128th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

Washington, D.C.

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P R O C E E D I N G S

(8:30 a.m.)

DR. BERGFELD: Okay. Finally we're at 8:30. We're going to open this meeting. Everybody is ready. And this is the 128th meeting of the CIR Panel. And before we go into anything, I want to welcome Lillian Gill, our Director, our new Director. And we want to say that we had the most wonderful entry last night, ate a wonderful dinner, and we thank you very much, Lillian, for that, your inaugural.

We have 18 ingredients to go over today. But first we have to go through the minutes, and so I would like to have approval of the minutes or any comments regarding them. Any motion to approve?

DR. BELSITO: So moved.

DR. BERGFELD: Second?

DR. SHANK: Second.

DR. BERGFELD: All those in favor? Unanimously approved. Before we move onto the Director's Report, I would like to say at the

beginning of the review of the 18 documents, to have any comments from the Panel members regarding handling the documents on the computer now since we are paperless. If there is any improvements, assistance that you might need, that we might just voice them to the office basically.

And so, Lillian, up to you to give us the Director's Report and, again, welcome.

DR. GILL: Thank you, Wilma. I want to give you an update on an item we mentioned last meeting and that you've seen in you reports, and that's the use of the data on the ECHA website. For the past three report cycles, CIR did not include the summaries from the data found on that website because it was unclear whether or not we had the legal authority to use that information.

When the Council was not able to assist us in getting permission to use it, what CIR had been doing is directing the reader, directing the Panel to the site where the information was found. We also learned from the Council that manufacturers would increasingly be submitting

their information to the Reach Program so that we would encounter this frequently in the future.

What we asked our legal counsel to do is give us an opinion on whether or not CIR could use that summary information. And on the 30th, we did get an opinion from our legal counsel that said CIR can use the data on that website. We can cite the date. We can use the summary information or summarize the information and include it in our reports without gaining permission from the author. Our legal counsel did tell us, though, we had to abide by the legal requirements for ECHA, which means that our website, when we link to their website, will only be to their legal notice. We can't link to the information.

They also said that we could, of course, use that summary information, the robust summary information, and that we did have to obtain permission if it were unidentified third party data. We did have to get permission. But they did distinguish between using the summary information and using the third party -- citing

the third party data.

We are still figuring out how to cite the use of the ECHA data. We've gotten some comments from counsel that says ECHA isn't the author of the information, so we'll clean that up in our report. But the good news is we are able to use that summary information in the reports and not give the Panel large matrices of information to go and find. So that should be very helpful.

I also wanted to give you an update on the insufficient data list that was established in 2010. CIR established the two-year window to allow industry to provide information on that list of ingredients on insufficient that were concluded insufficient data, but the ingredients continued to be used. Last year was the deadline, October 2012. A number of those ingredients were moved to the "use not supported" category.

Once that cleanup took place, six ingredients remained on that list: Achillea millifolium, hypericum. There were two PEG cocomides, the 5 and 15, and the acrylate

cross-polymers remain on the list. All but one have been dealt with. Achillea is the last one, and that's currently in the process before the Panel. And as of the end of September, we will move the acrylate cross-polymers to the "use not supported" list. So we have finally cleaned up that entire list of ingredients.

And finally, I wanted to mention that the schedule for our 2014 meetings has been posted, and the Panel received that schedule yesterday. I want to highlight that there will be a new location for CIR meetings. This has been a very convenient place to hold the meetings, but starting in -- with our March meeting, the March 17th meeting, our meetings will be held at the Washington Court Hotel on New Jersey Avenue in the District. So we will have a change of location for the meetings and a change of location for the offices as they will be moving. So at the next meeting, CIR will be in the midst of moving our office as well.

DR. BELSITO: To where?

DR. GILL: Around the corner.

(Laughter)

DR. GILL: We kept one location that was convenient that's still in the area.

DR. BERGFELD: Well, we hope you get all of the work done by the next meeting.

All right. Well, we're going to proceed then, and what I introduced was, I'd like to field some comments from the Panel members regarding the handling of the documents via jump sticks, and computer, and paperless. Any comments about any help that might be needed, or any setup or changes that would be suggested? Anyone?

DR. SHANK: It would be helpful, at least to me, maybe others, if the reports, not all of the supplemental stuff, but just the actual report itself, could be provided not only in PDF, but also Word. I realize the problem of taking all the supplemental stuff, which is scanned, and converting that. That's easy to do in PDF, but it's hard to convert that to Word. But if the report itself could actually be provided in both.

It's not a big deal because I convert them anyway, and then I provide my comments in both PDF and Word. But I find it much easier to make comments, rearrange sentences and things in Word rather than PDF. So that's just a suggestion.

DR. BERGFELD: Don? Paul?

DR. SNYDER: So Kevin has been supplying me separate Word documents because I made that request right out of the gate. And so, I think that should be doable, and I mean, and I find it much easy -- much easier to use.

And the only other thing that I would add is if in the PDF, I'd rather get multiple PDFs, particularly when there's large articles or old reports, instead of them all streamed together, if they could be separated. I have two screens, and I can have lots of things open at one time and try to facilitate the review process of trying to be in one place and then scroll to another place and trying to find something.

So if we could have not quite so many

documents strung together in a row, for me that would be to my advantage.

DR. BERGFELD: Dan, any comment?

DR. LIEBLER: I'm happy with the current setup. As you guys know, I'm sort of an early adopter, but I'm very comfortable with it.

And, you know, I don't know if everybody is familiar with using something like the bookmark functions and so on in the PDFs that help you jump around to different parts of the document. It seems like every time get a new set, they're a little bit better, more conveniently bookmarked. So I'd like to compliment the staff on that, particularly Kevin.

DR. BERGFELD: Ron Hill?

DR. HILL: Yeah. On that, though, I don't know how much extra effort I'm actually asking for, but certain sections, like the references and maybe the beginning of the figures, if there's any way that those could be bookmarked before they're sent out. I don't know. I know your timelines are very short, so, I mean, adding

them on our own, I guess, is always the option. But that's the most frequent, if they don't get broken up, and even within a long document. But, yeah, I guess Adobe allows adding those ourselves, so I guess we can do that.

DR. BERGFELD: Tom? Jim? We're good. All right. Well, thank you very much. So we'll proceed then with the first of the 18, and these are final reports. And Dr. Belsito is leading off with the isethionate.

DR. BELSITO: Yeah. These are the isethionate salts. And at the June meeting, we issued a tentative amended report with a conclusion of "safe in the present practice of use, concentration, and cosmetics when formulated to be non-irritating."

There was a question as to whether this was used in a baby powder that could be potentially aerosolized. And we subsequently found that this was not the case, in fact, that it was used in a wipe. It doesn't change our conclusion of "safe as used when formulated to be

non- irritating," but it does change some of the discussion concerning the respiratory boilerplate.

So there were a few edits, but safe is used when formulated to be non-irritating.

DR. BERGFELD: And that's a motion to move?

DR. BELSITO: Uh-huh.

DR. BERGFELD: Second?

DR. MARKS: Second.

DR. BERGFELD: Any other discussion regarding this document?

DR. BELSITO: Minor changes within the document, but nothing substantive. We've given them to the writer.

DR. BERGFELD: Good. All right. Seeing no other comments. I call the question.

All those of favor of "safe?" Unanimous. Thank you. Moving onto the next, Dr. Marks, alumina.

DR. MARKS: In June of this year, the Panel looked at the assessment of alumina and aluminum hydroxide and issued a tentative report

with "safe" as the conclusion. We're at the stage of the final safety assessment.

In our team discussion, industry had a number of editorial inputs which they thought were significant. And so, we felt we should table the issuing of the final safety report with a "safe" conclusion until we see industry's edits.

DR. BELSITO: Second.

DR. BERGFELD: Second. There is no discussion on the table. So all those in favor to table, please indicate by raising your hand.

Unanimous. So we'll be moving on. Is there any comment that you want to make specifically to that table, other than the industry will supply some information?

DR. MARKS: No, unless Halyna wants to make any comments.

DR. BRESLAWEC: I'm not sure that additional information is necessary; rather, a rewrite of the document that places the toxicological information in context.

DR. BERGFELD: Thank you. So a

clarification of that.

All right. Moving onto the next ingredient then, achillea. Dr. Belsito?

DR. BELSITO: Yeah. The June meeting, we had some new sensitization data, .04 percent, which allowed us to evaluate the safety of these ingredients at their highest use concentration. And we agreed that they were "safe as used." We also discussed the LLNA on a mixture and felt that that was somewhat of a problematic way of assessing sensitization of mixtures.

We then raised the issue of having multiple botanicals in a single product that may contain things like sensitizers, that the total impact might cause problems in a final formulation, heavy metals, et cetera, things like that. And we looked at some boilerplates, which I guess we'll get to later.

Having said all that, we felt that the conclusion that we reached was "safe in the present practice of use, and concentration, and cosmetics." The Council raised the issue of

addending a bit by saying when formulated to be non-sensitizing, and our team actually thought that was a good idea because it will reflect back to the discussion regarding potential allergens, sensitizing allergens, in that botanical product that could be stacked upon other botanicals to create an issue.

So a little bit of a change in the conclusion, "safe when formulated to be non-sensitizing." I'm not a legal expert, so I don't know if this has to go out for another 60-day final or whether we are done with it.

DR. BERGFELD: Well, let us make a ruling on the safety, and then we'll discuss that.

DR. BELSITO: Okay. "Safe when formulated to be non-sensitizing."

DR. BERGFELD: Is there a second?

DR. MARKS: Second.

DR. BERGFELD: All right. I'm going to call for the vote then.

All those in favor of "safe?" Okay, unanimous. Can we get an opinion on whether it

has to go out again for comment? Halyna maybe or Lillian?

DR. GILL: I think we've changed that conclusion. It went out originally as a safe conclusion, and with the change of "conclusion," I think we will have to re-issue that for comment.

DR. BERGFELD: So this will go out again with the change of "conclusion." I think that's reasonable.

DR. BELSITO: Uh-huh.

DR. BERGFELD: I'd like to point out, too, that we had this discussion yesterday that this is only the second time that we have put the restriction into the conclusion of "non-sensitizing." Before it's been "non-irritating," but this is "non-sensitizing," a little bit different to make everybody aware of that.

DR. MARKS: Yeah, and our team really wanted to have that elucidated, as you've explained, Don, in the discussion, because it is unusual to say. The idea of combining botanicals

and the level of an ingredient might then rise to the threshold of being sensitizing, I think, is important to explain in the discussion.

DR. HILL: I also liked it because it picked up the possibility of variations in source materials that some -- potentially could occur in this case.

DR. BERGFELD: Any other comment regarding this? None? All right. We've ruled on that as "safe," and we're going to send it out again for a second look at the conclusion.

We're looking now at the next ingredient, tromethamine. Dr. Marks?

DR. MARKS: So in June of this year, we issued a tentative report for the tromethamine ingredients, and the conclusion was "safe." I move that we issue a final safety assessment for these ingredients with a conclusion of "safe."

DR. BELSITO: Second.

DR. BERGFELD: Second. Any further discussion? Yes, Don?

DR. BELSITO: Yeah. We had in our

discussion taken out the issue of the nitrosation boiler point because it was said that there were no secondary amines. But on page 16 of the PDF, it clearly says as impurity, secondary amines, and hydros were present at a maximum.05 percent way, and nitrosamines at 50 parts per million. So I thought we had to add back that nitrosation language into the discussion.

DR. BERGFELD: Comment? Jim? Fine? Any other comments? Ron Hill?

DR. HILL: I'd just like, and this will probably be back to industry. There was a comment in here about unstabled freezing, which chemically makes no sense to me. And so, I'm thinking the instability has more to do with either crystalline form or hydroscopicity or something stable at room temperature. It can't be unstable chemically from freezing.

So if we could get some clarification of that language since this is going out with my name on it before it gets into the Journal, that would be great.

DR. BERGFELD: All right. Any other comments before we vote?

All those in favor of a "safe" with these changes? Thank you. Unanimous. Moving onto the next ingredient then is the hair dye. Dr. Belsito?

DR. BELSITO: Yes. This is hydroxypropyl bis and hydroxyethyl phenylenediamine. And in June, we noted that this compound had minimal penetration through the skin and virtually no toxicity when used as a hair dye. And came to a "safe as used" conclusion, and we'll maintain that and go forward as "safe as used" as a hair dye.

DR. BERGFELD: That's the motion. Second?

DR. MARKS: Second.

DR. BERGFELD: Any further discussion? Yes, Don, please?

DR. BELSITO: Well, just it's a boilerplate issue -- let me see if I can come to it -- on, again, page 20 of the PDF, I guess I've

missed this before. But it says, "The Panel noted that use of oxidated hair dye formulations involves exposures to precursors and coupling agents, as well as to their reaction products. While reaction intermediates may be formed, human exposure is to the precursors and coupling agents and to reaction products and not to reaction intermediates."

And I thought that last sentence, "While reaction intermediates may be formed, human exposure is to the precursors and coupling agents and to reaction products, not to reaction intermediates," should be deleted because, A, there is exposure to the intermediates; they're formed on the scalp, and, B, at least for the case of paraphenylenediamine, Brandowski's base, which is an intermediate, is thought to be a sensitizer, at least in some people.

So that statement is not correct in that sentence, and the boilerplate should be deleted.

DR. BERGFELD: Any other comments?

DR. HILL: I certainly would agree with

that.

DR. BERGFELD: Okay. So no other comment, and we can make that change. I'll call for the vote.

All those in favor of "safe?" Thank you. It's "safe" unanimously. Moving onto the next ingredient, Dr. Marks, is sulfosuccinates.

DR. MARKS: So we have before us a final amended safety assessment, a draft final amended safety assessment of dialykl sulfosuccinates. There are eight ingredients. You previously found them to be "safe when formulated to be non-irritating."

I move that we issue a final amended assessment with that conclusion, "safe when formulated to be non- irritating."

DR. BELSITO: Second.

DR. BERGFELD: Second. Discussion? Seeing none, I call for the vote. All those in favor of "safe?" Thank you. Unanimous. Moving onto the next ingredient, Dr. Belsito, is the PEG-PPG ethers.

DR. BELSITO: Okay. So the June meeting, we decided we could add 131 alkyl PEG-PPG ethers into this report, bringing some summary data from the prior reports on PPGs and PEGs. A little bit in the discussion about dioxane as a contaminant, but our lack of our concern due to the low levels, and go forward with a "safe as used" conclusion for these ingredients.

DR. BERGFELD: A motion? Is that a motion, or do you have other things to add?

DR. MARKS: Yeah. I would just amend the motion slightly.

DR. BELSITO: "When formulated not to be irritating."

DR. MARKS: Correct. Second.

DR. BERGFELD: Second. Any other discussion regarding this ingredient?

Seeing none, call for the question. All those in favor, raise your hands? Thank you. Unanimous. And moving onto the next is methyl glucose. Dr.

Marks?

DR. MARKS: In June of this year, the Panel issued a tentative report for the methyl glucose polyethers and esters with a "safe" conclusion. We're at the stage now to issue a final report.

I move that we do that with a "safe" conclusion.

DR. BERGFELD: Is there a second?

DR. BELSITO: Second.

DR. BERGFELD: Second. Any discussion?

DR. BELSITO: I'm still having problems navigating through this.

DR. MARKS: Well, our -- there were several paragraphs in the discussion, and we felt the revised paragraph on page 35 was the better of the two starting with "Wilbur." I think I caught that correctly, right, Ron Shank?

DR. SHANK: Yes.

DR. MARKS: And then there was some comments in the memo which we felt the reproductive and development toxicity we felt were fine.

DR. BELSITO: Yeah. I guess our only comment was in the language of the conclusion where it said -- there we go -- the "CIR Expert Panel concluded that these cosmetic ingredients," and then there was a list. I just thought that the -- instead of "these cosmetic ingredients," the family should be referenced there, and it should be "the following methyl glucose polyethers and esters."

DR. BERGFELD: Is that agreeable?

DR. MARKS: Yes.

DR. BERGFELD: Yes. Any other additions, edits?

DR. BELSITO: Minor edits.

DR. BERGFELD: Discussion? Minor edits? Ron Hill?

DR. HILL: Yeah, I think it's a minor edit. But in the discussion -- let's see, I guess it would be -- it's the second full paragraph on the last page of the discussion. It says, "Unlikely that systemic toxicity would result from repeated ingestion." I'm wondering if we could

change that to "repeated incidental ingestion from reported cosmetic uses," or something like that. I'm just trying to figure --

DR. BERGFELD: That sounds reasonable.

DR. BELSITO: Well, we actually -- that was one of our edits --

DR. HILL: Okay. All right.

DR. BELSITO: -- that sentence. We said, "The use concentration reported up to one percent are considered low, such that toxicity would not result from" --

DR. LIEBLER: "Cosmetic use of lipsticks."

DR. BELSITO: "Cosmetic use in lipsticks," thank you. And I think the word is easier.

DR. SNYDER: Yeah. Yeah, good.

DR. BERGFELD: So this addresses the same. So the preference is Don's edit?

DR. HILL: I like his, yes.

DR. BERGFELD: Thank you. Any other comments? Seeing none, I call the question. All

those in favor, please indicate by raising your hand. Thank you. Unanimous.

Then moving onto the last in this final report group, the polyquats. Dr. Belsito?

DR. BELSITO: Okay. At the June meeting, we issued a tentative report with a conclusion of "safe in the present practice of use and concentration in cosmetics." We received some wave two data indicating that polyquaternium-

Does not contain an acrylic monomer, and that the polyquaternium-39 contains less than one part per million acrylamide monomer. So it's satisfying any concerns we had about the presence of some unreacted acrylamide in these products. And so, we're very comfortable going ahead with "safe in the present practice of use and concentration" for these two.

DR. MARKS: Second.

DR. BERGFELD: Second. Any other comments, edits, that are important?

Seeing none, call the question. All those in favor, please indicate by raising your

hands. Thank you. Unanimous. Now, we're going to move on to Reports Advancing.

And this first one here is the phytosterols by Dr. Marks.

DR. MARKS: I suspect that now we'll get into discussion among the different -- the two teams as we move onto the next set of ingredients.

So this is the first time seeing this report. There are 27 ingredients. We felt at this point there were no safety issues. These ingredients are ubiquitous in plants, part of the diet, so we move to issue a tentative report with a phytosterols as "safe as used."

DR. BELSITO: Second.

DR. BERGFELD: Second. Any comments, other comments? Don?

DR. BELSITO: Yeah. We just thought that there might be additional literature out there on betacytosterols that didn't seem to be captured or searched. And we just ask that that additional information be brought into the document when we look at it.

The only other comment is that we thought that diosgenin should be deleted from the -- this report as its present in other botanicals, sort of as our approach to whether to include an ingredient, specific chemical ingredient, in a group of mixtures like this. If it was present only in that botanical product, a significant amount, then -- and it had cosmetic use, it might be reasonable to include it. If it were present in other botanicals, had no apparent cosmetic use, not to include. So we decided to drop diosgenin. It's already been reviewed anyway.

DR. BERGFELD: That's fine with your team?

DR. MARKS: That's fine.

DR. BERGFELD: All right. Any other discussion?

DR. BELSITO: In the discussion, we need the usual plant caveat that we've established under the boilerplate. We do not really need a botanical discussion because this doesn't really seem to have any of the sensitizers that we worry

about in other plants, such as achillea.

DR. BERGFELD: Agreeable?

DR. MARKS: Yes.

DR. BERGFELD: Okay. Any other comments? Ron Hill?

DR. HILL: This is really an editorial thing, but I'm not sure which all staff members are involved besides Lillian Becker. In referring to the PEG soy report, I just wanted to make sure that in the document that it's clear that the data that's being pulled in basically for the purposes of read-across doesn't pertain to the pegulated materials, which are different. So I just want to make sure whoever is involved in the writing of this that we're not suggesting that the pegulated materials assist with read- across in any way because that's not reasonable to think.

DR. BERGFELD: Okay. I will call then for the question.

All those in favor of a "safe" conclusion and going forward with this particular document, please raise your hands.

Thank you. It's approved with those editorial comments and general comments.

The next item is rosmarinus. Dr. Belsito?

DR. BELSITO: Yes. This is the first time we're looking at these 12 ingredients of rosmarinus officinalis. And again, we thought that rosmarinic acid should be removed from this report. It has no reported uses, and, therefore, we had no sense at what concentration it might be used. And we also got some soft information that it may be present in other botanical products as well.

Having said that, we also thought that the wax should be deleted. Dr. Liebler may want to comment, but he felt this was chemically dissimilar from the other components of rosmarinus officinalis that we were reviewing. And you can comment. I'll continue going.

The water --

DR. BERGFELD: He's ready to comment.

DR. BELSITO: You ready?

DR. LIEBLER: I'd just make the comment that I'm not going to comment.

(Laughter)

DR. BELSITO: Okay. So anyway, he thought the wax was dissimilar, so we're removing those two ingredients. And then it appears that the water extracts are -- may be used only as fragrance ingredients. We're waiting for some information from RIFM. If they are, then it's not in the purview of this Panel to review them, and those would be deleted.

We had a lot of data on the whole plant, a little less on component parts. But we felt that by and large the plant data covered the compositions that we needed. And that -- but it was still insufficient for sensitization of the leaf extract at 10 percent. And since we're going with an "insufficient," if the composition of the flower, which we didn't have a lot of information on, was available, we would like to see that. In terms of helping the Panel develop a discussion, we would need the pesticide heavy metal inhalation

boilerplates.

And the specific components of concern are caffeic acid, thujone, and terpenes, especially linalool/linalyl acetate acetate, limonene methyl eugenol. And then the discussion of the fact that there were reproductive effects on both males and females, but at very high doses that weren't relevant to use in a cosmetic product.

So developing a discussion, hopefully going ahead with eventually a "safe as used." But at this point, sensitization of the leaf extract at 10 percent, composition of the flower, if available.

DR. BERGFELD: So it's an insufficient notice --

DR. BELSITO: Insufficient notice.

DR. BERGFELD: -- that you're making a motion for. Is there a second?

DR. MARKS: Second.

DR. BERGFELD: Any other comments about the needs?

DR. MARKS: I think Don has addressed most of them. We were concerned in the text that said with a reference with a PDR herbal that rosemary should not be used in pregnancy. So you may have addressed it, Don, in terms of your saying, yeah, the amount should not be a safety issue, but we want that clarified. Ron Shank, if you want to comment more?

DR. SHANK: Yeah. I'd like to know what the writers of the PDR herbal had in mind when they said that rosemary preparation should not be used during pregnancy. I think that needs to be explained.

DR. HILL: And I had added to that the concern that we didn't have any reproductive toxicology data on the oil. And I'm not sure we have enough composition on the oil specifically to know how that relates to the other ingredients that we're studying in this group. So it's sort of a combined concern between those two things.

DR. MARKS: So I think it's just delve more into the pregnancy issue and the insufficient

data notice.

And then the last thing was Ron Hill wanted to know what was meant by the manufacturer when you used "deodorize." So again, I think that's a minor point, but it would be perhaps nice to clarify that. If you want to comment, Ron Hill, you may.

DR. HILL: Just depending on how that process is actually conducted. I mean if it's just absorption with activated carbon, then that presents no concerns whatsoever. But if there is chemistry involved, for example, some sort of bleaching, then that creates the potential for creating new chemicals that we might like to know something about.

DR. MARKS: So I think the two big data points we need is either a max or an HRIPT for the leaf extract at 10 percent. Undiluted, the leaf extract is a sensitizer, so is it safe at 10 percent? And then the second is clarify the issue of pregnancy and repo and development toxicity.

DR. BERGFELD: Have we captured it all

then? Is there something that's been left out? No?

DR. MARKS: No.

DR. BERGFELD: Lillian, are you comfortable with what we've got in that list, because it went on and on.

DR. GILL: I have it.

DR. BERGFELD: Okay. Now, I call for the question. It's going out as an insufficient data notice.

All those in favor? Thank you. Unanimous. The next item on the list is the alkyl betaines.

Dr. Marks?

DR. MARKS: So this is the first time we've seen these 11 ingredients. Our team felt all 11 were okay. When looking at the data, particularly the summary sheets that we received yesterday, we felt we could move forward with a tentative report, "safe as used." And that's a motion.

DR. BERGFELD: Is there a second from

the Belsito team?

No? All right. Any comments to be made?

DR. BELSITO: Yeah. We want to congratulate Christina for trying to get through the ECHA site. I've also tried to get through it, and it's a series of clicking and clicking and trying to sort through lots of information. But we've not yet gone through the betaine report completely. We have gone through the C12 14 aklyl betaines.

And I think the data will support safety, but we felt that we were still lacking impurities in manufacturing. And we weren't able to obtain that, at least in our brief attempt yesterday to look at the ECHA site since this is the first time that we've seen it. We haven't seen all the data that would be available on betaine itself.

We thought we would go "insufficient for impurities in manufacturing" and get all of the data from the ECHA site into a document and look

at it again.

DR. BERGFELD: Dr. Marks?

DR. MARKS: So I'll ask Ron Shank and/or Tom to comment on the manufacturing and impurities.

DR. SHANK: I think we have sufficient test data to cover the safety of the use of these in cosmetics. And I don't think the method or manufacture or impurities would help me, but it might help the chemists.

DR. BERGFELD: Dan?

DR. LIEBLER: I felt that -- I didn't expect that there would be anything remarkable in that information, but we just don't have it, and we normally have it in our reports. And it seems like it's gettable information. And since the getting process has just been formally approved now for us to be able to access the rest of these data, I think we should do that.

DR. BERGFELD: Ron Hill?

DR. HILL: I rather -- I'm operating on the assumption that n-dimethylglycine is being

alkylated, and that's the way these things are made. So I guess the only end result issue in my mind on the impurities, if that's true, but I'm conjecturing, and it would be nice to have that confirmed, is if there is an n-dimethylglycine, I guess is are nitrosamines a worry in that particular case?

But I also had opposition method of manufacture down here, and it was a method of manufacture question.

I still feel strongly that betaine itself should be separated from these long chain alkyl betaines because the data from one is not relevant to another. And I think toxicologically, they should be separated. I think it would make for a nice clean report on the betaine and a nice, much cleaner and much more useful in terms of read-across report if we just used then the long-chain aklyl grouping. And there was at least one opinion from industry that suggested that that's how we should've gone on this.

So I realize -- I don't think that that

would demand much more work from the staff, but that's just my thinking on it. So I'll leave that up to you all.

DR. MARKS: So I have no problem in terms of "insufficient data." I mean, that's -- I think we didn't think it would really change the conclusion. Neither do you. But let's get it because it is a usual part of the safety assessment. Is that fine, Ron Shank? Yeah.

DR. SHANK: Yes.

DR. BERGFELD: Since we're in discussion, Halyna?

DR. BRESLAWEC: Yeah. "Insufficient data" is, I think, generally used when you don't know if the information is out there. And I think based on your discussion, it's pretty clear that the information is there, but it has not been accessed. And so, we would recommend your considering tabling it. Obviously your decision.

DR. BERGFELD: Don?

DR. BELSITO: I'm not sure, Halyna, is you're saying the information is out there and

it's in the ECHA report, we really looked and it didn't seem to be. It seemed to be a whole bunch of different regulations as to safety precautions in terms of manufacturing with all of these codes, procedural codes. It didn't give a this is reactive with this, and this, and these are the impurities. It was not straightforward like that.

And, you know, I tried going through some tabs last night. Christina was tabbing away during our meeting yesterday. I don't think that information as we would want it is there, but it may be. I mean, there are so many tabs to try and go through, and you tab on it, and there are multiple tabs below it. And that ECHA, it's very difficult to get through it.

DR. BERGFELD: Carol?

MS. EISENMANN: I saw in the composition section for the mixture was that sodium glycelate and sodium chloride were other components that had sold as 20 to 40 percent active, that they made the powder just for testing. That's what I saw under composition.

And, yes, under manufacturer, you know, it's done in a closed procedure, and then mostly the focus was use in that area rather than manufacture.

DR. BELSITO: Right.

MS. EISENMANN: But there was a little bit of information on composition, in the composition section. It didn't give amounts, but it gave what I just said.

DR. BERGFELD: Ron Hill?

DR. HILL: I have to say I appreciate that there is a desire to supply that kind of information in a way that doesn't give away trade secrets, and so I appreciate that that's always true with manufacturing processes. And so, if we can get how to get the information we're looking for without having to compromise something, that would -- I'm just tossing out I appreciate that aspect of it.

DR. BERGFELD: Halyna, do you care to comment again? No? So we have no motion on the table. We have one suggestion of tabling. And,

Halyna, we have another for insufficient. I'd like to hear a motion.

DR. BELSITO: I'd like to move this ahead, and hopefully we can get that information if it's not available on the ECHA website from one of the manufacturers at the next meeting, and be able to go with this as a final say rather than slowing down the process by tabling it, I mean, because there's a huge amount of information.

And, you know, it's always possible, as Ron said, that when we look at all of the studies, and we haven't seen all of the studies, you know, that we may feel that, you know, there are no concerns about impurities because at the levels they're used in these studies, we're seeing no toxic effects. And those are levels are higher than what we're using in cosmetics or whatever.

But I just don't think we've had adequate time to look at all the information, and there clearly is one piece of information that seems to be missing, and that's method of manufacturing impurities. So I'd like to go ahead

with an "insufficient" and move this along.

DR. BERGFELD: And that's a motion.

DR. BELSITO: Yes.

DR. BERGFELD: Is there a second?

DR. MARKS: Second.

DR. BERGFELD: Ron Hill?

DR. HILL: Yeah, one last comment is that besides the n-dimethylglycine, which is probably in there nitrosating potential, if the reaction is done in the way I think it is, then we have long chain alkylating agents, and that would present a concern if they were there. So there's some indication as to how those are removed, if that's the way it's done, would also be helpful to us.

And that's the kind of toxicology where you might not have seen any incident in the studies, but that still could be there. And over time, long duration use of some product with such a thing present could present a hazard more subtle than --

DR. BERGFELD: So you're supporting the

methods of manufacturing the request.

DR. HILL: Yes, at least get some parameters for what sorts of things we're interested in finding out about.

DR. BERGFELD: Any other discussion? No? I'm going to call the question for "insufficient data notice." Unanimous? All right. There was something put on the table about separating this group of ingredients. Any support for that?

DR. LIEBLER: Yeah. I think Ron's point about betaine having somewhat different characteristics in terms of polarity, hydrophobicity is chemically -- I agree with him on the chemistry. But I don't think it is worth separating that out and to do a separate report. And largely because there are a lot of uses for betaine itself.

And the issue is more a matter of degree rather than a totally different profile, use profile, and physiochemical -- physical chemical properties. So I think these all should stay

together.

DR. BERGFELD: Thank you. Any other comments related to this?

No? We'll move on then to the next ingredient, which are the wheat proteins. Dr. Belsito?

DR. BELSITO: Yes. Hydrolyzed wheat protein and hydrolyzed wheat gluten. So at the last -- at the March meeting actually, we were asked to look at a whole group of hydrolyzed proteins, and we said, whoa, we just can't do this. So let's split them down and let's start with a hydrolyzed protein of greatest use, which was wheat, which is what we're doing now.

And at that time, we had issued an insufficient data announcement requesting methods of manufacturing, composition, characterization specifications for hydrolyzed wheat protein and when wheat proteins were combined with other amino acids. We're particularly concerned about reports coming out of Japan about hydrolyzed wheat proteins causing reactions in soaps. So we've

gotten a lot of new data, including some wave two data from the Council or at least one of the manufacturers pointing out various things.

We looked at this report. We thought it was a very well-written report. And in terms of reactions to wheat proteins, it appears that if the peptide length is less than or equal to 30, it will not cross link and bind IGE and cause reactions. However, it also appeared that if you tape strip skin, at least in mice, you could sensitize them to these wheat proteins. And it wasn't clear the molecular weight or amino acid length of the hydrolyzed wheat proteins that were used in those studies. And it also appeared that when applied to mucus membranes of the eye, you could also sensitize individuals.

So we felt that we could go ahead with a "safe as used," minimize peptide lengths above 30 amino acids long, but that we would need to put a restriction that this not be used on damaged skin, and with a robust discussion in the discussion about the sensitization of mice on tape stripped

skin, that it should not be used in products that could contact the mucus membranes, which would actually eliminate a little over 100 currently registered products that could, and not in products that could be inhaled.

To eliminate those restrictions, i.e., damaged skin, mucus membranes, inhalation, what we really need to know is can you sensitize to the hydrolyzed wheat proteins with amino acids that are 30 or smaller in size. And that we don't know because the studies that were done on mice that were sensitizing them were 45 --

DR. SNYDER: Forty to 50.

DR. BELSITO: Four hundred and fifty?

DR. SNYDER: Forty to 50.

DR. BELSITO: Forty to 50 kilodaltons, which are much larger than 30 amino acids. But we don't know whether amino acids will sensitize. So the issue here is that we know that you can apparently eliminate elicitation with a cutoff at 30, but do you eliminate sensitization, and that's the information we need to know to eliminate those

restrictions on damaged skin mucus membranes and inhalation.

DR. SHANK: But you still say it's safe?

DR. BELSITO: Safe, but not to be used in those products.

DR. SHANK: With all of that?

DR. BELSITO: Yes. We said formaldehyde formalin was "safe with elimination of hair straightening products." I mean, this can be safely used in a shampoo if they're less than 30 amino acids.

DR. BERGFELD: Dr. Marks?

DR. MARKS: So we struggled with how to deal with this, and we're quite concerned about the type one reactions and anaphylaxis. And we didn't quite understand or felt we had the expertise to come to a conclusion.

So we actually suggested tabling this report and ask that an expert on wheat type one reactions to speak to the Panel and sort through this and help us arrive at a conclusion. There are over a thousand uses. This is very important.

There's been these serious adverse events, particularly in Japan, and so we felt we needed more expertise. But if your team feels that -- comfortable moving forward, that will -- our team will discuss it, although I'm not sure we're prepared to move forward as "safe."

DR. BERGFELD: Ron Shank, any comment?

DR. SHANK: I find the immunotoxicity data confusing, and I don't have sufficient expertise in immunology to tease this out. These ingredients are widely used and have been, but we have not seen outside of Japan apparently this very serious type one response. So before we could go to safety, I would say we need to hear from an expert in this field.

DR. BERGFELD: Comment, Paul?

DR. SNYDER: I don't have a problem with having an expert come in, but I think as Don stated, we labored over this. I think that when you finally look at the data, I think the data on the elicitation is quite good, but there's a cutoff point.

But the question we don't know is, at what point do you get sensitized by peptides, certain peptides? And that's the critical thing that we don't know. And if we knew that, then we could tell them to formulate, to not contain those, and then that would resolve all of our issues.

But I don't have a problem. If it would help others understand the immunology behind it, I'm okay with that.

DR. BERGFELD: Dan?

DR. LIEBLER: So I think the suggestion is not a bad one of having an expert come and speak with us because I think if you look at this, almost everything we have in the report supports safety, as long as the size distribution of the hydrolyzed peptides is kept below some threshold amount. And 30 seems to be -- we're using it as a kind of a magic number, but it's probably somewhere in that neighborhood.

The thing that really throws a wrench in the works in our interpretation is this mouse

study, the tape stripping mouse study. And, you know, admittedly we have to, because we're uncertain of the circumstances of those experiments, we're having to kind of work around that in our, you know, proposed assessment here, as Don laid out.

So it might be if we do have an expert come and talk with us, I think one thing we would to do is have that person really give us their input on what they -- how they would asses this mouse study. Now, there might be -- it might not be possible for them to fully assess it if we cannot know what the position of the test material was in that experiment. I think it's a big --

DR. BELSITO: (off mic)

DR. LIEBLER: Well, I don't see it very well, you know, very well laid out. I suspect it's not known well enough to get to our major point, because I think the characterization of the size of the proteins used is not adequate.

So, you know, it's a big unknown. It throws a wrench in the works, and it perhaps would

allow time for any more data to emerge if that's possible.

DR. BERGFELD: Ron Hill?

DR. HILL: Yeah, because the interesting complication here is the suggestion that smaller peptides are either via disulfide linkages or some other, they say, entangling. I don't know about that. But I certainly can envision through essentially repolymerization, but through disulfide linkages that we're building up big enough molecules, and then they come to the end where they say if we keep everything below 3,000 molecular weight, theoretically that should solve the problem. I have to think my way through that theory and really read in depth the references list that's here and anything else I can find.

And then, so the characterization issue, that's part of it because on the day of the testing, if that process is actually occurring in a sample, then you really need to know right then by some means what's actually in there to be tested. And I thought on the tape stripping, it

sort of is in accord with the data that suggests that on intact skin, in order to get much sensitization, there's some words barely in there for detecting, I think, it was IgE. So I'm a little concerned what does "barely" mean.

But in order to get robust sensitization, it was the SDS, the surfactant, that allowed, I assume, compromising the barrier function of the skin that allowed these things to do something. And I guess this is the first I had really encountered how much -- to what extent if I have a shampoo that has this stuff in it, I rinse it off, is it maybe contacting the mucus membranes in my eye. I even got to thinking, if you're living in a place where the showers don't work as well as they did in this building, you know, that maybe you're leaving more on than if you can rinse well. So that is a little crazy, but not maybe that crazy when we're talking anaphylactic reactions. So there were unknown parameters, I agree.

DR. BERGFELD: So, Don?

DR. BELSITO: Again, you know, the issue in Japan, as you just pointed out, was with soap. And so, you're having that surfactant. You're having damage. I mean, these proteins -- stratum corneum is going to an excellent barrier for any protein.

So what you're concerned about is areas of skin with no stratum corneum or a very weak stratum or damaged stratum corneum, and mucosa, which has no stratum corneum. So that's when you're going to start absorbing the proteins.

So, I mean, our restrictions are very, very extensive. And probably industry is, you know, going to hopefully come forward with some data to show us that, you know, with the restricted size length, you can sensitize. But, I mean, quite clearly, you know, in terms of an expert, I'm not sure what an expert is going to tell you that's not in this report. When you get below 30, you can't get, you know, dynameric cross-linking of IgE, and you can't trigger mass cells, period and amen. Above that, you can.

And so, you know, IgE reactions are going to occur with larger molecules. So if you're concerned about the reaction to sensitized individuals, limiting the size will satisfy that.

The question really is, can you sensitize an individual with those smaller molecules, and we don't know. You know, what is the epitope that's coming out and will it sensitize. So that was our issue. And, therefore, since sensitization can only occur when there's no stratum corneum, and we put in the restrictions not undamaged skin, not for inhaled products, and not for products that can contact the mucus membranes.

DR. HILL: But the complication that I think remains sitting in my mind then is the potential for these smaller peptides to grow, again, I guess based on mostly disulfide. I'm not sure what other mechanisms would be involved that could do that --

DR. BELSITO: I can't comment on it.

DR. HILL: I know.

DR. BELSITO: If in formulation these can re- aggregate into longer amino acids, Dan, you may want to comment --

DR. HILL: So what assurances would we want to see in order to conclude, you know, that we have to assure that this won't happen, this is what causes it to happen. And I don't know if you have an expert in on immunology that they're still going to be able to address that particular issue unless they've really thought this through. This is new to me. I haven't encountered this before.

DR. BELSITO: An immunologist wouldn't be able to probably answer whether these can aggregate. Dan might be able to.

DR. LIEBLER: Yeah. I don't really think so. I mean, you know, my lab --

DR. HILL: That's what they're suggesting in here.

DR. LIEBLER: Yeah, I know. My lab does proteomics for a living pretty much. And, you know, we digest proteins, and in some cases we don't reduce and alkylate. We just digest without

reduction. And we never have an issue of, you know, forming of larger structures by re-oxidation. So, I mean, I think it's probably -- it would require a very highly oxidizing environment, and that's probably not applicable in this case. So I don't think that's the issue.

I think, you know, quality control in these hydrolysis chemistries, and preparation, and batch checking to make sure that you've actually got the high stuff down below some threshold. We don't know what it is, but it should be very low. And, you know, I think I think that's probably already being done in industry. The capacity exists to assess that.

The problem is with some of these experiments, we don't know what the characterization of the test material was. In this mouse, you know, study, for example, I just don't think it's well enough characterized to allow us to figure out what's going on and how applicable this result is to use of commercial products in humans.

DR. HILL: My gut reaction when I saw that large protein in there was, well, they've got bacterial growth in their raw materials such that it's kicking out, lypo- polysaccharides or something that's causing it, and that was the whole source of the problem. But just a conjecture.

DR. BERGFELD: Jim?

DR. MARKS: Yeah. I'd like to point out that it's not just to the soaps there's been reactions reported to. There was an eyelid cream and body moisturizer, two separate case reports, contact urticaria to that. So I think it's more than just -- and I don't know where the sources -- the one reference actually didn't appear to be Japanese authors, but it looked like it was a secondary report.

DR. BERGFELD: Well, we have two motions that have not been seconded that have to the table. One is to "safe" with great restrictions, and the second is "insufficient." So I'd like to hear a final motion.

DR. MARKS: Table, not "insufficient."

DR. BERGFELD: Oh, excuse me. "Table," thank you.

DR. MARKS: And, again, if I were going to err, I'd prefer to err on the safe side and have somebody who deals with this and understands type one reactions, possibly somebody who can relate back to natural rubber latex, contact urticarian anaphylaxis epidemic which occurred, and then when limits were placed on natural rubber latex gloves, we saw that disappear.

I just would feel more comfortable setting the limits, and perhaps not a whole bunch of restrictions if we understand perhaps a little bit more. We may not get any further, I agree, Don, but our team felt more comfortable.

DR. BERGFELD: Don? Well, a couple of things. First of all, I'm not sure that this is comparable to the natural rubber latex. I tried searching because, as you know, with natural rubber latex, it was a series of about six Hev proteins that were shown to be problematic. And,

therefore, by removing those Hev proteins from the latex sources, they essentially got rid of the epidemic.

When I tried searching for, you know, key proteins in wheat because I thought of that approach, say, okay, eliminate these, I couldn't find them. Now, I didn't do an extensive and exhaustive search, and that is maybe something that can be done to see if you can identify the epitopes that are sensitizing for the vast majority of people. That's one way of getting around it.

My only concern with tabling this to get an expert in is I'm not sure that they can tell us whether peptides of 30 or less will or will not be sensitizing. And, therefore, we're still going to be missing that critical data that we feel is necessary.

So I would like to go forward with our motion, you know, and get an expert to talk to us. But, I mean, this is the first time we're looking for it, you know. We can table it later on if it

appears that we're going to need more time to address issues that we need. But I would just like to see this, you know, progressing because if you read labels and if we're that concerned about the safety of this, you see the number of uses out there.

So, you know, if you're telling me you're concerned, then I think we need to move ahead. And by tabling it, we're not moving ahead. We're just stalling it.

DR. BERGFELD: Response? No response? Is there a motion?

DR. HILL: Could you read that list of restrictions you're proposing again? I think I've got it.

DR. BELSITO: Okay, hold on. So we're saying that these hydrolyzed wheat proteins are safe when they are formulated to minimize peptides greater than or equal to 30 amino acids in length. But they should not be used on damaged skin, on products that could contact mucus membranes, and on products that could be incidentally inhaled.

DR. BERGFELD: Are you making that a motion?

DR. BELSITO: That was my motion originally.

DR. BERGFELD: Well, restating it.

DR. BELSITO: Yeah.

DR. BERGFELD: Is there a second?

DR. SHANK: When you say they can't be used on mucus membranes and inhalation, they being the 30 amino acid links and smaller?

DR. BELSITO: Well, we've already said that what's out there should be 30 amino acids and less. I mean, we're saying anything with significant content above 30 amino acids would be unsafe, or the safety is not known. We're saying that below, you know, 30 or below will not cross-link IgE, will not trigger the anaphylactic reaction, so we're not concerned about those lengths of hydrolyzed wheat proteins in individuals who are already sensitized.

But the question we don't have it, will they induce sensitization in people who are not

sensitized who could then be exposed to wheat in food or whatever and develop anaphylactic reactions as a result of sensitization to a cosmetic product?

DR. HILL: So your motion is that restriction and in addition to --

DR. BELSITO: In addition --

DR. HILL: -- damaged skin, mucus membranes, inhalation.

DR. BELSITO: Right.

DR. BERGFELD: Paul, did you want to speak?

DR. SNYDER: Well, I as just going to reiterate. I think, to me, the immunologic data is pretty strong that there's a cutoff for elicitation. It's clear that we've got good data, that less than 30 amino acids in length, you cannot -- even in people who are sensitized, you will not elicit a reaction, a type one reaction.

What we don't have, and we have good data saying that if you have damaged skin and you're exposed to greater than 30 amino acid

length hydrolyzed proteins, you will be sensitized. And so, that's the two solid pieces of data we have.

What we don't have is, where is the cutoff for sensitization? And so, we can't link the sensitization with the elicitation cutoff right now. If we got that data that we tell -- advise to not have certain peptide links in the final product, then I'm quite comfortable we would be safe.

DR. BELSITO: I mean, we can move ahead, try and identify an expert who looks at protein sensitization and digests of proteins of albumin, whatever you want, and come in and say, oh, yeah. I mean, if you have a, you know, a peptide smaller than this, nothing is going to happen immunologically, that'll solve our problem, you know. But at least we're moving ahead.

And, you know, because, again, I think if you're that concerned about the possibility that, you know, there's over 1,000 products out there, then to stall it, I think is a mistake.

DR. BERGFELD: Jim?

DR. MARKS: Second.

DR. BERGFELD: Thank you. Anyone want to make a comment before I call the vote?

DR. LIEBLER: Yes.

DR. BERGFELD: I think the discussion is the main thing.

DR. LIEBLER: So one of the points that was raised last time was a lack of information about how these were prepared and characterized. You can make -- do enzymatic hydrolysis. You can do modified acid-based hydrolysis. And we didn't have much of anything. Now we have minimal information in table two.

This is an opportunity to get, if there's more information available from industry, on the methods used to characterize these and ensure that the components over 30 amino acids are on the top end of the weight range is minimized, that would be particularly valuable here in helping us formulate our conclusion.

And so, I'd like to emphasize that if

it's possible to squeeze harder for that information, we should try and do that.

DR. BERGFELD: Halyna, do you wish to comment at all?

DR. BRESLAWEC: We will certainly look for that information and provide it if we have it.

DR. BERGFELD: All right. Thank you. I'm going to call the question then. I see no one needing to speak.

All those in favor with regard to "safe" with all the restrictions as stated?

Unanimous. A wonderful discussion. Thank you. Moving onto the next ingredient then, the alkyl amides. Dr. Marks?

DR. MARKS: In June, the Panel issued an "insufficient data" announcement. We wanted dermal irritation sensitization for lauroyl lysine and sodium lauroyl glutamate. We received information on both of these. We felt that lauroyl lysine could be safe. And then the sodium lauroyl glutamate limit its use in leave-ons to -- four percent, I'm sorry, and in rinse-offs to 40

percent.

So we would move forward with these 115 ingredients to issue a tentative report with, again, a "safe" conclusion, except for SLG, four percent for leave- ons and 40 percent for rinse-offs. That's a motion.

DR. BERGFELD: Don?

DR. BELSITO: That's their current use.

DR. MARKS: Yes.

DR. BELSITO: So why are you restricting it if we just say -- we didn't need to restrict that because that's the highest leave-on as four percent, and the highest rinse- off is 40 percent for the glutamate. So we just said --

DR. MARKS: I'm sorry, I meant 2.5 percent leave- on and 30 percent rinse-off, so it does limit it. That's the data we have. I'm sorry. I was reading the wrong line in my notes.

DR. BELSITO: Well, we have data that the highest test concentration was five percent, and that was a mild irritant, but not a sensitizer. And so, we thought that we could go

with a "safe under the intended conditions of use when formulated to be non-irritating." We didn't see any issues with sensitization, and not putting any concentration limits on them.

DR. BERGFELD: Comment?

DR. MARKS: Where was the five percent, Don? I have wave two, the max was okay at 2.5 percent. So I missed that five percent, I guess, with the SLG.

DR. BELSITO: Let me -- it was in wave two.

DR. MARKS: Okay.

DR. BELSITO: They were induced at five percent and challenged at 2.5 percent.

DR. MARKS: Okay.

DR. BELSITO: So the induction was five percent.

DR. MARKS: Okay. Fine.

DR. BERGFELD: So are you agreeing --

DR. MARKS: Yes, "safe."

DR. BERGFELD: -- to take a wave at the restriction?

DR. MARKS: Correct. Yes.

DR. BERGFELD: So your amended motion. Are you going to second that?

DR. BELSITO: I will second that one.

DR. BERGFELD: Any other discussion? Ron Hill?

DR. HILL: I will say that this is not a consensus opinion because I was troubled by the idea that we only have data on two amino acids effectively, particularly when you separate, which I do, in terms of read-across all the acetylated amino acids. And furthermore, we have the information that came to us this time that the lysine amino acid was not alpha acetylated, but rather epsilon amino acetylated.

So, and the only other data that we have for amino acids is the silk amino acids, and we only have an LLNA, and it's on a mixture because it is the silk amino acid. So I'm -- even though I doubt that there's any problem with all these other amino acids that we haven't looked at -- we have phenyl alamine. We still haven't addressed

the malonyl -- particular malonyl issue. And so, I'm uncomfortable with the read-across.

DR. BELSITO: Yes, I have that.

DR. BERGFELD: Okay.

DR. HILL: And so, that's where I stand.

DR. BERGFELD: Okay. Dan, can I have your --

DR. HILL: I'm perfectly comfortable with the data on the lysine and for all the glutamates because I think we have more than adequate data. But for all these other amino acid and acyl long-chain amides, I'm not comfortable at all. And the rest of my concerns have been captured in the transcript, so.

DR. BERGFELD: Dan?

DR. LIEBLER: I note Ron's concerns. I don't share them.

DR. BERGFELD: Okay. Don?

DR. BELSITO: Yes. There were several TEA- containing compounds in this group. So in the discussion, we need to point that out, talk about possible amine impurities and nitrosation,

so that usual boilerplate in the discussion.

DR. BERGFELD: Okay.

DR. HILL: And reference the TEA review because we had a TEA group of some sort that we looked at not long ago.

DR. BERGFELD: Any other comments? The motion has been made, and I believe seconded, to go forward. And we're not going to restrict the concentrations --

DR. MARKS: Correct.

DR. BERGFELD: -- as used.

DR. BELSITO: Just -- no, "formulated to be non- sensitizing."

DR. BERGFELD: "Formulated to be non-irritating."

DR. BELSITO: "Non-irritating."

DR. BERGFELD: "Non-irritating." That one is good.

All those in favor, please indicate by raising your hand.

Those abstaining?

DR. HILL: No, opposed.

DR. BERGFELD: Opposed? One opposed. Thank you. Moving then to the next ingredient, formic acid.

Dr. Belsito?

DR. BELSITO: Yeah. So in June, we decided to reopen this because had information that not only was formic acid used as a pH adjuster, but also as a preservative, and also to incorporate sodium formate into the report. And that has been done, and we're ready to go ahead with a conclusion that "safe as used when formulated to be non- irritating."

DR. MARKS: Second.

DR. BERGFELD: Second. Any discussion regarding this motion?

DR. BELSITO: Well, go ahead.

DR. MARKS: No, go ahead.

DR. BELSITO: Just one thing. In the use table, it said that the highest dermal contact was.02, and the highest leave-on was.2 in a non-coloring hair product. So that dermal contact needs to be corrected to.2 as well because it's

our understanding that a non-coloring hair product would also contact the scalp, which is skin. And then just some minor edits.

DR. MARKS: Fine.

DR. BERGFELD: Any other -- fine? No other discussion?

(No response.)

DR. BERGFELD: I'll call the question then. All those in favor of "safe, non-irritating?" Thank you. Unanimous. The next one is chamomile. Dr. Marks?

DR. MARKS: So this is the second time we've seen this report. However, now the German chamomile has been split out from the Roman chamomile nobilis. And so, this, the chamomilla recutita, the German chamomile, we felt we could move onto a tentative report with a "safe up to 0.4 percent," based on an HRIPT in wave two that showed the 0.4 percent as "safe."

Its use concentration is up to 0.5 percent flower extract and 0.61 percent in the extract. But we decided to limit it to the 0.4

percent. Even though there are small differences, it turns out to be 1,000 to 2,000 parts per million difference.

So again, move "safe up to 0.4 percent" in the chamomilla recutita.

DR. BERGFELD: And you're putting that in the conclusion, the restriction?

DR. MARKS: Yes.

DR. BERGFELD: Don?

DR. BELSITO: Well, we had -- we thought that the flower ingredients were okay. We're a little concerned that we had no information really about the composition of the stem and the leaf. And there was some information that at least the composition of the root was significantly different from other parts of the plant.

So we thought that the components that were prepared from the chamomilla recutita flower were safe as used, and the others were, at this point, insufficient for composition of the plant and the leaf.

We also wanted clarification of exactly

what chamilosin was because it appeared in both reports, and in the anthemis report, it said that chamilosin was 10.5 percent anthemis nobilis. And if, in fact, it's anthemis nobilis, then the information on chamilosin, unless it also happens to contain chamomilla recutita, would need to be removed from this report.

And the last issue is the data that we got on chamomile teas and extracts where it wasn't clear which chamomile was being used. It's my understanding that chamomile tea is from chamomile from chamomilla recutita, and that the homeopathic uses of chamomile when referred to as chamomile are also chamomilla recutita, but that's just my understanding. I don't think there's any clear definition unless we can get it from that PDR that was referenced in other botanical that would tell us. Chamilosin I actually think is chamomilla recutita and not anthemis nobilis, but that needs to be clarified.

But having said all that, the flower ingredients we're okay with. The other components

of the plant were not, "insufficient for composition."

DR. MARKS: So, Don, you didn't feel the difference in concentrations between the HRIPT and what it's being used with would be -- raise any concern for sensitivity?

DR. BELSITO: Of the flower ingredients?

DR. MARKS: Yeah, the flower extract and the extract.

DR. BELSITO: No. I mean, we had an HRIPT a.4 percent.

DR. MARKS: Right.

DR. BELSITO: And I thought that was fine. But we don't know what's in the other ingredients.

DR. MARKS: But we have a use of 0.5 percent. So you didn't think that difference between --

DR. BELSITO: I didn't think it was a huge difference. We did discuss -- some of my teammates were concerned about, you know, the number of case reports here. But it was pointed

out that those were special populations who are known to be allergic to compositae plants, that this is a member of the compositae. They share a lot of the same allergens. And so, you really weren't looking at any kind of data from the population in general, that these were very select populations, which raised the discussion as to whether, you know, just for people who aren't dermatologists and may not understand when they see data under the heading of "provocative testing," if we somehow can maybe asterisk it and say, you know, provocative testing is testing on people with skin disease who are thought to be allergic and are not representative of incidence rates in the general population. That may one way of handling it.

But, no, I thought, you know, the difference between.4 and.5 for these, particularly given the level of, you know, the turpenes of concern didn't bother me.

DR. MARKS: Okay. Composition? So you want an "insufficient data for composition of" --

DR. BELSITO: "Sufficient" for all the extracts of the flower, but "insufficient" for the whole plant and the leaf.

DR. BERGFELD: I see part of Marks' team wagging their heads.

DR. BELSITO: We have --

DR. BERGFELD: Is that agreeable?

DR. MARKS: Yeah.

DR. SHANK: Basically --

DR. MARKS: Yes. I'll second that motion, Don.

DR. BERGFELD: That was a motion?

DR. BELSITO: Yes.

DR. BERGFELD: Because we had another motion. All right, so we have a second motion. Halyna?

DR. BRESLAWEC: I would ask the Panel to discuss whether they believe that "formulating to be non- sensitizing" would be a conclusion that they would consider, especially since this is a similar. This is the same category, the compositae family, as the achillea, for which a

"formulated to be non-sensitizing" conclusion is reached.

DR. BELSITO: A very important point, and I would agree. Yes.

DR. BERGFELD: So you're applying that to what?

DR. BELSITO: Again, I think for all the botanicals in which we're looking at sensitizing components that are below the levels of concern, we should have obviously the botanical discussion, pointing out the specific components that could be of concern when stacked on other botanicals and reinforce that in the conclusion by saying, "when formulated to be non-sensitizing." Yes, I would agree.

DR. BERGFELD: So what you've actually said, you're going to expand your discussion to include that -- expand the discussion, but put into your conclusion, the statement should be "formulated to be non-sensitizing." Okay.

DR. BELSITO: Correct.

DR. BERGFELD: Okay. So we have a --

DR. SHANK: Can I just ask a question? When we say "when formulated to be non-sensitizing," what is that saying to the formulator? Do they have to test their formulas and demonstrate that it's non-sensitizing? Irritation is an easy test, but sensitization is much more involved. So what are we saying to the formulator specifically?

DR. BELSITO: I think what we're saying to them is we're also pointing out the specific, you know, ingredients components of the botanical products that would be of concern. And usually those are fragrance ingredients that are in the botanicals. So, for instance, something like the chamomilla recutita has linalool, which is a known fragrance sensitizer. It has linalool acetate.

So we would be going through, and there are usually, again, going to be terpenes, terpenoids, and listing those of concern. And so, what we're telling the manufacturer is if you're combining this with another botanical that also has high levels of linalool, then you need to go

back and you need to really then go to RIFM and look at the data that RIFM has set in terms of limits of use of these fragrance ingredients in fragranced products. Those limits exist for most of the things we're going to be concerned about. And then, you'd better not be stacking linalool above a level that would be restricted by IFRA.

So the International Fragrance Research Association sets limits on fragrance ingredients that are sensitizers. And the limits are actually set using a QRA approach. And as you've seen, as we will get to idyl propyl and butyl carbonate, where the Europeans have also put a lower limit on an underarm deodorant. Underarm deodorants typically have lower limits because they're braided skin. If you shave your underarms, they're occluded. They're more absorptive.

So what we're telling manufacturers is, these are the components of concern. If it's pulegone, we know it's toxic levels. You'd better keep your levels less than that. If it's a sensitizer, almost all of them are going to be

fragrance ingredients. They can go to IFRA and look at the IFRA dossiers and see where those cutoffs have been set. So that's what we're telling them.

DR. BERGFELD: Jim?

DR. MARKS: Don, I wanted you to clear up in the last meeting, not this one, you had asked for absorption. Was that still necessary?

DR. BELSITO: No, I didn't think it was necessary.

DR. MARKS: Okay, good.

MR. JOHNSON: I have a question to ask?

DR. BERGFELD: Okay, Wilbur?

MR. JOHNSON: Yes. Dr. Belsito, for the discussion, you want that expanded to specifically mention those components that are of concern relating to their sensitization potential.

DR. BELSITO: You know, it's unfortunate that we're doing botanicals before we've looked at how we're going to approach botanical boilerplates. But, yes, I think in general, when we are doing these botanical products, we have to

point out those components of a botanical that we're concerned about.

And, you know, in this case, there's farnesene, there's linalool, and linalool acetate, azulene. And just point out, you know, what we're concerned about with these individual chemicals, whether it's a toxic endpoint or carcinogenic endpoint, a sensitizer endpoint. And, you know, say, yo', in these specific products, we're not seeing an issue if they were used singly at the levels we're told they're used. But we're concerned that these components could be in another botanical that could be stacked into a product and could exceed these levels. So that's what we're going to say. And all of that will need to be I the discussion.

Now, not to skip ahead too much, but we sort of thought, well, you can do boilerplates for pesticides. You can do boilerplates for aflatoxin. You can do an introductory boilerplate for botanical in general, but it's very difficult to create a schema that is going to address all

the botanicals. So really, when you're creating a discussion, you've got some guidelines, but it's going to be case by case depending on the botanical.

Like the phytosterols, I don't think we need a botanical discussion. There's nothing really in them of concern. With others where you get things like pulegone, thujone, and, in particular, a lot of them you're going to get, you know, these "fragrance sensitizers," you know, we'll need to point those out, you know, just as examples of what the Panel is concerned about.

DR. MARKS: Okay.

DR. BERGFELD: Looking at any other discussion? Now, we have a motion that has been placed and it's been seconded. And would you restate that motion after all this discussion?

DR. BELSITO: Yes, that the flower -- those components of the chamomilla recutita that are derived from the flower are safe as used when formulated to be non- sensitizing. Those components that are derived from other parts of

the plant are insufficient, and the insufficiency is composition of those parts.

DR. BERGFELD: Thank you. I'd like to call for the question then.

All those in favor of this conclusion? Thank you. Unanimous. We're moving onto the other half of this ingredient. Dr. Belsito, you started the discussion here, anthemis nobilis.

DR. BELSITO: Okay. Okay. So again, in this one, we need to clarify what chamilosin, and it's either anthemis nobilis or chamomilla recutita, and get it out of the inappropriate document and into the appropriate document.

And then having said that, we had extensive composition of the plant as a whole, as opposed to what we got with chamomilla recutita. And so, while we had lesser information about the flower, what we had was really the type of information we needed from the flower, which were the essential oils, and the potential fragrance ingredients, and sensitizers.

So for this particular group, the

anthemis nobilis, we thought we could go "safe as used when formulated to be non-sensitizing." Again, a discussion, the pesticide boilerplate, and, you know, identifying those components of concern.

DR. BERGFELD: Is there a second or a comment?

DR. MARKS: Yeah. Let me make a comment because that's -- we had not considered that conclusion. We felt we could say the linalool flower extracts are safe because we have the sensitization data to support that. We didn't have the sensitization for water and powder, so we thought we would split that out and make it "insufficient." But if you use the conclusion "non-sensitizing," I guess that covers it.

So with that in mind, just as long as it's captured in this discussion, we'll second the motion. Team?

DR. SLAGA: Yeah.

MR. JOHNSON: Can I ask a question?

DR. BERGFELD: Wilbur?

MR. JOHNSON: Dr. Belsito, I guess with respect to expansion of this discussion, do you have any specific components that you would like to be addressed in that discussion?

DR. BELSITO: Hold on, Wilbur. Actually for this one, there was nothing -- in terms of the components, the angelate, the tryglate, there was nothing that really jumped out. So, you know, I don't think we need to really mention any components. Just go with "formulated to be non-sensitizing."

MR. JOHNSON: Thank you.

DR. BERGFELD: Any other discussion, or needs, or edits? Ron Shank?

DR. SHANK: I'd like to make one comment. We're developing a clear pattern here saying when "formulated to be non-sensitizing." And what do we do about all the compounds that have -- reviewed before and we've said they're insufficient because we don't have sensitization data? Do we go back to all of those and say we've changed the conclusion to "safe if they're

formulated to be non- sensitizing?"

DR. BELSITO: No, because I think the difference here, the only other time we did that was with cocoamidyl propyl betaine or betaine because of the issue of the impurities and the difficulties of really fully assessing that. But really to date, we've been dealing with a pure compound, you know? I mean, you know, either it contains so much iodopropynyl butylcarbamate or doesn't. And you're not going to get iodopropynyl butylcarbamate being brought into the formulation by some other product.

Here, you know, particularly with botanicals, I mean, read a label on some of these shampoos. I mean, you just start, and there are 10 in a row. And so, the concern with the botanicals are they're not a single pure ingredient, and you can stack component upon component upon component to get to a level in the finished product that is not safe.

So I think that's the twist here in the issue is that it's not a pure chemical that you

can easily restrict.

DR. SNYDER: I think it goes to the very fact of the stacking of the different components within a final product. So you can say "safe as used," but that's taking only that single botanical. But the three botanicals in sum total, they exceed the levels which will cause sensitization, which we clearly have negative data on. I think that's what we're trying to alleviate. We're trying to give them some guidance to make sure that they monitor the levels of known sensitizers in the final product.

DR. BERGFELD: Could I just ask a point of clarification. This word, "stacking," has been used a lot. The definition is? Is it scientific?

DR. SNYDER: I think it would be better to say the cumulative nature of the product formulation.

DR. BERGFELD: Okay, thank you.

DR. BELSITO: It's like bio handling.

(Laughter)

DR. HILL: If we're going to go there,

then I like "aggregate" better than cumulative, but that's just me.

DR. BERGFELD: Okay.

DR. BELSITO: "Aggregate" is good. I like that.

DR. BERGFELD: Okay. I'm going to call for the question. All those in favor of the conclusion that's been proposed, please indicate by raising your hands.

Thank you. Unanimous. Well, we're going onto the last bit, which are the re-reviews. And the first in this group is Dr. Marks and butylcarbamate.

DR. MARKS: So in 1996, the expert panel issued a safety assessment on iodopropynyl butylcarbamate with a conclusion it's "safe at concentrations less than 0.1 percent." And it should not be used in products intended to be aerosolized.

What really in the memo from Wilbur and looking at what now, the European Union has set a number of restrictions on, which in wave two it

indicated that these restrictions were based on iodine exposure. We had a robust discussion, and our team felt there was not a concern with iodine released. And so, our panel or our team moves that we do not open this report.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion? Obviously you'll need to elucidate or expand what you want to have appear in the final report.

DR. MARKS: Exactly. Yeah, it's going to really do with the iodine exposure and our lack of concern of exposure to that.

DR. BERGFELD: And you think you've said enough about that?

DR. MARKS: Yes.

DR. BERGFELD: Thank you. All right. Any other comments about not reopening the particular document?

None? Call the question. All those in favor? Thank you. Unanimous. Then, Lillian, you're up on the re-review summaries.

DR. GILL: This was the re-review

summary for polyvinylpyrrolidone and retinol and retinyl palmitate. This just captures the Panel's review of the new information and of the updated use data at the last meeting and their reaffirmation that these should not be reopened.

DR. BERGFELD: Any comments regarding either one of these particular summaries?

None? Well then, they're approved unanimously. Now, the next discussion, the new area, is the botanical boilerplate/guideline.

DR. BELSITO: Retinol?

DR. BERGFELD: No, together. Okay, unless you had a comment?

DR. BELSITO: We just had a minor editorial comment on the retinol/retinyl palmitate. Simply in the discussion that we struck that first sentence was retinol/retinyl palmitate. The panel recognized the high public/media visibility of concern raised by new studies. We got rid of that statement, "recognized the high public/media visibility of concern," and just said for retinol/retinyl

palmitate, the panel reviewed the photocarcinogenesis study and went on with the rest of the statement.

DR. BERGFELD: That's all right. We can go back to either one of these documents if you care to add it?

DR. BELSITO: No, that was it.

DR. BERGFELD: That was it?

DR. BELSITO: Yes.

DR. BERGFELD: All right. We'll move onto the boilerplate then. Dr. Belsito?

DR. BELSITO: Yes. So we got a lot of information on the boilerplates, and then we were handed comments from the Council yesterday at the beginning of the meeting. And we actually liked the Council's suggestions. We thought they were much more concise and to the point. So this is -- I will call your attention to the handout that we got yesterday, that we liked the idea of handling in the abstract any point about plant used as a food or specific constituent that might be found in other plants. And that we'd say because

formulations may contain more than one botanical ingredient, caution was urged to avoid reaching the levels of toxicity for constituent. And industry should use GMP to limit impurities. And so, we liked that statement.

We liked the boilerplate for the heavy metal pesticides. And to quote, "The expert expressed concern about pesticide residues and heavy metals that may present in botanical ingredients." They stressed that the cosmetic industry should continue to use GMP to limit these impurities.

We also liked their suggestion for aflotoxin, where instead of saying the panel adopted the USDA designations, says the panel recognizes the USDA designations since I don't think it's in our purview to adopt their designation.

The issue came down to how to handle the discussion and make boilerplates. And what we ended up saying is that there can be some general guidance, but short of an opening paragraph

boilerplate where it's necessary, and the one that the Council we thought was good, which says, "As botanical ingredients derived from natural plant sources are complex mixtures, the Panel expressed concern that multiple botanical ingredients may each contribute to the final concentration of a single component. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects." And then, from there we would go on and identify any particular components of the plant we were concerned about.

But as to how you actually structure those paragraphs, there's no way that you can create a boiler point other than to say you attack each individual ingredient for its end point toxicologic concern. So if there are one or two that we're concerned about carcinogenicity, there would be a paragraph about that. If there are one or two that we're concerned about neurotoxicity, there'd be a paragraph about that. If there are

one or two that we're concerned about sensitization, there'd be a paragraph about that.

DR. BERGFELD: Would you suggest restructuring the guideline in any way?

DR. BELSITO: No.

DR. BERGFELD: Oh.

DR. BELSITO: I mean, I thought the Council's suggestions were very good. And, you know, basically their opening paragraph sort of gives guidance as to where we're going to go. You know, it says that we're concerned that we not reach levels that cause sensitization or other adverse effects, and these are the particular components that we're concerned about, and these are the end points that we're concerned about with these components.

DR. BERGFELD: Jim, any comment?

DR. MARKS: We concur.

DR. BERGFELD: Any comments by the Panel members regarding the boilerplate or the approach to the boilerplate.

DR. MARKS: Yeah. Probably the only

comment would be we, as Don used, once we got down to the specifics in the discussion, it's really a guidance document rather than --

DR. SLAGA: Than a boilerplate.

DR. MARKS: -- a boilerplate. But that's semantics.

DR. BERGFELD: Lillian, do you need any more from the Panel regarding the guidance document on botanicals?

DR. GILL: No. I think --

DR. BERGFELD: You think you have it, picked it up? Any comments from the Panel about any other proceedings or preparation? Don?

DR. BELSITO: Yeah. I would just like to mention something that Dr. Gill had mentioned yesterday so that it is in the actual meeting of today's meeting, and that is that hopefully the Panel will in march of 2014 begin to look at the issue of sensitization to methylisothiazolinone and begin to review that. It's a very hot button issue in Europe. I don't think that we can put together all of the information for the December

meeting, but hopefully we can begin to look at it at our March meeting.

DR. BERGFELD: Thank you. Halyna, any comment regarding the recommendation?

DR. BRESLAWEC: The industry is very actively working both in the United States and with our colleagues in Europe and Cosmetics Europe to develop additional data on that. And we're following the issue with real interest, and hopefully we'll have more information by the time the Panel meets on that. But it is, it's a very hot button issue, and we recognize that.

DR. BERGFELD: Thank you. I'd like to make some concluding remarks, if I might.

The panel members are in need of getting the compendiums, whether that be electronically or print. My preference for myself is both. I would also suggest that we take a look at the policies and the boilerplates that now exist that are being used by the writers just to take a look, to update ourselves.

DR. GILL: We do have a project for the

latter half of this year and next year taking a look at all of the boilerplates and making sure that the language is appropriation, that they're updated and they're dated following good practices to make sure that what we're citing is current. So we are -- we do have that project underway, and Monice has that on her desk.

DR. BERGFELD: We also have on the website some white paper issues, so we do need to take a look at those as well. One that comes to mind is the hair dyes, but I know there are a couple of others. We probably should review that. Don?

DR. BELSITO: Just one other point that I'd like to point out, and this is something that Halyna and I had a little opportunity to discuss in Belgium, and that is there used to be a publication Cosmetic Industry on Call, where you could easily identify an individual in a company if you as a physician were having problems with that or had a patient who seemed to be reacting to a specific cosmetic product. That has seemed to

go by the way side, and certainly the version I have is terribly outdated. I think that that is a very valuable piece of information and tool.

Apparently it was stopped because there wasn't really a lot of requests for it, but I think part of a lack of requests was the fact that dermatologists, in particular, were not aware that this document existed. And it's something that perhaps either the Council or the CIR, whosever purview that is, may consider trying to do that, you know. It's very easy in electronic format. And then, also, you know, broadcast the availability of that to individuals, dermatologists, other interested parties, who would like access to that information.

DR. BRESLAWEC: Yeah. The Council did Cosmetics on Call for quite a long time, worked together with the American Association -- Academy for Dermatology, distributed at some point paper directories of individuals to call within individual companies with issues. We switched that over to a computer-based system and

monitoring the use. The use was practically non-existent. And we had no complaints from anybody when the lists were not updated.

Our interpretation was that with Google availability and the companies putting their phone numbers on the back of cosmetics, that that eliminated the need for it, but we've heard from several sources that it would be a good thing to start up again, especially with direct access to individuals within companies from physicians that are having patient concerns. So we are considering revamping and reintroducing something along those lines again.

DR. BERGFELD: It seems to me before Alan left that he was engaged in a marketing project to market the CIR and the information that they have, as well as these types of resources. I wonder at some point we could get updated on where you are with that, because a lot that Don says is that the derms are just not knowledgeable that exist for them.

DR. BRESLAWEC: With regard to CIR

marketing, I think Lillian has got the --

DR. BERGFELD: Lillian has got that? Yeah.

DR. GILL: Yes.

DR. BERGFELD: Another thing for your list, another item to --

DR. GILL: But I'm not sure that this particular project we're talking about is CIR's purview.

DR. BRESLAWEC: No, the Cosmetics on Call is a Council initiative, and it will be handled as such. But what I'm hearing is that the CIR Expert is interested in us doing that, and that message is received.

DR. BERGFELD: Thank you. Well, I think that we've come to the end of our meeting, and so we're going to adjourn and say we'll look forward to seeing everyone in early December, December 9th and 10th. And we'll be sure to send a message over to Curt as to when the meeting occurs.

So happy holidays. We're adjourned.

(Whereupon, at 10:18 a.m., the

PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Carleton J. Anderson, III, notary public in and for the District of Columbia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the District of Columbia

My Commission Expires: March 31, 2017