Safety Assessment of Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: August 16, 2013
Panel Meeting Date: September 9-10, 2013

The 2013 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 Director is Lillian J. Gill, DPA. This report was prepared by Christina Burnett, Scientific Analyst/Writer, Bart Heldreth, Ph.D., Chemist CIR, and Ivan Boyer, Ph.D., Toxicologist CIR.
To: CIR Expert Panel Members and Liaisons  
From: Christina L. Burnett  
Scientific Writer/Analyst  
Date: August 16, 2013  
Subject: Draft Tentative Safety Assessment of Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten

At the March 2013 meeting, the Panel tabled further discussion on animal- and plant-derived hydrolyzed proteins to allow CIR staff to reorganize the report and to analyze further data from Japan regarding Type 1 allergic reactions to hydrolyzed wheat protein in a soap product. The staff has decided to group hydrolyzed wheat protein and hydrolyzed wheat gluten in one report in order to facilitate consideration of the concern about hydrolyzed wheat protein in Japan and not dilute the evaluation with other unrelated ingredients. The review of the other animal- and plant-derived hydrolyzed proteins will be performed sometime in the future.

Prior to being tabled, the Panel had issued an insufficient data announcement with the following data needs: (1) method of manufacturing data for hydrolyzed wheat protein; and (2) composition and characterization specifications of hydrolyzed wheat protein, including molecular structure and molecular weight ranges from several suppliers to determine if there is a consistency in cosmetic grade hydrolyzed wheat protein.

Since the March meeting, updated VCRP data were received and incorporated into the report. No substantial changes were made in the number of uses. No additional new unpublished data were received. The Council has provided comments on the March version of the report, which have been considered. The comments and 2013 raw FDA VCRP data are in the panel book package for your review.

The available Type 1 hypersensitivity studies concerning reactions to hydrolyzed wheat protein that have mainly originated from Japan have been incorporated into the report.

The Panel should carefully review the abstract, discussion, and conclusion of this report and determine if the data are still insufficient to support safety of these ingredients and issue a Tentative Safety Assessment with such a conclusion. If the data needs have been satisfactorily filled, the Panel should issue a Tentative Safety Assessment with a new conclusion and appropriate discussion.
SAFETY ASSESSMENT FLOW CHART

Public Comment | CIR | Expert Panel | Re-Reviews | Report Color
---|---|---|---|---
60 day public comment period | Draft Priority List | DRAFT PRIORITY LIST | Re-review to Panel | Buff Cover
ANNOUNCED | Draft Priority List | PRIORITY LIST | | Buff Cover

May 2013: SLR

Decision not to reopen the report*

YES | NO |
---|---|

NO | YES*

Draft Report | Draft Amended Report | Green Cover 1st time
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60 day public comment period | Table | Draft TR ISD
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ISD Notice | Table | Draft Amended Tentative Report
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60 day public comment period | Table | Draft Amended Final Report
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Draft TR ISD | Table | Blue Cover
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Tentative Report | Tentative Amended Report
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Draft TR | Table | Different Concl.
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Issue TR | Table | Blue Cover
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Final Report | Issue FR
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*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision
Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten History

**May 2012** – Scientific Literature Reviews announced separately for Source Amino Acids and Hydrolyzed Source Proteins.

**December 2012** - The CIR Expert Panel combined the 2 reports into 1 and retitled it “plant- and animal-derived amino acids and hydrolyzed proteins”. The Panel also removed the ingredient hydrolyzed spinal protein from review as it is a prohibited ingredient. The Panel requested additional data to support the safety of 75 plant- and animal-derived amino acids and hydrolyzed proteins. The additional data needed are: (1) method of manufacturing data for both plant and animal-derived amino acids and hydrolyzed proteins, especially for hydrolyzed wheat protein; and (2) composition and characterization specifications of plant and animal-derived amino acids and hydrolyzed proteins, including molecular structure and molecular weight ranges from several suppliers to determine if there is a consistency in cosmetic grade plant and animal-derived hydrolyzed proteins, especially hydrolyzed wheat protein.

**March 2013 and Post Meeting** – The Expert Panel tabled further discussion on animal- and plant-derived hydrolyzed proteins to allow CIR staff to reorganize the report and to analyze further data from Japan regarding Type 1 allergic reactions to hydrolyzed wheat protein in a soap product. The staff has decided to group hydrolyzed wheat protein and hydrolyzed wheat gluten in one report in order to facilitate consideration of the concern about hydrolyzed wheat protein in Japan and not dilute the evaluation with other unrelated ingredients. The review of the other animal- and plant-derived hydrolyzed proteins will be performed sometime in the future. Prior to being tabled, the Panel had issued an insufficient data announcement with the following data needs: (1) method of manufacturing data for hydrolyzed wheat protein; and (2) composition and characterization specifications of hydrolyzed wheat protein, including molecular structure and molecular weight ranges from several suppliers to determine if there is a consistency in cosmetic grade hydrolyzed wheat protein.
<table>
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<tr>
<th>Ingredient</th>
<th>Reported Use</th>
<th>Composition/Impurities</th>
<th>Method of Manufacturing</th>
<th>Irritation/Sensitization - Animal</th>
<th>Irritation/Sensitization - Human</th>
<th>Ocular/Mucousal</th>
<th>Case Studies</th>
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<td>Hydrolyzed Wheat Gluten</td>
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"X" indicates that data were available in a category for the ingredient.
Search Strategy for Hydrolyzed Wheat Protein & Hydrolyzed Wheat Gluten
(Performed by Christina Burnett and Ivan Boyer)

February-April 2012: SCIFINDER search for Hydrolyzed Proteins (55 substances, searched under INCI names and CAS No.):

Initial search for “adverse effect, including toxicity” yielded 18 references.

Also performed searches using the following search terms (no limits for reference type):

“Hydrolyzed Proteins in Cosmetics” (yield = 30 references);
“Skin Sensitization – Hydrolyzed Proteins” (yield = 1 reference);
“Bioactive Peptides - Cosmetics” (yield = 18 references);
“Skin Irritation – Polypeptides” (yield = 23 references);
“Skin Sensitization – Polypeptides” (yield = 11 references);
“Biogenic Peptides” (yield = 1 reference);
“Bioactive Peptides – Toxicity” (yield = 28 references);
“Bioactive Peptides – Skin Irritation” (yield = 1 reference);
“Hydrolyzed Proteins Chicken Cells in vitro” (yield = 1 reference); and
“Hydrolyzed Protein Irritation” (yield = 7 references).

Many of the references were patents or efficacy reports.

13 references were ordered.

Search updated January 18, 2013.

June-July: SCIFINDER and PubMed search for Hydrolyzed Wheat and CAS Nos. 100684-25-1, 70084-87-6, 100209-50-5, and 222400-28-4

Additional 9 references were ordered.
Minutes from Team and Full Panel Meetings on Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten

(Discussed as Animal- & Plant-Derived Hydrolyzed Proteins with Animal- & Plant-Derived Amino Acids)

March 18, 2013

Dr. Belsito's Team

DR. BELSITO: Okay. Oh, boy, Christina, animal and plant derived amino acids.

MS. BURNETT: I already got apologies from the other group.

DR. BELSITO: Apologies for wanting you to combine them or apologies for

MS. BURNETT: Yes.

DR. BELSITO: Okay. So where do we find these?

MS. BURNETT: It's under it's the one that looks weird AAHPRN.

DR. BELSITO: AAHPRN, yes. Alcohol, PRN, please.

MS. BURNETT: Amino acid.

DR. ANDERSEN: You guys combined them. You deserve what you get.

DR. BELSITO: Okay. Well, hey, we didn't. We did not. Okay?

DR. LIEBLER: Assess the apology?

DR. BELSITO: So the Japanese web site for you who didn't check actually is available in English now, and it goes through step by step there issues with hydrolyzed wheat protein.

There are lots of issues with this, but I think there were a couple of things in the report that caught my eye. And one was that if you derivatize these both with enzyme and acid hydrolysis you will very likely get very short chain amino acids that were likely to be less than 30 and lack much in the way of sensitization or activity.

Or, we could simply limit it to less than 30 amino acids if you believe that single report.

Or, there are a lot of data that need to be done. So, you know, I guess the biggest issue is I don't think they've resolved although we got a handout here. My take is the Japanese it's an ongoing investigation as to what's causing the issue in this hydrolyzed wheat protein because when they test them for typical wheat grass, they're negative; when they test them for gliadin, they're negative; when they test for gluten, they're negative.

So it seems to be some weird combination that the body doesn't normally digest when you eat wheat, right, because these people also don't have a problem eating wheat, if I remember correctly.

Those were my points.

DR. BRESLAWEC: This issue just continues to be very, very hot in Japan.

DR. BELSITO: They've called another sort of mini congress of the participants. I mean, essentially, they're still trying to sort out why it happened, but it was primarily with one manufacturer of a soap product.

DR. BRESLAWEC: One manufacturer's soap product used in the shower, possible aerosolization.
DR. BELSITO: Aerosolization.

DR. EISENMANN: It was a face soap too, I think. The eye area, I think, was a problematic area too.

And in those abstracts, I think there are three studies that have been published out of the research that's ongoing there. I thought it might be helpful if you were aware of those studies too, and I will update you.

I think the last one might be helpful, where they looked at different times of hydrolysis to see if it had any effect on the ability of the protein to cause a reaction.

DR. BELSITO: So here they say in that final one, even with prolonged hydrolyzation they can still activate IgE mediated mechanisms.

DR. LIEBLER: Where are you, Don?

DR. BELSITO: These are abstracts that were sent the final one, Nakamura.

DR. LIEBLER: Okay.

DR. BELSITO: Evaluation of Allergenicity of Acid Hydrolyzed Wheat Protein.

DR. LIEBLER: Okay.

DR. BELSITO: Okay, and then we have in the report itself in this, they don't in this, we're not told what the molecular weights were and how many amino acids they got it down to, at least not in the abstract, because we have that statement in the text on page 39, again that I've alluded to before, that when you get these protein allergens down to 30 amino acid residues, a molecular weight of 3,000 daltons, it greatly reduces Type 1 reactions. But then it says, this hypothesis needs further testing, and that's Reference 49.

And then there was the extraction methods. Although this was prolonged hydrolyzation, that still didn't help.

DR. LIEBLER: So something's fishy there.

DR. BELSITO: Well, you can have some derive from fish.

(Laughter)

DR. BRESLAWEC: Is fish an animal?

DR. LIEBLER: Saying prolonged hydrolysis and moderate hydrolysis and so forth that's all kind of it's all too imprecise for the information that we need.

It's possible that their hydrolysis conditions weren't achieving the desired result, but the only way to really demonstrate how a complete hydrolysis is, is to analyze the samples by mass spectrometry. That's the state of the art for analyzing peptides and proteins today.

DR. ANDERSEN: Show the distribution.

DR. LIEBLER: And you show the molecular weight distributions.

And this might be a situation where there might need to be some type of standard and a limit, but I don't know that based on what we're seeing if we have well enough characterized mixtures or ingredients that were studied in these tests that really tell us what's the relationship between lengths and biological adverse effects.
So, you're right, Don. Enzymatic hydrolysis tends to give you longer pieces, and depending on the structure of the protein and the enzyme used, there could be very long peptides generated just because of the amino (inaudible), the protease use and the cleavage sites that nature puts into the proteins. So proteins that are peptides, polypeptides that are longer, particularly over several thousand molecular weights, strike me as more likely to be able to produce epitopes that would produce interesting or adverse biological effects.

You have a greater chance of that happening with enzymatically hydrolyzed proteins than with acid hydrolysis because if you do acid hydrolysis right you're going to get these things down to, you know, small peptides under a dozen amino acids in length.

DR. BELSITO: But they say here even with acid hydrolysis they have issues.

DR. LIEBLER: So that either be two things going on in my opinion.

One is that their acid hydrolysis conditions weren't sufficient to actually hydrolyze the protein sufficiently, and if they didn't verify it by some kind of analytical method, like mass spectrometry, they wouldn't know.

The other possibility is that there's something else in their sample other than protein that is resistant to the acid that's producing the effect. Just because they say wheat protein doesn't mean the only molecules in that sample are wheat polypeptides. So it could be some glycan

DR. BRESLAWEC: It could be something other than the wheat?

DR. LIEBLER: Exactly. It could be these are likely lots of glycoproteins, and it might be that the antigen involved is a glycan and that the glycan may be stable, or at least somewhat stable, to the hydrolysis conditions they used.

DR. BELSITO: Halyna?

DR. BRESLAWEC: I would like to reiterate our proposal that this group be limited to the parent protein for the review.

So look at all the wheat peptides and hydrolyzed proteins. Look at those separately. Consider what the issues are. See if there are other things from the wheat that may be causing some of these problems. And then move on to the soy group and the silk group.

DR. BELSITO: Well, I assume we don't have a problem with that because considering that wheat was the highest used followed by soy I thought we had very limited data on them.

DR. BRESLAWEC: I think there are issues that are arising that need attention.

DR. EISENMANN: And you know the proteins themselves are actually in the dictionary too, unfortunately.

DR. BELSITO: Mm hmm.

DR. EISENMANN: But then maybe if you had information about the starting protein, that might help. Starting proteins in the mixtures

DR. BELSITO: Yes.

DR. EISENMANN: That might help. I don't know.

DR. LIEBLER: Are there uses for unhydrolyzed wheat protein?
DR. EISENMANN: I think there are few but not a lot. I mean, I haven't surveyed for it yet. I think there are a few in the VCRP but not a lot.

DR. BRESLAWEC: I think there was 32 wheat ingredients.

DR. EISENMANN: See, then there's

DR. BRESLAWEC: There's 25 silk and 27 soy. But we can also expand

DR. EISENMANN: There's also this, you know, hydroxypropyltrimonium hydrolyzed wheat protein or the Tamata hydrolyzed wheat protein would go better in a wheat protein report than a protein.

DR. LIEBLER: Right. I agree.

DR. EISENMANN: So you could do it that way instead of all different sources.

DR. LIEBLER: So you're envisioning a report that would be wheat proteins and their hydrolysis products and derivatives?

DR. EISENMANN: Yes.

DR. BELSITO: Mm hmm.

DR. BRESLAWEC: And, again, the top three there are wheat, soy and silk. And after that the incidence rate, or the use, of those ingredients just drops really dramatically.

DR. LIEBLER: Mm hmm. Well, that would be a little easier for us to deal with.

DR. BELSITO: Yes, I mean, I think it makes sense because the potential allergens in each of these are going to be very different and what's left after the hydrolysis or enzymatic degradation is going to be different. Yes, I mean, it certainly would help me wrap my arms around it just like the palmitoyl group, looking at specifically defined amino acid sequences. Otherwise, I just didn't know how to deal with this.

DR. BRESLAWEC: And that way we don't have to request the removal of hydrolyzed hemp seed protein for this one.

DR. BELSITO: I don't know. The people in Oregon may want to see that.

DR. SNYDER: So we are not going to use the molecular weight?

DR. BELSITO: We're going to actually, I guess, table this and split it up into multiple documents, probably only three of which will ever come to fruition. Wheat, silk and soy at least in our lifetime.

DR. ANDERSEN: Well, the fourth piece is the source amino acids.

DR. BELSITO: Right.

DR. ANDERSEN: Which was at jeopardy under the combined package.

DR. BELSITO: Right.

DR. ANDERSEN: It can be simplified back to where it was.

DR. BELSITO: Right.
DR. LIEBLER: That's good.

DR. BELSITO: So we are resplitting them, and with the hydrolyzed we're looking at wheat as the first. Is that correct?

DR. LIEBLER: Sounds good to me.

DR. ANDERSEN: That's what you're going to propose, Dr. Weber.

DR. BELSITO: Paul, are you proposing this?

DR. SNYDER: Sure.

DR. BELSITO: Are you writing everything down?

DR. SNYDER: If I need to. But again we had no molecular weight data on wheat. We had it for lots of other things.

DR. EISENMANN: There is some in there.

DR. SNYDER: Well, the table 2 doesn't have anything, and so I guess that's why I was raising the issue because of these.

We do have these references that state that the protein allergenicity is in a molecular weight range between three and five kDa, and so I just wanted to make sure that we if we're going to go there, we need to make sure we get adequate data to address that issue because we need to specify.

DR. EISENMANN: But I've got that summarized within several suppliers, and then there's some data in Wave 2.

DR. BRESLAWEC: I was going to say there are data in Wave 2.

DR. SNYDER: In Wave 2, okay.

DR. LIEBLER: So I think for the intact proteins that are like extracts from wheat or silk or soy we're not going to be expecting the degree of chemical characterization as we are of the derivatives, either the hydrolysis products or the modified hydrolysis products. But for those, I think probably mass spectrometry and a description of the molecular weight range will be very important those intermediate ones that are going to be kind of tricky.

DR. SNYDER: And then this issue of the glycan contaminants we raised

DR. LIEBLER: Mm hmm.

DR. SNYDER: So we need better impurities data or

DR. LIEBLER: Well, analytically, it's going to be very hard because there are many different I would say probably at least a third to a half of the proteins are glycosylated. And for the N linked glycosylations, there is a huge diversity of structures, and the analytical methods to assess those definitively are still not very well developed and not straightforward that they could get a contract lab to do it. I mean, it's still really a research problem in glycan characterization, particularly glycoprotein characterization. That's an area that's in relative infancy. So, if you had a peptide fraction that produced some kind of a response and you hypothesized that glycosylation was responsible, you could fractionate the mixture and do some biochemical manipulations to try and test that hypothesis, but it would probably be beyond the scope of what we'd be asking industry to do.
Dr. Marks' Team

DR. MARKS: Our next set of ingredients is the animal and plant amino acids and hydrolyzed proteins. Christina, you're still up.

MS. BURNETT: The file names are in house conventions for us that probably are not translating well for you guys.

DR. MARKS: In December the panel combined the hydrolyzed proteins in the amino acid reports and issued an insufficient data announcement. We wanted method of manufacturing especially for the hydrolyzed wheat protein and we wanted composition and characterization specification for hydrolyzed proteins. We didn't get much, and Wave 2 when I looked at it didn't help me much. That was an insufficient data announcement. Now we're to the point of issuing a report. Do we have a tentative report with an insufficient data conclusion or looking back at this do we really need those data that we've said in our original conclusion?

DR. SLAGA: My recollection is that this group recommended safe as used and it was Belsito's team that wanted we felt there was enough method of manufacture and what addition we got I thought was sufficient.

DR. MARKS: Let me look at the paper. Is that how you remember it, too, that we were going to move forward?

DR. SHANK: Yes, but since then the allergenicity reaction to wheat hydrology has come up and apparently these are Type I allergic reactions which do not show up in HRIPT tests.

DR. MARKS: That's correct.

DR. SHANK: Therefore I would recommend, and I don't want the staff to shoot me or hang me right here, separating the amino acids from the hydrolyzed proteins and I do remember saying I think we should combine the two. I was totally wrong, but then I didn't know about the allergenicity response to hydrolyzed wheat protein. I apologize, but that's my recommendation and then the amino acids would be safe as used. Then we have a problem. Maybe another way out of this is to take hydrolyzed wheat protein out, leave the document as is and then it's safe as used. Then do something else do with hydrolyzed wheat protein. I apologize for that, staff people.

DR. MARKS: I think I may have been the one who combine the two and change the name. At any rate, we're sort of ducking the wheat if we take it out and since this is not a re review and a no brainer, we can tackle the problem with this and alert the cosmetic ingredient formulators that there is a problem with wheat. I'm not so sure the tack to take it out is the right one. It's the easier way to go about it, but we could do safe for all the ingredients except for wheat and say that's unsafe or insufficient.

DR. SHANK: What bothers me with that is I'm not that good for skin testing for allergens, but if hydrolyzed what protein was missed in the standard sensitization tests, what does this do with all of the other hydrolyzed proteins? Could we have missed some more? I don't know.

DR. HILL: That was the point I was about to make.

DR. ANSELL: We would agree to the separating wheat out specifically not so much to ignore it but, rather, because it is a significant issue. It is under intensive research in Japan right now who are generating data concerning whether the allergy is real and how it's arising. We had provided an abstract which had been translated and think that more data that's going to be relevant to that consideration will become available over some time.

DR. HILL: Would information that came out of that give us enough to know this is something very unique to wheat or a more general concern that means we need to have a look at all the other protein hydrolyzates? I remember the flow of the discussion that went to combining it which was in some cases there was reason to believe that some of these protein hydrolyzates would be hydrolyzed all the way down to amino acids and be dipeptides and tripeptides.
The idea was it was artificial to separate them if that was the case and we didn't have any information at that point to know for sure that we were looking at tripeptides and above let's say hypothetically and then the separation became artificial. That's the gist of the discussion as I remember it and how we ended up concluding that maybe we ought to combine them. But the original question I ask in this long babble was will we get information from the wheat studies that will tell us something about whether there is concern with the remaining ones. I don't guess we can table, but I suppose could reopen down the line if we find that to be true, pare it out and go forward, but in my mind I had that question mark once you see that information with wheat and maybe it's not a real question mark and we don't need to worry about it in which case we're right back to where we were.

DR. MARKS: First is there are no standardized tests to detect I shouldn't say no standardized tests of the skin, but that's what we're dealing with here and I guess one could say if you went to (inaudible) would have prick testing. I didn't look at this abstract so I don't know how they did it, whether they did prick testing or whether they applied the wheat protein on the skin. When I look at these it could be applied to other things although the protein is the one that we're concerned about. Does it cause a Type 1 and presumably immunologic, but there are also nonimmunologic mechanisms that contact (inaudible). When you look down the proteins, there's soy milk, there is yeast, there's yogurt, there's a whole bunch of different ones which apparently unless they're not being used I would have thought would have come to light via the experience of what's happened in Japan and I suspect it's also the processing of the protein that makes a difference too. It certainly was the case if you look at natural rubber latex, we used latex for years to make gloves and then at the onset of the HIV epidemic a lot of the manufacturing was transferred to the Pacific Rim with a different manufacturing process and there was residual natural rubber latex protein in the gloves and then we saw the outbreak of a huge amount of natural rubber latex Type I allergy occurring after that. If we break out the proteins I don't know that we're going to be able to say they're all safe because they've been screened with this test. From an allergic point of view for an allergist you pick your top Type I allergens and things like wheat is there, peanut is there and I see hazelnut in there. It certainly would be safer perhaps to break out the proteins and then eliminate the possibility of having contact (inaudible) or a systemic Type I reaction.

DR. ANSELL: To the question of grouping the families, indeed that has been our position since the very beginning, that this grouping should be based on the proteins. That's not to suggest that all the soys could not reasonably be grouped and that at some point we may determine that the soys and the (inaudible) could then be rejoined, but we think that based on the process along is not the appropriate way to form a family, the hydrolysis being the nucleating point of the family as opposed to the parent protein. We also do not think because of the points that Ron has just raised that we necessarily would join amino acids with higher forms either full proteins or peptides and amino acids, that they need to be looked at.

DR. HILL: We just had a big amount of information, and I could understand why, how far down it was hydrolyzed. If you remember when we had the big grouping that it was different, but with the big grouping of vegetable oils one of the things we did is we looked at the fatty acid compositions and we used that to do a lot of recross and it wouldn't happen in the same way with proteins anyway. I'm thinking that the dependence of the Type I may be more what the concentrations are there in the particular product that's causing the sensitization and perhaps even what else is there in the formulation. We don't approve it that way. We deal with ingredients in general.

DR. ANSELL: And that of course is the subject of why this is happening in Japan and market surveillance is not indicating that it's an issue anywhere else or certainly not in the U.S. or Europe where we have robust market assessments.

DR. MARKS: Ron, going back, your original suggestion is to split out the (inaudible) plant amino acids as one report and have a second report with the hydrolyzed proteins and considering deleting wheat since that seems to be the difficult one or you could put insufficient for what at this point because we have a problem that appeared with wheat in Japan and perhaps not elsewhere.
DR. SHANK: For part one, separating the amino acids from the protein hydrolyzates, I favor that. Handing the protein hydrolyzates, if hydrolyzed wheat protein is used in North America and Europe without an allergic response and in Asia with an allergic response, there must be some difference in the preparation and we should find out what that is and handle that in the hydrolyzed protein report separately.

DR. HILL: Do we also know that what's going on in Asia is not a difference in susceptibility to that kind of reaction? I don't remember what the incidence of HLA 57 is in that population versus U.S. and Europe, but it could partly be given by that.

DR. ANSELL: It's not our suggestion that we ignore it. I think it's a real issue, but it's our suggestion that it's under intensive research in Japan and that we allow that to inform the decision as we go forward. Linda may have a different opinion, but whether we separate it out or table it, we should recognize that the effect is occurring, that it is being examined and that it should be made available to the panel. I think our suggestion is to separate it.

MS. LORENTZ: I think the recent memo says to look at it more by protein and I think the original suggestion from the (inaudible) was to look at wheat first and see what kind of issues that gives you and that might then be helpful for the following on how you can group, et cetera, just take the one with the most issues, get the understanding from that and go forward.

DR. MARKS: Do you like the idea of the motion I'll make tomorrow is tabling this so that these can be separated?

DR. SHANK: Do you have to table it to separate it and then approve the amino acids? As for the amino acids I think we can conclude safe as used.

DR. MARKS: We didn't feel at the last meeting in December that we needed more method of manufacturing or composition.

DR. SHANK: Correct.

DR. MARKS: So we'll stick to our point of view from the last meeting. Yes, we could move for a tentative report with a safe conclusion for the amino acids and then handle the protein group separately to either table that for more information or move forward with a tentative report with that. Wilma?

DR. BERGFELD: Always when you have data that's quasi promised you would like to know what time period you're dealing with. Are we dealing with 10 years? Five years? Two years? Never?

DR. ANSELL: I'll call and ask Carol who's been tracking it more carefully.

DR. BERGFELD: I think that should be part of the suggestion, that if it's a reasonable time period then tabling it. If it isn't, we have to move forward.

DR. MARKS: That's fair, except tomorrow morning we have to make the actually right now we're making the decision unless something changes for our team between now and tomorrow. The amino acids will safe and that would be a tentative report obviously. Then for the protein group it's going to be do we table or do we move forward and issue a tentative report with insufficient data?

DR. ANSELL: Not to cite the staff's area, but the process and procedures of allowing you to keep a report open while you develop data. That's not to suggest it's completely open ended as Wilma is suggesting, that there be some expectation that the data is being developed and under a reasonable pace. But I don't think the the CIR rules wholly envision that you can develop data and during that time keep the report open. Whether that's a table or how you want to handle it administratively, I don't know, but I don't think you're forced to decide to go insufficient to close the report.
DR. MARKS: I think speaking to Wilma's point that if it's an insufficient you have a clock going, that if you table there isn't a clock although we could take it up at the next meeting in June and say if we haven't gotten anything more then we can decide whether or not we want to move on.

DR. ANSELL: I think Wilma's clock is wholly appropriate, but the clock should be measuring the development of the data and not the 60 day review that will be precipitated by a decision.

DR. MARKS: Ron Hill?

DR. HILL: I'm still a little bit unclear. Are proposing that the amino acids would be separated out and that next time we would be seeing a draft final report? That seemed to be what Dr. Shank was suggesting.

DR. MARKS: Out of this meeting if I have the procedure correct there would be a draft tentative report sent out for public comment with a conclusion of safe.

DR. HILL: Because I remember one of the questions that came up when I was looking at the amino acids related to this method of manufacturing thing was the extent that we could know that the source amino acids were just amino acids, monomers or sated monomers and not contaminated with di, tri, tetra, small peptides. That was part of the thought process behind combining them. I didn't look, but I don't see that we got a lot of additional information on that subject. If we're going to go with draft tentative, that was one of the pieces of information I felt like was still lacking.

DR. SHANK: Repeat that again, Ron.

DR. HILL: That because the method of manufacture is hydrolysis of proteins down to supposedly individual amino acids, do we have information telling us the extent to which those are not contaminated by di, tri, tetra, small peptides? That information I didn't was there and I still don't see that it's there. If we combined them it was less of an issue in the sense that we will be looking at peptides and amino acids together. If we don't combine them going back to amino acids then personally I would like to see information that we don't have small peptide contamination at any significant levels. Normally we would expect them to penetrate the skin, but some are biologically active, possibly sensitizing in theory; not likely, but in theory.

DR. MARKS: That gets back to the insufficient, the composition and characterization that was the second insufficient data need. Ron Shank and Tom, I'm not as concerned about the sensitization of the di, tri, tetra peptide compared to the are either one of you have any other toxicologic concern? If we don't have that composition would you feel that you couldn't move forward with a safe conclusion? Because Ron I feel it sounds like you're concerned that moving forward with a safe conclusion if you don't have better characterization of the composition.

DR. HILL: What you need for sensitization is the possibility of heptin formation and I don't have any sense for when we have di, tri, tetrapeptides sitting there on the skin, to the extent that that could possibly translate into something unusual. I doubt it. Maybe I need to do some literature research and see what I find on that subject.

DR. MARKS: Tomorrow it seems pretty clear we're going to move forward to separating the amino acid ingredients from the proteins. How do we want to move forward with amino acids? Do we want to suggest a draft tentative report? I don't think we can go to draft final report because we haven't seen it all separated out, but what's your sense of that?

DR. SHANK: To have a draft tentative final for the amino acids only with the conclusion that they are safe as used. And for the hydrolyzed proteins, that would have to be tabled. That's my suggestion.

DR. MARKS: Tom or the other Ron?
DR. SLAGA: I agree with that.

DR. HILL: I'm okay with that too.

DR. BERGFELD: Do you want to put in the discussion Ron Hill's?

DR. HILL: I would like to know whether that's a real issue. I need to do some literature searching. Anybody else is welcome to do the same and we'll send the info because if we can put that issue to bed then there's no problem in my mind.

DR. MARKS: Are there any other comments? Jay?

DR. ANSELL: No other comments.

DR. MARKS: Rachel, do you have anything? What is this?

MS. WEINTRAUB: Everything that I have on my list has already been brought up.

DR. MARKS: What I didn't do is flip the memo over. Thank you, Christina. Number 3 is to remove the suggestion from the Science and Support Committee and also remove the hydrolyzed hemp seed protein. The panel chooses not to reorganize this report. It should be removed to remain consistent with previous CRIR panel decisions.

DR. HILL: I'm not sure why we would need to do that on the basis that any process I can conceive of for isolating proteins would seem to leave behind any significant concentrations of THC even though it's a relatively potent molecule. If we had analytical information to suggest that ain't any of it in there at detectable levels of significant levels then why would we pare that out? How shall I say this to be politically correct? A great use of a cash crop that has a lot of not so great uses? A widely cultivated cash crop? I don't know. I guess precedent has been set according to what's in the memo, but to me it seems as long as you can assure that that isn't there in significant amounts, why pare it out? And leave the onus on the people who want to market it to document that.

DR. ANSELL: Our comment is based on consistency, and although we know that consistency can be the hobgoblin of small minds, to put it back in and then throw a whole series of obligations in terms of identification and quantification of potential THC and materials of little interest would bring us back to our original suggestion of just for consistency since we have removed it in previous reports.

DR. HILL: We can always have a conclusion that says safe except insufficient in that particular one and then somewhere down the line if somebody wants to do that, again I think it's up to them. The whole system is based on this isn't it? I'm putting it out there for consideration since we're tabling it anyway.

DR. MARKS: Wilma, you were going to say something I thought.

DR. BERGFELD: I forgot.

DR. MARKS: Christina pointed out that if we go on the use table what page is that?

MS. BURNETT: Page 28 PDF.

DR. MARKS: It's not being used, although that's again not a reason because we always cover if an ingredient isn't going to be used if it were going to be used in the future. Ron and Tom, your sense is just leave it out or put it in and have to spend as much time as we just spent trying to dance around?

DR. SLAGA: I don't have any problem with leaving it in especially if it's being tabled.
DR. BERGFELD: Do you want to make some kind of note about Ron Hill's concerns?

DR. HILL: Like I say, I'm pro economic activity and I'm pointing out that this is a pretty widely cultivated plant. I'm putting that out there for consideration.

DR. MARKS: Ron Shank, what do you think? Isn't this a cash crop in California? That's one of the states where you can grow this medicinally.

DR. SHANK: If it's tabled just leave it in and see what we find out about the other proteins.

DR. MARKS: How's that, Jay? We haven't decided to delete it but we haven't decided to include it. We're kicking the can down the street here for another meeting.

DR. ANSELL: Number 3 on the back side of our recommendations.

DR. MARKS: Tomorrow I think I have this that we're going to split these two ingredients, the motion for the amino acids is that's going to be safe and we're going to table the hydrolyzed proteins until we get more data, that specifically we're concerned about the wheat and Type I reactions. Are there any other comments? Then we're going to think about hemp. From the last meeting we're not concerned about method of manufacturing and composition so that I'll address that tomorrow.
March 19, 2013

Full Panel

DR. MARKS: So, in December, the expert panel combined the hydrolyzed proteins and the source amino acid reports and issued an insufficient data announcement on the safety of this newly named plant and animal derived hydrolyzed proteins amino acid ingredients. The data that the panel wanted to see was more on method and manufacturing and more on composition and characterization.

Actually, our team at that meeting felt that we did have enough data on that, but our motion today is that we split these two ingredients again and that we issue a draft tentative report with safe for the animal and plant amino acids and if we table the hydrolyzed proteins because of the concern the reports of type one or immediate hypersensitivity reactions specifically to wheat proteins, but we wanted to look into that whole issue in more depth and we did not feel the method of manufacturing and the composition of the amino acids would delay issuing a safe report.

So, the motion is to split these, to issue the animal and plant amino acids with a conclusion as a tentative safe report and to table the hydrolyzed proteins until we get more data.

SPEAKER: Second.

DR. BERGFELD: A second, all right. The motion's been made and seconded. How about some comments? Paul?

DR. SNYDER: So, we had a similar discussion with a slightly different outcomes. So, we thought that we maybe had erred in how we combined the ingredients previously, and, so, we proposed to table and to modify the grouping and limit to the parent ingredient.

And, so, we thought first we would try to have the writers draft a document focusing on wheat as the parent ingredient, followed by soy, followed by silk. Those are the three highest uses, and then the last would be a document containing the source amino acids. We felt that that grouping might allow us to most efficiently move through the entire group with safety, using the parent compound and also basing it on the number of uses in cosmetics.

DR. BERGFELD: For clarification, you're going to continue to have one document or you're thinking two?

DR. SNYDER: I think it would likely end up being four documents.

DR. BERGFELD: Four documents.

DR. SNYDER: Is that your understanding from the discussion yesterday? Alan, is that your understanding from yesterday?

DR. ANDERSEN: Yes, I think as I heard it, although I still put the amino acids first in my thinking, but then the argument was made that the focus for the look at the hydrolyzed protein ought to be on the particular source, wheat being a huge usage, soy being a huge usage, and I forget what the third one was.

DR. GILL: Silk.

DR. BERGFELD: Silk.

SPEAKER: Silk.
DR. ANDERSEN: Silk. So, the focus would be on wheat, soy, and silk as three separate reports. Amino acids would be the fourth. I understand that pattern. I'm still not sure that we couldn't now move forward with the amino acids.

SPEAKER: Yes.

DR. ANDERSEN: Because it's essentially ready to take that next step. But I get it that some more work needs to be done on the hydrolyzed proteins part.

DR. BERGFELD: Dan?

DR. LIEBLER: So, we spent a lot more of our time yesterday talking about the proteins and the hydrolyzed proteins and we kind of didn't really focus on the amino acids, but I think it seems pretty straightforward to spin out the amino acid part and deal with those because I don't think we have real issues there.

So, that report could move right to the front of the queue and then the suggestion that we had was focusing on source specific proteins and possibly the hydrolyzed components thereof for wheat and silk and soy.

DR. BERGFELD: So, with a minor amendment to Jim's motion, this could move forward, and that is the

DR. LIEBLER: Right.

DR. MARKS: And I think actually

DR. BERGFELD: You think it would be

DR. MARKS: if you would approve moving forward

DR. SHANK: Second.

DR. BERGFELD: Second.

DR. MARKS: forward the amino acids table

SPEAKER: Yes.

DR. MARKS: The hydrolyzed proteins, and then we'll deal with whether we group them together and perhaps have an un safer part of it or have three different individual groups. I mean, the trend, obviously, has been to try if you're going to talk about hydrolyzed proteins that do it as one whole group, but, perhaps, these ingredients wouldn't lend it, although we've dealt before with a particular ingredient in a group and carve that out and either say insufficient or unsafe or whatever.

So, I think the motion is in the line other than moving forward with amino acids with a safe and if you feel that's fine, then I guess you can second the motion.

DR. BERGFELD: Well, no, it

DR. MARKS: Or I should say support it.

DR. BERGFELD: It was seconded.

DR. MARKS: It was seconded by Ron Shank here. So, Ron's pushing it.

DR. BERGFELD: And Ron Hill wants to make a statement.
DR. HILL: Yes, there is in my mind still an unresolved piece with the amino acids and it was part of the rationale for combining them with the hydrolyzed proteins in the first place, which is there's at least suggestion from the relatively limited method of manufacture information that we have that in some cases these amino acids are produced by enzymatic methodology as opposed to exhaustive chemical hydrolysis. And, so, I still don't see that we have information that assures that we're down to individual amino acids and there aren't small peptides in there as impurities even at significant levels. And I would still like information to the extent because at least hypothetically, there's the possibility for sensitization if there were residual small peptides. I mean, it's a modest possibility because we would expect dermal penetration to be small, but it's depending on exposure to, for example, mucus membranes or inhalation or this sort of issue. It's not totally put to bed in my mind.

And, so, that was part of the rationale, okay, amino acids are produced by enzymatic methods; in some cases, small peptides are produced by enzymatic methods in some cases. That was in my mind part of the rationale for lumping them up. I'm not that everybody else was on that page. So, I agree we should separate it out. In general, I think we have most of what we need to conclude safe, but I'm not quite there yet.

DR. BERGFELD: Dan?

DR. LIEBLER: Yes, so, I think that's very reasonable and it just means that the method of manufacture has to be sufficiently detailed as well as the analytical methods apply to characterize the products.

DR. BERGFELD: So, what I hear is is that the amino acids may not be able to go forward without that information or they go forward with an insufficient with that. Alan?

DR. ANDERSEN: Well, I think the message from the panel in terms of the safety of these, as we had originally defined it, source amino acids, is that you're okay with their safety if they are, in fact, amino acids, and there's no reason we can't state in the discussion that that is the panel's expectation and note the concern that methods of manufacture are an issue and enzymatic degradation, if used, should not result in residual di tripeptides and reiterate the panel's expectation is that these will be chopped all the way down to individual amino acids.

DR. BERGFELD: Would that be acceptable?

DR. SNYDER: Yes.

DR. ANDERSEN: Yes.

DR. BERGFELD: All right, so, we have a motion to proceed with Jim Marks' motion.

Will you restate it, please?

DR. MARKS: That we move forward with a tentative draft report for the animal and plant amino acids with a conclusion of safe and the caveat dealing with the issue of individual amino acids, that what we expect in a final ingredient and that we table the hydrolyzed proteins for another time and another place and deal with the issues of whether or not we will have separate reports for these proteins or perhaps combine it and deal with a type one hypersensitivity reactions.

DR. BERGFELD: Any other discussion? I'll call for the question. (No response)

DR. BERGFELD: All those in favor please indicate by raising your hands. (Hands raised)

DR. BERGFELD: Unanimous. Thank you, that was an excellent discussion.
Safety Assessment of Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: August 16, 2013
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DRAFT ABSTRACT
The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of hydrolyzed wheat protein and hydrolyzed wheat gluten, which function as skin and hair conditioning agents. After reviewing the relevant animal and human data presented, the Panel concluded the data are insufficient to support the safety of these cosmetic ingredients. The Panel determined that the following additional data are needed: (1) method of manufacturing data, especially for hydrolyzed wheat protein; and (2) composition and characterization specifications, including molecular structure and molecular weight ranges from several suppliers to determine if there is a consistency in cosmetic grade hydrolyzed wheat protein.

INTRODUCTION
This safety assessment is of hydrolyzed wheat protein (HWP) and hydrolyzed wheat gluten, which are each mixtures of amino acids and peptides of varying length, derived from wheat sources. These ingredients function as skin and hair conditioning agents in personal care products. The CIR Panel previously has reviewed the safety of α-amino acids, animal- and plant-derived amino acids, hydrolyzed collagen, hydrolyzed corn protein, and Triticum Vulgare (wheat) gluten and concluded that these ingredients are safe for use in cosmetic ingredients.1-7

CHEMISTRY
The ingredients in this group are interrelated because they each are prepared from wheat proteins by partial hydrolysis to yield cosmetically acceptable raw materials. The definitions of these ingredients are presented in Table 1. Wheat gluten typically represents about 85% of wheat protein, and consists of the water-insoluble fraction of wheat proteins, including gliadins and glutenins.8 The remaining 15% of wheat proteins consists of water-soluble, non-gluten proteins, including albumins and globulins.

These protein derivatives are prepared by subjecting wheat proteins to enzymatic (e.g., papain hydrolysis) or other chemical hydrolyses (e.g., acid or steam hydrolysis). The resulting polypeptide-, oligopeptide-, and peptide-containing products are used as conditioning agents in hair and skin products. Methods used to manufacture protein hydrolysates typically yield broad molecular weight (MW) distributions of peptides, 500-30,000 daltons (Da).9-11 However, certain enzymes, such as papain, can routinely yield narrower distributions, 500-10,000 Da.9,11 For example, if the average molecular weight of an amino acid is 135 Da, then, under the broader distribution figures, these ingredients are approximately 4 to 220 amino acids in length (and approximately 4 to 74 amino acids in length under the narrower distribution).12

Method of Manufacturing
A supplier reported that HWP (MW = 350) may be prepared by both alkaline and enzyme hydrolysis.13 These processes occur for several hours until the desired molecular weight is reached. The final product is a 25% water solution of HWP. Summary information that includes this data along with additional data from other suppliers can be found in Table 2.

HWP contained in a facial soap that is associated with anaphylaxis reactions in Japan was produced from gluten by partial hydrolysis with hydrogen chloride at 95°C for 40 min.14 The molecular weight of the main band of HWP as determined with sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was 40-50 kDa, which was larger than the main band in gluten.

Impurities
A supplier of HWP (MW = 350) reported levels of heavy metals and arsenic at < 5 ppm and 0.5 ppm, respectively.13

USE
Cosmetic
The HWP and hydrolyzed wheat gluten function primarily as hair conditioning agents and skin conditioning agents (miscellaneous) in cosmetic formulations.15 Additional functions may include film formers (HWP).

Table 3 presents the current product-formulation data for HWP and hydrolyzed wheat gluten. According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), HWP has the most reported uses in cosmetic and personal care products, with a total of 1077; approximately half of those uses are in non-coloring hair products.16 Hydrolyzed wheat gluten has a total of 78 uses in cosmetic and personal care products with about half of the uses reported to be hair tints.
In the Personal Care Products Council’s use concentration survey, HWP had a wide maximum use concentration range of $2.0 \times 10^{-5}$ to 1.7%, with the 1.7% reported in rinse-off non-coloring hair products.\textsuperscript{17} Hydrolyzed wheat gluten had a maximum use concentration range of 0.005% to 0.09%, with 0.09% reported in eye makeup preparations.

HWP is used in cosmetic sprays, including aerosol and pump hair spray products, and could possibly be inhaled. The maximum concentration HWP reported to be used in a spray product is 0.5% in a pump hair spray. HWP and hydrolyzed wheat gluten are not restricted from use in any way under the rules governing cosmetic products in the European Union.\textsuperscript{22}

**Non-Cosmetic**

The FDA determined that the use of peptones as direct food substances is generally recognized as safe (GRAS). These GRAS peptones are defined as “the variable mixture of polypeptides, oligopeptides, and amino acids that are produced by partial hydrolysis of casein, animal tissue, soy protein isolate, gelatin, defatted fatty tissue, egg albumin, or lactalbumin (whey protein) (21 CFR §184.1553).

The FDA defines the term “protein” to mean any α-amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.\textsuperscript{23} The FDA considers a “peptide” to be any polymer composed of 40 or fewer amino acids.

The FDA requires allergen labeling when major allergens are included in food. The major allergens are milk, egg, fish, Crustacean shellfish, tree nuts, wheat, peanuts, and soybeans.\textsuperscript{24}

**TOXICOKINETICS**

No published toxicokinetics studies on HWP and hydrolyzed wheat gluten were discovered and no unpublished data were submitted.

**TOXICOLOGICAL STUDIES**

The proteins that serve as the sources of HWP and hydrolyzed gluten that are described in this safety assessment are found in the foods we consume daily. Toxicities from dermal exposure, other than irritation and sensitization, would not be expected to be different from oral exposures and as such not of concern by the CIR Expert Panel. Irritation and sensitization are of concern, and the focus in this report. Data from the previous safety assessment on α-amino acids support that mixtures of amino acids would not likely be irritants or sensitizers.

**GENOTOXICITY**

No published genotoxicity studies on HWP and hydrolyzed wheat gluten were discovered and no unpublished data were submitted.

**CARCINOGENICITY**

No published carcinogenicity studies on HWP and hydrolyzed wheat gluten were discovered and no unpublished data were submitted.

**IRRITATION AND SENSITIZATION**

[From the CIR Safety Assessment of α-amino acids]\textsuperscript{1}: Cysteine HCl and methionine were used as negative controls in in vitro assays to predict potential skin irritants. In separate efficacy studies, arginine, cysteine, and glycine did not produce any adverse effects in rats, guinea pigs, or mouse skin models. Glutamic acid was used as a negative control in an in vitro study to identify skin sensitizers. HRIPT studies of many products containing amino acid ingredients concluded that products containing these ingredients were not dermal irritants or sensitizers. In several validation studies for in vitro phototoxicity assays, histidine was used as a negative control. Magnesium aspartate up to 0.5% and 1% tyrosine were not phototoxic in assays using yeast.

**Irritation**

**Dermal – Non-Human**

In a primary dermal irritation study in 6 New Zealand white rabbits, acid- and enzyme-hydrolyzed HWP was not a primary skin irritant (primary skin irritation score = 0.50; a score of 5+ indicates a primary dermal
irritant). The 25% aq. solution (MW = 350) was applied for 24 h to 2.5 cm² sites that were clipped, abraded, and occluded.

**Dermal - Human**

HWP was non-irritating in a human irritation patch test performed in 42 subjects. The HWP was tested at 25% aq. solution (MW = 350), and the subjects received a single dermal dose under occlusive conditions for 48 h.

**Ocular – Non-Human**

In an ocular irritation study in 6 albino rabbits, HWP (25% aq. solution, MW = 350) was not a primary eye irritant.

**Sensitization**

**Dermal - Non-Human**

The possibility of a transdermal pathway for sensitization to gluten and acid-hydrolyzed HWP was studied using BALB/c mice. The 7-week-old female mice were shaved and tape stripped 10 times to remove the stratum corneum, exposed to HWP or gluten (500 µg/mouse) via transdermal patches for 3 to 4 cycles (each cycle consisting of 3 days with the patch on followed by 4 days without the patch), 3 days/week, with and without sodium dodecyl sulfate (SDS). Active systemic anaphylaxis (ASA) was then induced by intraperitoneal injection of HWP or gluten, respective of the material used during the transdermal exposure. Rectal temperature, scores of anaphylactic responses, and plasma histamine levels were measured. Dose-dependent production of IgE and IgG1 were observed. The i.p. injection of HWP caused ASA in the mice exposed transdermally to HWP, with decreased rectal temperatures, increased anaphylaxis scores, and increased plasma histamine levels. The i.p injection of gluten clearly induced ASA in the mice transdermally exposed to gluten in the presence of SDS, but not in the absence of SDS. When compared to the vehicle control group, the content of HWP-specific IgE and IgG1 were significantly increased in the HWP groups with and without SDS and in the gluten-with-SDS group; IgE in the gluten–without-SDS group was barely increased. The serum content of gluten-specific IgE was significantly increased in the gluten-with-SDS group and both HWP groups, but barely increased in the gluten-without-SDS group, when compared to the vehicle-control group. The serum IgG1 contents of gluten with and without SDS and HWP without SDS were also significantly increased, but there were individual difference in the gluten-without-SDS group that showed that SDS had an important role in sensitization by transdermal exposure. Following elicitation of the immediate hypersensitivity reactions, harvested splenocytes were restimulated with HWP for 72 h. The secretion of IL-4, IL-5, and IL-10 was increased while that of IL-2 and interferon (IFN)-γ were significantly decreased, demonstrating that transdermal sensitization with HWP was associated with Th2-dominant helper T-cell activation.

**Dermal - Human**

In an occlusive human repeated insult patch test (HRIPIT) of 52 subjects, no dermal irritation or sensitization was observed in response to HWP (25% aq. solution, MW = 350). A study of sensitization to protein hydrolysates in hair-care products was performed in 3 groups of patients. The first group, which was comprised of 11 hairdressers with hand dermatitis, submitted to scratch and prick tests with 22 trademarked protein hydrolysates, including 2 HWP trademarked hydrolysates. The second group was comprised of 2160 consecutive adults with suspected allergic respiratory disease: they were subjected to skin prick tests with hydroxypropyl trimonium hydrolyzed collagen, hydrolyzed collagen and/or hydrolyzed milk protein. The third group of 28 adult patients with atopic dermatitis was also tested with 1 to 3 of the hydrolysates tested in group 2 via a skin prick test. Positive reactions were seen in a total of 12 patients (all female with atopic dermatitis) to the hydroxypropyl trimonium hydrolyzed collagen, hydrolyzed collagen and/or hydrolyzed milk protein. No adverse reactions to the HWP trademarked hydrolysates were observed.

**Type 1 Hypersensitivity**

There have been several reports of Type 1 (i.e., immediate) hypersensitivity reactions to personal care products that contain HWP, as summarized below. An allergen must have at least 2 IgE epitopes, and each epitope must be at least 15 amino-acid residues long, to trigger a Type 1 hypersensitivity reaction. At least two IgE epitopes are needed for this reaction, because when 2 or more IgE molecules bind to the allergen, and each bound IgE binds, in turn, to a receptor on the surface of a mast cell or basophil, the receptors become cross-linked to each other. Cross linking triggers the Type 1 reaction.
The sera from 5 European patients were studied to determine the reactivity of IgE with hydrolyzed gluten. In 4 of the patients, immediate contact hypersensitivity to HWP (IHHWP) manifested as urticaria in response to either dermal contact with HWP (2 patients) or the ingestion of processed foods containing HWP (2 patients), without sensitivity to traditional wheat food products. The fifth patient (control) exhibited conventional wheat-dependent exercise-induced anaphylaxis (CO-WDEIA) in response to ingesting traditional wheat food products without exhibiting sensitivity to HWP.

The IgE reactivity of sera from the IHHWP patients and the CO-WDEIA patient was characterized using extracts of 4 hydrolyzed gluten preparations (enzymatically- or acid-hydrolyzed), total unmodified wheat protein (UWP), and UWP fractions (i.e., albumins/globulins, gliadins, and glutenins, including high-molecular weight glutenin subunits [HMW-GS] and low-molecular weight glutenin subunits [LMW-GS]). The IgE cross-reactivity of the sera was examined from one IHHWP patient with the extracts of one HWP preparation and UWP. Finally, the relative molecular size distributions of two HWP preparations (one the product of acid hydrolysis with a low degree of deamidation and the other the product of enzymatic hydrolysis) was characterized, and the binding of IgE in the serum of one IHHWP patient was determined using the separated polypeptide fractions of two HWP preparations.

The results showed reactivity of serum IgE from the IHHWP patients, especially with the albumins/globulins fraction and less so with the gliadins and LMW-GS fractions, but not with the HMW-GS fraction of UWP. Reactivity of serum IgE from one of the IHHWP patients was observed with the ω5-gliadin of UWP; this patient distinctly exhibited exercise-induced allergic reactions (urticarial) to ingestion of HWP in processed foods. Reactivity of serum IgE from the CO-WDEIA patient was observed with ω5-gliadin and LMW-GS fractions, but not with the HMW-GS fraction of UWP.

Binding patterns of serum IgE from the IHHWP patients to HWP preparations varied by IHHWP patient and by HWP preparation, but in no case did the IgEs bind to HWP polypeptides less than 30 kDa. The binding of serum IgE to UWP or to the albumins/globulins fraction of UWP was partially inhibited by HWP. However, the binding of serum IgE to HWP was almost completely inhibited by UWP or HWP. Based on these results, the authors suggested that almost all of the epitopes in the HWP preparation tested were also available in UWP. The molecular-size profiles of two of the HWP preparations ranged from <5 kDa to > 1,000 kDa, and both preparations contained substantial amounts of high molecular-weight constituents. Binding of IgE in the serum of the IHHWP patient was greatest to the highest molecular-weight fractions of both of these HWP preparations (400 kDa to 1,000 kDa), weaker to intermediate molecular-weight fractions (30 kDa to 400 kDa), and faint or undetectable to the lowest molecular-weight fractions (< 30 kDa).

Overall, the authors concluded that most IgE epitopes in UWP are conserved in HWP produced by industrial hydrolysis processes, and the production of new epitopes in the hydrolysates does not appear to contribute substantially to the differences in allergic responses in IHHWP patients compared with CO-WDEIA patients. Additionally, epitopes in UWP appear to be destroyed in HWP polypeptides less than about 30 kDa. Analysis of HWP fractions under non-reducing, non-dissociating conditions suggested that differences in allergic responses between IHHWP patients and CO-WDEIA patients may be attributable to hydrolysis-induced re-organization in HWP of epitopes that already exist in UWP; re-organization through entanglements, S-S bond interchanges, or non-covalent interactions among the HWP polypeptides may produce relatively soluble, high molecular-weight polypeptide aggregates that can present multiple epitopes efficiently to trigger allergic responses to HWP.

In a Japanese study, wheat protein hydrolysates that were produced by enzymatic hydrolysis had higher concentrations of peptides with molecular weights greater than 1,050 Da, compared with those produced by acid hydrolysis, which had extremely low concentrations of peptides with molecular weights greater than 1,050 Da. Investigation of the reactivity of these 2 types of hydrolysates revealed that the acid hydrolysates rarely inhibited IgE binding whereas enzymatic hydrolysates clearly inhibited the binding of IgE to wheat proteins. IgE of patients that had Type 1 hypersensitivity to HWP through percutaneous and rhinoconjunctival exposure to a facial soap containing HWP reacted with high molecular weight polypeptide aggregates. However, an in vitro elicitation test using IgE from different categories of wheat-allergic patients (including patients sensitized to commercial HWP produced by acid hydrolysis, pediatric patients with food allergy to native wheat, adult patients exhibiting wheat-dependent exercise-induced anaphylaxis (WDEIA), and non-atopic healthy adults) revealed that gluten acid-hydrolyzed to various extents retained the ability to activate mast cells in patients sensitized by exposure to commercial acid-hydrolyzed HWP. It is theorized that limiting the size of proteins or polypeptides to no more than approximately 30 amino acid residues (MW=3000 Da) would greatly reduce the potential for causing Type 1 reactions.

A study was performed comparing 5 Japanese women exhibiting both contact allergy (rhinoconjunctival reactions) to HWP in a facial soap and WDEIA reactions to eating “normal wheat products” such as bread, pasta, and pastries (referred to as HWP-WDEIA patients) with 18 Japanese women exhibiting CO-WDEIA
The authors distinguished the 5 Japanese HWP-WDEIA patients from European patients exhibiting IHHP (see study above), some of whom also exhibited allergic reactions to foods containing HWP, but none with allergic reactions to eating “normal wheat products.”

Positive skin prick tests were obtained for HWP in all 5 of the HWP-WDEIA patients, in contrast to the CO-WDEIA patients. Sera from HWP-WDEIA patients exhibited statistically-significantly elevated IgE reactivity with HWP, compared to reactivity with each of the wheat-protein fractions (i.e., albumins/globulins, gliadins, and glutenins). In contrast, sera from CO-WDEIA patients exhibited statistically-significantly elevated reactivity with the gliadins fraction of wheat proteins, compared to reactivity with HWP.

Sera from the HWP-WDEIA patients exhibited statistically-significantly elevated IgE reactivity with HWP, gluten, wheat flour, and each of the wheat-protein fractions, and statistically-significantly reduced reactivity with recombinant ω5-gliadin, compared to sera from CO-WDEIA patients. Based on these results, the authors suggested that sensitization of HWP-WDEIA patients to components of the gliadin fraction other than ω5-gliadin may help explain the elevated reactivity of sera from HWP-WDEIA patients with the complete gliadin fraction.

Pre-incubation of sera from HWP-WDEIA patients with HWP completely inhibited IgE reactivity with wheat extracts, but pre-incubation with wheat extracts did not inhibit reactivity with HWP. Conversely, pre-incubation of sera from CO-WDEIA patients with HWP only weakly inhibited reactivity with wheat extracts, while pre-incubation with wheat extracts strongly inhibited reactivity with HWP. Based on these results, the authors suggested that the reactivity of sera from CO-WDEIA patients with HWP is attributable to IgE epitopes that survive the hydrolysis of wheat proteins.

Overall, the authors concluded: (1) HWP-WDEIA is a clinical phenotype distinct from CO-WDEIA, as well as from the contact sensitivity to HWP observed in European patients that do not exhibit sensitivity to ingesting “normal wheat products,” (2) the use of a facial soap containing HWP caused both primary contact dermal / rhinoconjunctival sensitization to HWP and, secondarily, WDEIA sensitization to ingested wheat proteins in the HWP-WDEIA patients, and (3) sensitization to gliadins other than ω5-gliadin (e.g., ω1-2-gliadin and γ-gliadin) may be more important than sensitization to ω5-gliadin in the pathogenesis of HWP-WDEIA, compared with the pathogenesis of CO-WDEIA.34

In another study, the allergic reactions of a group of Japanese patients diagnosed with HWP-WDEIA were found likely to have been sensitized primarily through percutaneous and/or rhinoconjunctival exposures to HWP (acid-hydrolyzed UWP) in a facial soap.8 The authors noted that, by 2010, more than 1300 patients who had used the soap exhibited facial angioedema after use, tested positive for sensitivity to the HWP in skin-prick tests and positive for serum IgE reactivity with the HWP, and developed WDEIA reactions in response to eating natural UWP. Angioedema predominated in the HWP-WDEIA patients, especially angioedema of the eyelids, in contrast to the urticarial wheals predominating in CO-WDEIA patients. The onset of allergic reactions in the HWP-WDEIA patients typically was 1 month to 5 years after starting to use the soap. Many of these patients developed WDEIA in response to eating wheat food products at about the same time as, or subsequent to, the onset of urticarial reactions to the soap.

About half of the HWP-WDEIA patients tested positive in skin-prick tests for sensitivity to wheat and bread. Almost all of the HWP-WDEIA patients tested positive in skin-prick tests for sensitivity to solutions of the soap or the HWP in the soap, in contrast to CO-WDEIA patients, none of whom exhibited sensitivity to these solutions. Only about 7% of HWP-WDEIA patients exhibited serum IgE reactivity with ω5-gliadin, compared to 80% of CO-WDEIA patients. Reactivity with ω5-gliadin among the few positive HWP-WDEIA patients was substantially weaker than the corresponding reactivity among the CO-WDEIA patients. About 17% of HWP-WDEIA patients exhibited serum IgE reactivity with ω5-gliadin and/or HMW-GS, compared to about 94% of CO-WDEIA patients. On the other hand, 70% or more HWP-WDEIA patients exhibited serum IgE reactivity with wheat protein or gluten, compared to only 30% to 40% of CO-WDEIA patients. Sera from HWP-WDEIA patients exhibited IgE binding to HWP polypeptides and to water-soluble and water-insoluble constituents of UWP, but not to purified ω5-gliadin. In comparison, serum IgE from CO-WDEIA patients bound to ω5-gliadin, as well as to the water-soluble and water-insoluble constituents of UWP, but not to the polypeptides of the HWP preparation. Pre-incubation of sera from the HWP-WDEIA patients with solutions of the HWP preparation resulted in concentration-dependent inhibition of the binding of IgE to HWP polypeptides. HWP, but not purified ω5-gliadin, up-regulated the CD203c (an ecto-enzyme on the cell membranes of basophils and mast cells) in HWP-WDEIA patients. However, ω5-gliadin, but not the HWP, up-regulated CD203c in cells from CO-WDEIA patients.

The authors suggested that (1) the hydrophilic constituents of HWP may play an important role in percutaneous and/or rhinoconjunctival sensitization to HWP, (2) production of HWP by acid hydrolysis of UWP will yield charged terminal amino- and carboxyl-groups that increase the water solubility of the HWP, compared to that of UWP, and (3) the surfactants in a soap product will likely facilitate the dermal penetration of the HWP.
polypeptides, and thereby help to increase the likelihood of sensitization through percutaneous/rhino-conjunctival exposures in people using such products.\textsuperscript{8}

Recommendations have been made to individuals with known protein hypersensitivity to minimize dermal exposure to botanical ingredients such as HWP and to not use products that have these constituents and can be incidentally inhaled.\textsuperscript{36} Additionally, it has been recommended that manufacturers of personal care products not use known or suspected allergens (including constituents of plants known to produce Type I hypersensitivity reactions or of plants that are in the same phylogenetic families as these plants) in products that may be incidentally inhaled (e.g., sprays, shampoos or shower gels, and, presumably, loose powder products as well).

**Phototoxicity**

No published phototoxicity studies on HWP and hydrolyzed wheat gluten were discovered and no unpublished data were submitted.

**CASE STUDIES**

A case of WDEIA in a non-atopic 40-year-old woman was reported in Japan.\textsuperscript{8} The patient developed facial wheals and nasal discharge while using an HWP- (Glupearl 19S-) containing facial soap (Cha no shizuku) over the course of a year. Additionally, she suffered multiple episodes of eyelid edema after eating bread or while working or walking during an 11-month period prior to diagnosis. Skin prick tests were positive with a solution of the soap or the HWP, but negative with wheat or bread. The patient also tested positive for WDEIA after ingesting wheat and aspirin together (aspirin, like exercise, is a well-known trigger of allergic reactions). SDS-PAGE and western blotting analyses showed that serum IgE from this patient reacted with polypeptides ranging from 15 to 250 kDa in the HWP preparation and with both the water-soluble and water-insoluble fractions of UWP, but not with ω5-gliadin.

An additional 3 cases of WDEIA were reported by the same researchers in Japan.\textsuperscript{37} The 3 female patients had used the same brand of soap that contained HWP. Skin prick tests revealed positive reactions to a 0.1% solution of the soap in physiological saline and to 0.1% HWP in physiological saline. Western blotting of the patients’ sera IgE yielded positive reactions with the HWP. The researchers concluded that WDEIA was attributable to cross reactivity to wheat protein induced by HWP exposures in these patients.

A 51-year-old Japanese woman had been using a facial soap containing HWP daily for several years.\textsuperscript{38} Approximately 3 months after she started to use the soap, she began to develop angioedema on the eyelids and urticarial rash on the face. She experienced similar episodes many times over a 5-year period when eating wheat-containing food followed by mild exercise, with clinical signs limited to her face. Five years after her initial use of the soap containing HWP, she had an anaphylactic reaction after ingesting normal wheat products and was suspected of having WDEIA. She had no history of atopic dermatitis, food hypersensitivities, or dry skin. The patient developed eyelid angioedema, dyspnea, and a generalized urticarial rash on her entire upper extremity following a skin prick test with the HWP from the soap diluted 1:10,000. An IgE test for wheat and gluten yielded 0.36 UA/ml and 0.40 UA/ml, respectively. Serum ω5 gliadin-specific IgE antibody titers were within normal limits. The patient did not have a mutation in human filaggrin (FLG), a defect that may disrupt skin barrier function.

In another case study, a 42-year-old woman reported an intense burning sensation over her face, neck, and scalp several hours after applying a moisturizing cream that contained HWP.\textsuperscript{39} Patch testing with the diluted ingredients of the moisturizing cream resulted in a positive reaction (D2+, D4+) to 50% aq. HWP. No reactions were observed from skin prick testing to standardized wheat extract or contact-urticaria testing with HWP.

Contact urticaria was reported in a 46-year-old woman.\textsuperscript{40} The patient developed the clinical signs after applying an eyelid cream and a body moisturizer that contained HWPs 3 months prior to consulting her physician. Strong positive reactions were observed from the preserved food, wheat gluten that was in the food, the cosmetic creams, and HWP in open application tests and skin prick tests. Further investigation revealed that the HWPs in the cosmetic creams were from the same manufacturer as the gluten in the preserved food.

A 27-year-old woman was reported to have a pruritic, erythematous, urticarial rash that became increasingly more intense after subsequent use of a moisturizing body cream that contained HWP.\textsuperscript{41} The wheat hydrolysate was not characterized in this study. Skin prick tests with common inhalant allergens, natural rubber latex, and cereal grains, including wheat, were negative. Also negative were the results of prick tests with a series of 21 protein allergens from plant and animal sources that included hen’s egg, cow’s milk, milk casein, almond, silk protein, aloe gel, papaya fruit, and hydrolyzed collagen. Total serum IgE was slightly elevated. The individual components of the body cream tested negative in an open application test, but a skin prick test was positive (8 mm) to HWP. Further IgE testing revealed that binding occurred specifically to wheat hydrolysate.
In another case study, a 64-year-old woman was reported to have itchy, erythematous, edematous lesions on the eyelids, face, and neck following use of a moisturizing cosmetic cream. Positive reactions (++) were observed to nickel sulfate, the cosmetic cream (tested neat), and to the HWP ingredient of the cream (10% aq.). Open testing with the HWP (10% aq.) was negative at 30 min.

A 23-year-old man with no history of atopy was reported to have a rash that occurred immediately after application of a face cream. The rash included highly pruritic wheals on the face and neck accompanied by bilateral palpebral edema. Other systemic symptoms were not observed. The patient reported a similar reaction previously to a sunscreen and did not report food-induced symptoms or intolerance. A nonblinded skin test with the face cream was negative. Patch testing with the cosmetics True Test panel and the patient’s own personal care products resulted in a positive (++) reaction to the patient’s face cream at 48 and 96 h; all other readings were negative. Patch testing with the components of the face cream resulted in a positive (++) reaction to 1% HWP in water at 48 and 96 h. Testing in 10 control subjects yielded negative results. The patient underwent further prick tests with flours and cereals, with positive results reported for malt (5 x 4 mm), cereal mix (7 x 5 mm), oats (5 x 5 mm), and hydrolyzed wheat extract (18 x 14 mm). Total IgE was 136 U/ml (reference range = 1-100 U/ml). Results of specific IgE testing to buckwheat, rice, oats, barley, rye, corn, common millet, soy, and wheat were negative.

In a case study of a 3-year-old girl with a history of moderate atopic dermatitis, eczema-like skin eruptions were observed following use of an emollient containing HWP. Scaly erythematous lesions were observed on her knees. No evidence of contact urticaria was observed. Closed patch tests with the European standard series and the emollient were positive (+) for the emollient on days 2 and 3. Additional patch tests with the individual components of the emollient yielded positive results (++) for palmitoyl HWP on days 2 and 3. Prick test, open test, and open patch test for palmitoyl HWP were negative, as were prick test and radioallergosorbent test with wheat.

**SUMMARY**

Hydrolyzed wheat gluten and HWP function primarily as skin and hair conditioning agents in personal care products. These protein derivatives are prepared by subjecting wheat proteins to enzymatic or other chemical, partial hydrolyses.

HWP has the most reported uses in cosmetic and personal care products, with a total of 1077; approximately half of those uses are in non-coloring hair products. Hydrolyzed wheat gluten has 78 reported uses, with about half of the uses reported to be in hair tints.

In the Personal Care Products Council’s use concentration survey, HWP had a wide maximum use concentration range of 2.0 x 10⁻⁵ to 1.7%, with the 1.7% reported in rinse-off non-coloring hair products. Hydrolyzed wheat gluten had a maximum use concentration range of 0.005% to 0.09%, with the 0.09% reported in eye makeup preparations.

The FDA determined the use of peptones as direct food substances are GRAS. Ocular and dermal irritation studies of HWP found this ingredient not to be a significant irritant. HRIPT studies of HWP concluded that this ingredient was not a dermal irritant during induction or sensitizers during challenge.

Multiple cases of allergic reactions, including Type 1 hypersensitivity reactions, were reported in individuals who had used personal care products that contained HWP. Several studies have been conducted to characterize the cause, manifestations, and mechanisms of these reactions, including tests of serum IgE binding and reactivity wheat protein, wheat protein fractions, and HWP and hydrolyzed gluten prepared using acid- and/or enzymatic-hydrolysis methods yielding products with varied polypeptide size profiles.

**DRAFT DISCUSSION**

The Panel acknowledged that the safety of α-amino acids as direct food additives has been well established based on extensive research of acute and chronic dietary exposures to these substances. The Panel determined that this body of research, coupled with the available irritation and sensitization data and use concentrations that are at levels much lower than those consumed daily in the diet, were a sufficient basis for determining the safety of amino acids in cosmetic products.

The Panel recognized that there are issues with sodium glutamate and phenylalanine in the diet for certain individuals. However, the Panel determined that these amino acids at the concentrations used in cosmetic products would not be significantly absorbed through topical application or incidental ingestion, and thus, would not cause systemic reactions.
While the *International Cosmetic Dictionary and Handbook* does not distinguish between the \( \alpha \)-amino acids used in cosmetics that are L-stereoisomers from those that are D-stereoisomers (or are mixtures of L- and D-stereoisomers), the Panel noted that the L-amino acids are Generally Recognized As Safe (GRAS) direct food additives by the FDA; methionine is GRAS as a racemic mixture, and glycine, which has no stereocenter, is also GRAS. Amino acids with a mixture of the 2 stereoisomers (DL-) have approved uses as food additives according to the USP Food Chemicals Codex. The safety assessment report addressing amino acid ingredients from plant and animal sources includes the D- and L- stereoisomers of these ingredients. The Panel does not anticipate that there are significant toxicological differences in cosmetic applications between the 2 stereoisomers of each of these ingredients.

The Panel discussed the issue of incidental inhalation exposure from aerosol and pump hair spray products. No inhalation data were available. These ingredients reportedly are used at concentrations up to 0.5% in cosmetic products that may be aerosolized.

The Panel also expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

Type I immediate hypersensitivity reactions could possibly occur following exposure to a protein-derived ingredient. Traditional human repeat insult patch tests and related tests do not detect Type I reactions. The Panel noted that these ingredients maybe used in aerosolized products, however, and incidental inhalation of allergenic peptides has the potential to cause Type I reactions in sensitized individuals. Thus, the Panel recommends that people with known allergies to wheat proteins avoid using personal care products that contain these ingredients and may be incidentally inhaled during use (e.g., spray or loose powder products).

The Panel requested additional data to support the safety of hydrolyzed wheat protein and hydrolyzed gluten described in this safety assessment. The additional data needed are:

1. Method of manufacturing data for hydrolyzed wheat protein; and
2. Composition and characterization specifications of hydrolyzed wheat protein, including molecular structure and molecular weight ranges from several suppliers to determine if there is a consistency in cosmetic grade ingredients.

While data are sought for method(s) of manufacture, it appears that the approaches used to prepare wheat amino acids and hydrolyzed wheat proteins would be fundamentally similar, and that the only real difference in the products would be the extent of hydrolysis – either complete hydrolysis to individual amino acids, potentially with some short peptides present, or partial hydrolysis to protein fragments of undetermined or unspecified lengths.

**DRAFT CONCLUSION**

The CIR Expert Panel concluded that the available data or information are insufficient to make a determination that hydrolyzed wheat protein and hydrolyzed wheat gluten are safe under the intended conditions of use.
### Table 1. Definitions and functions of the ingredients in this safety assessment. (The italicized text below represents additions made by CIR staff.)

<table>
<thead>
<tr>
<th>Ingredient CAS No.</th>
<th>Definition</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>Hydrolyzed Wheat Gluten 100684-25-1</td>
<td>Hydrolyzed Wheat Gluten is the partial hydrolysate of Triticum Vulgare (Wheat) Gluten derived by acid, enzyme or other method of hydrolysis.</td>
<td>Hair Conditioning Agent; Skin-Conditioning Agent-Misc.</td>
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<tr>
<td>Hydrolyzed Wheat Protein 70084-87-6 70084-87-6 70029-50-5 222400-28-4</td>
<td>Hydrolyzed Wheat Protein is the partial hydrolysate of wheat protein derived by acid, enzyme or other method of hydrolysis.</td>
<td>Film formers; Hair Conditioning Agent; Skin-Conditioning Agent-Misc.</td>
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</table>

### Table 2. Summary of information from suppliers of hydrolyzed wheat protein.*

<table>
<thead>
<tr>
<th>Source</th>
<th>Method of Manufacture</th>
<th>Molecular Weight</th>
<th>Nitrogen Content</th>
<th>Gluten Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 product defatted wheat germ</td>
<td>3 products enzyme hydrolysis</td>
<td>1 product average MW = 350 Da</td>
<td>1 product 12-15% nitrogen</td>
<td>1 product “gluten-free”</td>
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<tr>
<td>1 product alkaline and enzyme hydrolysis</td>
<td>1 product average MW = 2200 Da</td>
<td></td>
<td>1 product &lt; 100 ppm gluten</td>
<td>1 product about 50 ppm gluten</td>
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</table>

* Information includes data summarized in Anonymous, 2012.13

### Table 3. Frequency and concentration of use for plant- and animal-derived hydrolyzed proteins according to duration and type of exposure.16,17

<table>
<thead>
<tr>
<th>Hydrolyzed Wheat Gluten</th>
<th>Hydrolyzed Wheat Protein</th>
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<tbody>
<tr>
<td><strong>Totals</strong></td>
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<tr>
<td># of Uses</td>
<td>Conc. of Use</td>
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<tr>
<td>Leave-On</td>
<td>78</td>
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<tr>
<td>Rinse Off</td>
<td>13</td>
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<tr>
<td>Diluted for (Bath) Use</td>
<td>62</td>
</tr>
<tr>
<td>Eye Area</td>
<td>3</td>
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<tr>
<td>Incidental Ingestion</td>
<td>NR</td>
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<tr>
<td>Incidental Inhalation-Sprays</td>
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<td>Incidental Inhalation-Powder</td>
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<tr>
<td>Dermal Contact</td>
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</tr>
<tr>
<td>Deodorant (underarm)</td>
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<tr>
<td>Hair - Non-Coloring</td>
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<tr>
<td>Hair-Coloring</td>
<td>35</td>
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<tr>
<td>Nail</td>
<td>NR</td>
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<tr>
<td>Mucous Membrane</td>
<td>15</td>
</tr>
<tr>
<td>Baby Products</td>
<td>3</td>
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</tbody>
</table>

* 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.

NR = none reported
*0.03-0.05% in aerosol hair sprays; 0.0003-0.5% in pump hair sprays; and 0.002-0.02% in spray tonics, dressings, and other hair grooming aids.


28. AMA Laboratories Inc. 2006. 50 human subject repeat insult patch test sin irritation/sensitization evaluation (occlusive patch). Hydrolyzed Wheat Protein. AMA Ref. No.: MS06.RIPT.K9014O.50.SEI. Unpublished data submitted by the Personal Care Products Council.


### 2013 FDA VCRP RAW DATA

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<th>Category</th>
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<th>Code</th>
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<td></td>
<td>977016526</td>
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<td>01B - Baby Lotions, Oils, Powders, and Creams</td>
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<td>07B - Face Powders</td>
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<td>HYDROLYZED WHEAT PROTEIN</td>
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Memorandum

TO: F. Alan Andersen, Ph.D.
   Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
       Industry Liaison to the CIR Expert Panel

DATE: March 15, 2013


Key Issue
Memo - Rather than just the December meeting, meeting reports in English from all 7 of the Japanese Society of Allergology’s Special Committee for the Safety of Protein Hydrolysates in Cosmetics has been posted on their website. Although research is still ongoing, the following papers on research associated with the adverse reactions to a hydrolyzed wheat protein have been published and should be discussed in the CIR report (abstracts attached).


Abstract, Conclusion - As some additional information has been received, it is not appropriate to include a draft conclusion of insufficient data in this report. By definition, the amino acid ingredients are mixtures of amino acids. It is not clear why the insufficient data conclusion should also apply to the plant- and animal-derived amino acid ingredients. Based on the first three paragraphs of the Draft Discussion, it is not clear why the amino acid ingredients are still being given an insufficient data conclusion.

p.9 - Amino acids are not associated with Type I reactions. Therefore, in the paragraph in the Draft Discussion section concerning Type I reactions “amino acids” needs to be deleted from the following: “in response to dermal contact with amino acids or hydrolyzed protein ingredients are exceedingly rare.” Based on the recent experience in Japan, it is not clear why the Type I
allergy discussion focuses only on potential inhalation exposure. The cases in Japan concerned a facial soap. It is likely that mucous membrane exposure also plays a role in the development of Type I reactions.

Additional Comments
p.1 - The Introduction does not include a clear description of the ingredients included in this report. There are no salts of the amino acid ingredients included in this report, only salts of the hydrolyzed protein ingredients (which are mixtures that likely include salts of peptides and amino acids). It is not correct to state “amino acids of varying length”. The size of amino acids does not change. It is the hydrolyzed proteins or peptides (or protein fragments) that are of variable length because they contain a variable number of amino acids.

p.5 - In the last sentence under Toxicological Studies, please change “these ingredients” to “mixtures of amino acids” as this report includes both peptides and amino acids. The irritation and sensitization data on the α-amino acids help support the safety of mixtures of amino acids, but not the safety of the peptide ingredients.

p.6 - A brief summary of the sensitization data in the α-amino acids report should be added to the Sensitization section.

p.8 - The word “gliadins” appears for the first time on p.8. Somewhere in the report, please provide some information about gliadins. What are they? Why are they relevant?

p.8 - The last sentence of the Summary (“One case study reported a positive reaction a hair conditioner that contained hydrolyzed keratin in a prick test.”) is not complete.
Display Settings: Abstract


Sensitization to acid-hydrolyzed wheat protein by transdermal administration to BALB/c mice, and comparison with gluten.

Division of Novel Foods and Immunochemistry, National Institute of Health Sciences, Tokyo, Japan. akasaka@nihs.go.jp

Abstract

BACKGROUND: An increasing number of studies have shown that hydrolyzed wheat protein (HWP) can induce IgE-mediated hypersensitivity by skin contact and/or food ingestion. However, there has been no study of the sensitizing potential of HWP. In this study, the possibility of transdermal pathway for sensitization to acid-HWP (HWP1) was investigated using BALB/c mice, and compared with that of gluten.

METHODS: HWP1 or gluten (500 μg/mouse) was transdermally administered using patches. After three or four cycles of sensitization for 3 days/week, active systemic anaphylaxis (ASA) was induced by intraperitoneal injection of the antigen, and rectal temperatures, scores of anaphylactic responses, and plasma histamine levels were determined. Because HWP1 was included in facial soap in Japan, the effect of detergent on the sensitizing potential was also investigated.

RESULTS: Transdermal administration of HWP1 induced dose-dependent production of IgE and IgG1. After sensitization for 3 or 4 weeks, intraperitoneal injection of HWP1 caused ASA, leading to decreased rectal temperatures, increased anaphylaxis scores, and increased plasma histamine levels. In addition, splenocytes harvested after ASA produced IL-4, IL-5, and IL-10 by re-stimulation with HWP1. Transdermal exposure to gluten also induced IgE and IgG1 production, and intraperitoneal injection of gluten also induced ASA only in mice sensitized in the presence of sodium dodecyl sulfate.

CONCLUSIONS: Transdermal exposure to HWP1 is sufficient to activate key immune pathways necessary for sensitizing mice for immediate hypersensitivity reactions. This study shows that HWP has a sensitizing potential as well as gluten, whereas its allergenicity may be different from that of gluten.

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PMID:22994386[PubMed - in process]

Publication Types
Wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat protein in soap.

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Abstract
Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a specific form of wheat allergy typically induced by exercise after ingestion of wheat products. Wheat ω-5 gliadin is a major allergen associated with conventional WDEIA, and detection of serum immunoglobulin E (IgE) specific to recombinant ω-5 gliadin is a reliable method for its diagnosis. Recently, an increased incidence of a new subtype of WDEIA, which is likely to be sensitized via a percutaneous and/or rhinoconjunctival route to hydrolyzed wheat protein (HWP), has been observed. All of the patients with this new subtype had used the same brand of soap, which contained HWP. Approximately half of these patients developed contact allergy several months later and subsequently developed WDEIA. In each of these patients, contact allergy with soap exposure preceded food ingestion-induced reactions. Other patients directly developed generalized symptoms upon ingestion of wheat products. The predominant observed symptom of the new WDEIA subtype was angioedema of the eyelids; a number of patients developed anaphylaxis. This new subtype of WDEIA has little serum ω-5 gliadin-specific serum IgE.


LinkOut - more resources
Evaluation of Allergenicity of Acid-Hydrolyzed Wheat Protein Using an in vitro Elicitation Test.


Division of Novel Foods and Immunochemistry, National Institute of Health Sciences (NIHS), Tokyo, Japan.

Abstract

Background: We performed an in vitro elicitation test to determine the ability of different types of wheat-allergic patients' IgE to induce humanized mast cell activation after the addition of various time-treated acid-hydrolyzed wheat proteins (HWPs). Methods: The reactivity of heat- and various time-treated acid-hydrolyzed glutsens (acid-HGs) and commercial acid-HWP (HWP1), using serum IgE from wheat allergy accompanied by skin and rhinoconjunctival sensitization to HWP1 in the facial soap, pediatric subjects with food allergy to native wheat, adult wheat-dependent exercise-induced anaphylaxis subjects, and nonatopic healthy subjects, was elucidated by dot blot and a luciferase assay-based in vitro elicitation test (EXiLE test). Results: Serum from subjects sensitized with HWP1 reacted only to acid-HGs (acid-HGs treated for 0.5-3 or 6 h), but not native gluten, in the results of the dot blot. In contrast, sera from pediatric subjects sensitized with native wheat reacted to native gluten more strongly and showed only slight reactions to 0.5- to 1-hour-treated acid-HGs. The results of the in vitro elicitation test showed that acid hydrolyzation of the gluten attenuated antigen-induced luciferase expression in a time-dependent manner for sera from native-wheat-sensitized pediatric subjects. On the other hand, in the sera from HWP1-sensitized subjects, acid hydrolyzation of the gluten for 0.5 h dramatically increased luciferase expression. Conclusions: Even after prolonged hydrolyzation, acid-HGs still retained the ability to activate mast cells in the case of HWP1-sensitized subjects.

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PMID:23075478[PubMed - in process]

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Memorandum

TO: F. Alan Andersen, Ph.D.
   Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: March 18, 2013

SUBJECT: Grouping of Plant- and Animal-Derived Hydrolyzed Protein and Amino Acid Ingredients

The CIR Science and Support Committee (CIR SSC) remains concerned about the grouping of ingredients in the report on plant- and animal-derived hydrolyzed proteins and amino acids. We respectfully suggest that the CIR Expert Panel table the report so that it can be reorganized according to the following suggestions.

1. **Amino acid ingredients should not be reviewed with the hydrolyzed protein ingredients**
   Although derived from similar sources by similar methods of manufacture, the CIR SSC still believes that it is not appropriate to review the amino acid ingredients with the hydrolyzed protein ingredients. The safety of mixtures of amino acids derived from completely hydrolyzing proteins can be supported by the previous review of individual amino acids. In contrast, hydrolyzed proteins have significantly different biological properties, such as the potential to induce Type I allergy, that must be considered when assessing safety.

2. **Proposed Grouping - Group by Parent Protein**
   The CIR SSC also remains concerned about the grouping of hydrolyzed protein ingredients from various sources into one report. We suggest that protein ingredients from a specific source be grouped into one report that would include the parent protein (if listed as a cosmetic ingredient), the hydrolyzed protein, as well as derivatives of the hydrolyzed protein. The report would then include some basic information about the starting proteins and the potential for the starting proteins to induce an immunologic response. For example, a report on wheat protein ingredients would include Triticum Vulgare (Wheat) Germ Protein, Triticum Vulgare (Wheat) Protein, Triticum Vulgare (Wheat) Gluten, Hydrolyzed Wheat Protein, Palmitoyl Hydrolyzed Wheat Protein, Potassium Palmitoyl Hydrolyzed Wheat Protein, Sodium Palmitoyl Hydrolyzed Wheat Protein (the palmitoyl ingredients would be removed from the palmitoyl oligopeptide report) as well as about 25 other derivatives of Hydrolyzed Wheat Protein. Based on FDA VCRP data, reports on soy protein, Hydrolyzed Soy Protein (788 VCRP uses) and its derivatives (approximately 27 ingredients) and Silk, Hydrolyzed Silk (634 VCRP uses) and its
derivatives (approximately 25 ingredients) should also be prepared. The three reports would cover approximately 84 ingredients.

3. **Remove Hydrolyzed Hemp Seed Protein**

   If the CIR Expert Panel chooses not to reorganize this report by parent protein, Hydrolyzed Hemp Seed Protein should be removed from the report to remain consistent with previous CIR Expert Panel decisions not to review hemp seed-derived ingredients. In the past, the CIR Expert Panel has chosen not to review hemp-derived ingredients because of the potential to be contaminated with tetrahydrocannabinol (THC).