shave)	HYDROLYZED MILK PROTEIN	21
12F - Moisturizing	HYDROLYZED MILK PROTEIN	87
12G - Night	HYDROLYZED MILK PROTEIN	3
12H - Paste Masks (mud packs)	HYDROLYZED MILK PROTEIN	2
12J - Other Skin Care Preps	HYDROLYZED MILK PROTEIN	2
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10A - Bath Soaps and Detergents	HYDROLYZED YOGURT PROTEIN	4
12F - Moisturizing	HYDROLYZED YOGURT PROTEIN	1
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12C - Face and Neck (exc shave)	LACTOGLOBULIN	1
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02D - Other Bath Preparations	MILK PROTEIN	1
03B - Eyeliner	MILK PROTEIN	1
03D - Eye Lotion	MILK PROTEIN	1
03G - Other Eye Makeup Preparations	MILK PROTEIN	3
05A - Hair Conditioner	MILK PROTEIN	1
05I - Other Hair Preparations	MILK PROTEIN	3
10A - Bath Soaps and Detergents	MILK PROTEIN	3
10E - Other Personal Cleanliness Products	MILK PROTEIN	7
12A - Cleansing	MILK PROTEIN	4
12C - Face and Neck (exc shave)	MILK PROTEIN	4

12F - Moisturizing	MILK PROTEIN	3
12H - Paste Masks (mud packs)	MILK PROTEIN	2
12I - Skin Fresheners	MILK PROTEIN	1
12J - Other Skin Care Preps	MILK PROTEIN	1
12D - Body and Hand (exc shave)	MILK PROTEIN EXTRACT	2
12F - Moisturizing	MILK PROTEIN EXTRACT	1
12J - Other Skin Care Preps	MILK PROTEIN EXTRACT	1
12A - Cleansing	SODIUM CASEINATE	2
12H - Paste Masks (mud packs)	SODIUM CASEINATE	1
02A - Bath Oils, Tablets, and Salts	WHEY PROTEIN	1
03D - Eye Lotion	WHEY PROTEIN	8
03G - Other Eye Makeup Preparations	WHEY PROTEIN	8
05A - Hair Conditioner	WHEY PROTEIN	1
11F - Shaving Soap	WHEY PROTEIN	1
12A - Cleansing	WHEY PROTEIN	1
12C - Face and Neck (exc shave)	WHEY PROTEIN	11
12D - Body and Hand (exc shave)	WHEY PROTEIN	2
12F - Moisturizing	WHEY PROTEIN	14
12G - Night	WHEY PROTEIN	6
12H - Paste Masks (mud packs)	WHEY PROTEIN	1
12J - Other Skin Care Preps	WHEY PROTEIN	11
13C - Other Suntan Preparations	WHEY PROTEIN	2



Memorandum

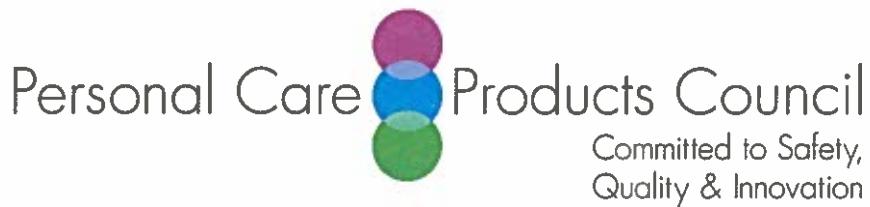
TO: Bart Heldreth, Ph.D., Interim Director
COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: July 6, 2017

SUBJECT: Concentration of Use by FDA Product Category: Lactoglobulin

Lactoglobulin was included in the May2017 concentration of use survey. No uses were reported.



Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: April 4, 2017

SUBJECT: Draft Report: Safety Assessment of Milk Proteins and Protein Derivatives as Used In Cosmetics (draft prepared for the April 10-11, 2017 CIR Expert Panel Meeting)

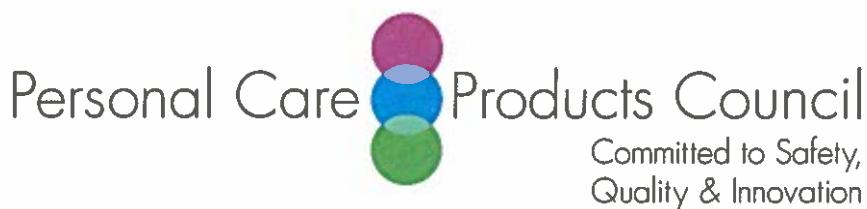
Cosmetic Use - No use concentrations for Lactoglobulin were provided by the Council because it has not yet been included in a concentration of use survey. This ingredient was not included in the title of the concentration of use table provided by the Council; therefore, it was not included in the concentration of use survey. It will be included in the next concentration of use survey.

Tumor Suppression, Summary - The title of reference 41 (reference cited for the example of tumor suppression of milk proteins) is: "Whey protein hydrolysate but not whole whey protein protects against 7,12-dimethylbenz(a)anthracene-induced mammary tumors in rats". The Tumor Suppression section states: "The authors of the study concluded that dietary intake of Whey Protein reduced DMBA-induced mammary tumor." It should be made clear that Hydrolyzed Whey Protein not "whole" Whey Protein reduced tumor numbers. If other studies have shown a benefit of Whey Protein itself, perhaps another example study should be added to the CIR report.

Clinical Studies - Please correct: "No adverse reactions Hydrolyzed Milk Protein were observed in 1271 patients tested."

Table 2 - The table includes NS (not surveyed) as a footnote, but NR is used for Lactoglobulin which has not yet been included in a Council concentration of use survey.

Reference 16 - Please correct: "15thth"



Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: May 3, 2017

SUBJECT: Comments on the Tentative Report: Safety Assessment of Bovine Milk Proteins and Protein Derivatives as Used In Cosmetics

Definition, last sentence - Is the following sentence correct? “However, the levels hydrolyzed proteins in yogurt are expected to be insignificant compared to the levels of hydrolyzed protein after processing to produce hydrolyzed yogurt protein.”

Impurities - In addition to citing 21CFR700.27, the World Organisation for Animal Health (OIE)

Terrestrial Animal Health Code chapter on BSE

http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_bse.htm should also be cited in the CIR report. The chapter on BSE states:

“When authorising import or transit of the following commodities and any products made from these commodities and containing no other tissues from cattle, Veterinary Authorities should not require any BSE related conditions, regardless of the BSE risk status of the cattle population of the exporting country, zone or compartment:

milk and milk products;...”

Cosmetic Use - Please state the product category in which Casein was reported to be used at a concentration of 2%.

Tumor Suppression, Summary - As the study (reference 44) cited in the report showed that Hydrolyzed Whey Protein but not Whey Protein itself reduced-DMBA-induced mammary tumor formation, it is not clear what supports the statement that Whey Protein suppresses tumor development. If this statement comes from a review paper, this should be clearly stated. It would also be helpful to provide one more example study in which Whey Protein itself was shown to suppress tumor development.

Table 5 - Is it necessary to present the phototoxicity study (reference 41) in Table 5 (dermal irritation) and Table 7 (phototoxicity/photosensitization)?